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The Effectiveness of European Regulatory Governance: The Case of Pharmaceutical Regulation

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Abbreviations

ADR	Adverse Drug Reaction
AESGP	Association of the European Self-Medication Industry
AI	Active Ingredient
API	Active Pharmaceutical Ingredient
BAK	Bundesapothekerkammer
BÄK	Bundesärztekammer (Arbeitsgemeinschaft der deutschen Ärztekammern)
BGA	Bundesgesundheitsamt
BSE	Bovine Spongiform Encephalopathy
CAT	Committee for Advanced Therapies
CFI	Court of First Instance
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Co-ordination Group for Mutual Recognition and Decentralised Procedures Human
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
CP	Centralized Procedure
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
CVMP	Committee for Medicinal Products for Veterinary Use
DDC	Drug Development Candidate
DG	Directorate General
DG Comp	Directorate General Competition
DG Sanco	Directorate General for Health and Consumers
DP	Decentralized Procedure
DTC	Direct-to-Customer advertising
EAEPC	European Association of Euro-Pharmaceutical Companies
EAHC	Executive Agency for Health and Consumers
ECA	European Chemicals Agency
ECJ	European Court of Justice
EDCD	European Centre for Disease Prevention and Control
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Environment Agency
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
EGA	European Generic Association
EMA	European Medicines Agency (formerly EMEA)
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	European Parliament
EPI	European Product index
EUCOPE AISBL	European Confederation of Pharmaceutical Entrepreneurs

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distributional Practice
GLP	Good Laboratory Practice
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
HMPC	Committee for Herbal Medicinal Products
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRA	International Regulatory Agency
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
NBE	New Biological Entity
NCE	New Chemical Entity
NME	National Execution Measures
NPM	New Public Management
NTA	Note to Applicants
OTC	Over-the-Counter Medicine
PD	Power Distance
PDCO	Paediatric Committee
PhVWP	Pharmacovigilance Working Party
PIL	Product Information Leaflet
PIP	Paediatric Investigation Plan
PSURS	Periodic Safety Update Report
RMS	Reference Member State
SPC	Standard Product Characteristics
UA	Uncertainty Avoidance
QP	Qualified Person

1. Introduction: European regulatory governance of pharmaceuticals

> "Since the beginning of its presence in the world, man has been fighting against pain, unhappiness, and diseases. For this purpose, several means have been tried; among them, the most frequently used has been (and is still) drugs." (Mbongue, 2005: 309)

> "Adverse drug reactions (ADRs – a response to a medicine which is noxious and unintended) present a major public health burden in the EU. […] It is estimated that 197,000 deaths per year in the EU are caused by ADRs and that the total societal cost of ADRs in the EU is €79 billion. [original emphasis]" (European Commission, 2008: 3)

Pharmaceuticals represent a commonly used therapeutic intervention and can help to avoid more extensive and costly forms of medical treatment (Lichtenberg, 1996; Neumann et al., 2000). Beyond its *functional* importance, the production of pharmaceuticals represents an important industrial sector, on the global and national scale. The same is true for the European Union (EU): due to its high-technology profile and the importance for employment and job growth, it ranked high on the EU's important Lisbon strategy and played a key role in the European Commission's new Europe 2020 strategy (European Commission, 2010; Koivusalo, 2006). Traditionally, the pharmaceutical sector has been the target of far reaching public intervention, transforming the pharmaceutical market and industry into one of the most highly regulated fields (Mossialos et al., 2004: 1). The main component of pharmaceutical regulation can be characterized as *safety regulation* of pharmaceutical products. Looking at the EU, the high degree of regulation has been mainly driven by a tragic event, namely the *Thalidomide* disaster.[1] However, regulation is not confined to pharmaceutical safety. Based on the peculiar character of pharmaceutical demand and supply, the control of pharmaceutical prices and expenditure represents another area of regulatory intervention. Given severe budget constraints and constantly rising pharmaceutical expenditure, European member states adopted a plethora of measures to regulate prices (Lauterbach, 2004; Zweifel et al., 2009). While the regulation of costs in EU member states has remained largely unaffected by EU influence, the opposite is true for the regulation of pharmaceutical safety. Since the *Thalidomide* crisis, supranational influence has constantly and continuously expanded in this regulatory field: Starting with the first directive issued in 1965, effectively establishing binding criteria for market approval (quality, safety and efficacy) to the creation of

[1] Released in 1957 in West Germany under the imprint *Contergan*, the sleeping pill caused peripheral neuritis in pregnant women and lead to the birth of babies with congenital anomalies in several thousand cases (Permanand, 2006: 1).

manufacturing standards, several attempts to establish European approval procedures and, perhaps most importantly, the creation of an independent EU agency, the European Medicines Agency (EMA) in 1995.[2]

1.1 Research questions

The witnessed developments raise two interrelated questions, forming the central pattern of investigation of this study.

The first question relates to the delegation of regulatory competencies in the pharmaceutical sector. Pharmaceuticals are important for the maintenance of public health but at the same time represent a consumption risk. Therefore, the need for public intervention arises. Governments play an important role in the financing of pharmaceuticals and the protection of their citizens from potentially harmful products. The protection of its citizens is one of the key tasks of the state. The evident delegation of regulatory powers to the European level in the field of risk regulation thus seems to be at odds with the member states' need to legitimize their activities. In light of this contradiction, the first question underlying this study is: why are member states willing to delegate competencies in the area of pharmaceutical regulation and in the field of risk regulation in more general terms?

Following from the witnessed delegation of (risk) regulatory tasks in the pharmaceutical sector, the second research question is, in how far the Europeanization of pharmaceutical regulation has impacted on the quality of regulation and its effectiveness. Delegation to the supranational level is commonly justified on efficiency grounds and functional reasons, while European regulatory quality seems to be perceived as a given (Dehousse, 2008; Haas, 1958; Majone, 1996b, 2006). However, the superiority of European regulation and the performance of the European regulatory state no longer remain unchallenged. While European regulatory activity has expanded in many fields, it does not seem to coincide with a higher acceptance of the European regulatory state and the European Union at large. In fact, the EU is claimed to face a severe social legitimatory crisis (Arnull & Wincott, 2002b), often related to a democratic deficit. As *better* output and therefore regulation seems to be the main lever in order to advance the social legitimacy of the European Union (Scharpf, 1999), the analysis of existing regulatory policy and governance structures is necessary. This is even more important given the constant evolution of European regulatory structures resulting in independent

[2] Until December 2009 the EMA has been called *European Agency for the Evaluation of Medicinal Products* (EMEA). For the sake of consistency, the term EMA will be used throughout this study.

regulatory agencies (Bernstein, 1972; Chiti, 2000) linked through a rather long chain of indirect legitimacy to the European demos.

The study thus tries to assess European pharmaceutical regulation against the backdrop of European integration, risk regulatory theory and the overall social legitimacy of the European Union. Before turning to the theoretical base, research design and structure of the inquiry, the present study has to be put into the context of former research on the subject.

1.2 Previous research on European pharmaceutical regulation

Even though pharmaceutical regulation and especially the respective independent regulatory agency (EMA) have been mentioned in a vast number of European studies, European pharmaceutical regulation still represents an under-researched field. Most studies mainly use the case of pharmaceutical regulation as an example of (successful) sectoral integration and/or to test theories of European integration (Kelemen, 2004; Majone, 1997, 1999; Vogel, 1998, 2001). A second strand of research focuses exclusively on the regulatory structure and more specifically the EMA as an example of a strong European independent agency (Borrás et al., 2007; Chiti, 2000; Eberlein & Grande, 2005; Fleischer, 2007; Groenleer, 2009; R. D. Kelemen, 2004). In contrast, only few authors have focused exclusively on the field of pharmaceutical regulation in their studies. The works of Jürgen Feick (Broscheid & Feick, 2005; Feick, 2000, 2002, 2004, 2005a, 2005b, 2008), John Abraham (Abraham, 1994, 2002a, 2003, 2005; Abraham & Davis, 2007; Abraham & Lewis, 2000) and Elias Mossialos (Mossialos & McKee, 2002; Mossialos et al., 1997; Permanand et al., 2006) have to be highlighted in this regard. Beyond the studies already mentioned, only three monographs, analyzing European pharmaceutical regulation from a political science perspective, have been published so far.

The first one, *Regulating medicines in Europe* by John Abraham and Graham Lewis (2000), reviews pharmaceutical regulation from the perspective of medical sociology and focuses on "how medicines are controlled in the European Union (EU), with particular emphasis on the sociology and political economy of medicines regulation" (2000: 1). Drawing on the political economy of regulation, Abraham & Lewis analysed both European level regulatory structures as well as national regulatory systems in Germany, Sweden and the UK. The study is based on interviews conducted with various stakeholders from both the private and public sphere. Abraham and Lewis identify a neo-corporate bias, regulatory capture and a strong focus on

efficiency in pharmaceutical regulation. Furthermore, the current system is classified as a closed system, ignoring the public interest and effectively blocking the inclusion of lay perceptions in drug approval (2000: 202-218).

As the title *EU pharmaceutical regulation – the politics of policy making* indicates, Govin Permanand (2006) focuses on the policy making process and the interaction of affected stakeholders leading to the European pharmaceutical regime. Instead of perceiving the confluence between industry's interests and the European Commission's free market agenda as a problem per se, he considers it as an explanatory factor for the emerging regulatory regime. Using a policy network approach, Permanand goes on to analyze European pharmaceutical regulation based on three case studies: the transformation of the property protection regime affecting pharmaceuticals, the establishment of the EMA and the lack of a reimbursement and pricing policy on the European level (2006: 13). As his interest is mainly on how "policies are made" (2006: 201) Permanand draws heavily on a concept by James Q. Wilson (1980), distinguishing between different distributions of policy costs and benefits and the resulting policy-making dynamics. Based on this *politics of policy* concept, Permanand derives at several conclusions regarding the emergence of the current European regulatory framework. In his view, pharmaceutical regulation is the result of a struggle between various stakeholder interests, although heavily influenced by industry's preferences. The dominance of industrial interests results from the consistency of industrial preferences over time, the confluence between the Commission's and the pharmaceutical industry's interests and the wish of the Commission to expand its power in "pharmaceutical matters" (Permanand, 2006: 194). Regarding his second research question he concludes that the current state of pharmaceutical regulation "shows a regime that ultimately favors producer interests before those of consumers" (2006: 204).

The latest in-depth study has been *Risk regulation in the single market: the governance of foodstuff and pharmaceuticals in the European Union* by Sebastian Krapohl (2008). Krapohl uses a comparative research design in order to answer three interrelated questions:

> "Why did different supranational regulatory institutions for products traded on the single market evolve? Are some regulatory institutions more efficient than others, and, if so, why? What are the factors that determine their democratic legitimacy and their acceptance by EU citizens?" (Krapohl, 2008: 2)

He applies a historical-institutionalist approach to analyse the respective regulatory regimes. Krapohl applies a more general research design as he traces the developments in the respective policy fields as a whole. While the study is partially designed to test hypotheses

derived from historical institutionalism regarding the institutional development in both sectors, emphasis is put on the efficiency and legitimacy of the regulatory regimes. Turning to the findings of his analysis, Krapohl views the emergence of European pharmaceutical regulation as the result of path-dependencies. The set-up of comparatively strong national regulatory agencies in the aftermath of the Thalidomide crisis rendered European integration via mutual recognition impossible and led to the emergence of a new European regulatory procedure and agency (Krapohl, 2008: 185). The efficiency of the regulatory regime in his view results from the credible commitment of member states, the high degree of legalisation and the continuous scrutiny of European courts. Finally, Krapohl identifies output legitimacy as the key lever to legitimize the European regulatory regime, as input legitimacy is limited by the credible commitments of member states to the respective regime (Krapohl, 2008: 185-189).

1.3 Research focus of the present study

Considering the research focus and approach of previous research on European pharmaceutical regulation, the present study differs in terms of the main research interests, the theoretical foundations and the design of the inquiry. The main aim is neither to test theories of European integration nor to reanalyze the policy-making process. Instead the study provides an analysis of regulatory quality and effectiveness, focusing on the governance of the sector and the implementation stage. Whereas Krapohl addresses the issue of regulatory quality to some extent, the efficiency of the current regulatory regime is not the main focus of the inquiry. Instead, the effectiveness of the current regime, depicting the degree of regulatory goal attainment, serves as a yardstick for evaluation. While the importance of regulatory governance and outcomes is at least mentioned by all previous studies, the concrete evaluation of regulatory governance features more prominently in this inquiry. It thus tries to provide a more inclusive analysis of European pharmaceutical regulation.

1.3.1 Theoretical approach, research design and methodology

The study applies a rational choice-institutionalist approach (Peters, 2000) to analyze the regulatory regime and to explain the emergence of European competencies in this sector. While sharing Krapohl's theoretical approach at least to a certain degree, it does not share the

perception that the emergence of European pharmaceutical regulation can be explained solely by invoking functional reasons e.g. being a credible commitment of the member states (Krapohl, 2008: 23). In contrast, it offers an additional (and micro-founded) explanatory factor for the delegation of risk regulation to the European level by drawing on the concept of blame avoidance (Hood, 2002; Hood & Rothstein, 2001; Weaver, 1986) and depoliticisation (Burnham, 2001; Flinders & Buller, 2006).[3] While an analysis of regulation must include preferences and goals of stakeholders, this study does not share the assumptions put forward by some of the previous works in the field. Acknowledging the importance of scientific objectivity (Weber, 1904), a more neutral perspective on stakeholders and the pharmaceutical industry more specifically is advocated.

In order to answer the underlying research questions, the study employs a predominantly qualitative approach, drawing on existing data, official documentation and secondary sources. In an attempt to derive partially generalisable results, quantitative data is utilized. Beyond publicly available basic health statistics as well as pharmaceutical market and demographic data, however, data availability and reliability proofed to be a major challenge.[4] As it will be discussed in greater detail, transparency is very limited in the pharmaceutical sector, expanding to the availability of data (Abraham & Lewis, 1998).[5] While market data would be principally available through specialized commercial providers, this would imply considerable costs. While it has been possible to obtain information by drawing on secondary sources, industrial associations and regulatory resources, data remains incomplete. The utilized data must be interpreted cautiously, since vested interests feature prominently in the pharmaceutical sector (Godlee, 2010; Wilson, 1980). Moreover, the reliability of health outcome data proofed to be problematic as well, calling for a cautious interpretation of the results presented in this study. In light of these restrictions, the study adopts a predominantly qualitative approach, incorporating quantitative analysis to complement (qualitatively) derived findings to the extent possible. The employed research design and methodology therefore partially draws on an approach that has recently risen to prominence within the

[3] The idea of using blame avoidance for the explanation has been mentioned, although to a very limited extent, by Jürgen Feick (2002).

[4] An additional indication of data restrictions can be seen in the relatively small number of comparative health economic studies of the European pharmaceutical sector.

[5] This problem seems to be specifically striking compared to the situation in the US. Furthermore, data shortages might explain the lack of previous research on European pharmaceutical regulation especially from the perspective of health economics.

social science under the common heading of triangulation.[6] By applying different methods and perspectives on the underlying research object, a more holistic understanding is enabled while the hazard of a systematic research bias, caused by the employment of single and unfitting analytical approaches, is effectively reduced (Pickel, 2009; Wolf, 2007).

The conclusions and findings developed in this study are mainly drawn from two types of sources. First, the study employs secondary literature from the field of political science, medicine, (health) economics and law as well as sociology, anthropology and psychology, partially covering the underlying research questions. Second, the inquiry uses primary sources, comprised of European legislation, in form of directives and regulations, official European and national documents as well as publications of national and European regulatory authorities, associations and interest groups. The methodological challenge must therefore be seen in the linkage of these specific sources, written for different purposes and heterogeneous target audiences and often resonating vested interests, with the overarching research questions of the present inquiry. In order to meet this challenge, interpretation of secondary sources, even though mainly based on a political science perspective, has to apply a multidisciplinary view on the regulation of pharmaceuticals including legal, economic, sociological and medical perspectives.

Turning to the actual research design, this study will focus on the analysis of European pharmaceutical regulation. This limitation seems to be justified by the *specific* character of pharmaceutical regulation, rendering the comparison to other regulatory fields unsuitable. The study thus tries to capture and evaluate (regulatory) developments on the policy, governance and outcome level throughout time. Given the specific regulatory structure of European pharmaceutical regulation, no in–depth assessment of national structures and their changes is pursued. Instead of assessing the relative degree of quality and effectiveness by comparing policy fields, the study develops a general, normative framework for the evaluation of regulation. The selected approach allows assessing developments over time and deriving more general conclusions on the overall effectiveness of European pharmaceutical regulation.

[6] Besides an increased number of textbooks addressing triangulation and the use of *mixed methods* (Creswell, 2009; Flick, 2008; Pickel, 2009), the *Journal of Mixed Methods Research*, published for the first time in 2007, dedicates itself to the advancement of the approach.

1.3.2 Scope of the study

Since pharmaceutical regulation represents a complex and multifaceted subject, it is necessary to clearly define the boundaries of this enquiry. The study investigates the regulation of pharmaceutical safety in the European Union, focusing on the regulation of prescription medicine, leaving the regulation of homeopathic and herbal medicine aside. While the inquiry focuses on the *old* EU 15 member states, the regulatory impact on the whole European Union of 27 member states will be discussed to the extent possible.[7] The research period covers the period from the beginnings of modern European pharmaceutical regulation in the late 1950s until the end of 2008, even though more recent developments in the sector will be considered as well.[8] In late 2007, a new legislative cycle of European pharmaceutical regulation has started and has still been ongoing at the time of writing.

While the regulation of reimbursement, pharmaceutical pricing and intellectual property rights are important in their own right an evaluation of these aspects is beyond the scope of this study.[9] However, due to their closeness and (perceived) impact on the effectiveness of European pharmaceutical regulation, these issues will be addressed to the extent possible. Another important aspect not covered in this study is the regulation of liability and compensation for pharmaceutical damages within the European Union.[10] While this is undoubtedly an important topic for further inquiry, the complexity of the issue would require a separate assessment.

1.4 Outline of the study

The study consists of two main parts. The first part, consisting of three chapters, develops the main research question and the framework for the subsequent assessment. The second part, consisting of four chapters focuses on the empirical investigation of European pharmaceutical regulation.

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7 The decision to focus on the EU 15 has been based on two reasons. While the accession member states have taken over most of the European pharmaceutical regulation the EU 15 were involved in the process of establishing the current regulatory framework. Moreover, the EU 15 and more specifically the founding members represent the overwhelming majority (roughly 70% market share) of the European pharmaceutical demand (DG Competition, 2009: 20).

8 In late 2007, a new legislative cycle of European pharmaceutical regulation has started and has still been ongoing at the time of writing.

9 For an overview covering most of the EU 15 member states see the recent OECD study (2008b).

10 Comparative research in this area has been very limited. For an overview of national and European developments, see (Cavaliere, 2004; Gaßner & Reich-Malter, 2006; Hodges, 2005; Jenke, 2004).

The second chapter starts with a discussion of European health policy. More specifically, it reassesses previously made claims that a European health policy has emerged. The quantitative method employed, using existing databases of European legislation will be introduced in order to substantiate former claims of a European health policy. The third chapter addresses the delegation of pharmaceutical and risk regulation in the European Union from a theoretical perspective. It proposes blame avoidance theory and more importantly the reduction of underlying (political) uncertainty as a complementing explanation for the delegation of risk regulatory competencies. By explaining delegation based on political preferences instead of purely functional reasons, the superiority of technocratic and neutral European regulation is put into question. In a second step, the relevance of regulatory quality in the European context will be discussed by drawing on the official European better regulation discourse. As it will be shown, the European Commission conceptualizes regulatory quality mainly as a question of efficiency, reflecting a strong economic business perspective on regulation. This proves to be a problem regarding the social legitimacy (Arnull, 2002) of the European regulatory state, which has not been tackled adequately by the ongoing better regulation debate on the European level emerging in the late 1990s. Consequently, an alternative conceptualization of regulatory quality emphasizing the importance of effectiveness from the perspective of European citizens is proposed in the following chapter. Moreover, a framework for the assessment of regulatory quality focusing on the legal framework, governance structures and outcomes is developed.

The second part starts with an introduction to the specific characteristics of the pharmaceutical market as well as regulatory goals, tools and challenges. Such an excursion seems to be necessary given the complexity of the pharmaceutical sector and shall facilitate the understanding of the empirical investigation conducted in the following three chapters.

The sixth chapter discusses the preconditions for effective regulation and engages in the analysis of the current regulatory framework by focusing on the policies on which regulation is based. Furthermore an overview of the developments leading to the present regulatory regime is provided. This allows for the assessment of the de jure effectiveness of the given regulatory system. Acknowledging the multi-national and multi-level character of the European regulatory state, the chapter will subsequently assess the transposition of and compliance with European regulation by European member states. The legal analysis is supplemented by the investigation of governance structures carried out in chapter seven. Based on the (neo)institutionalist claim that institutions matter and that the quality and

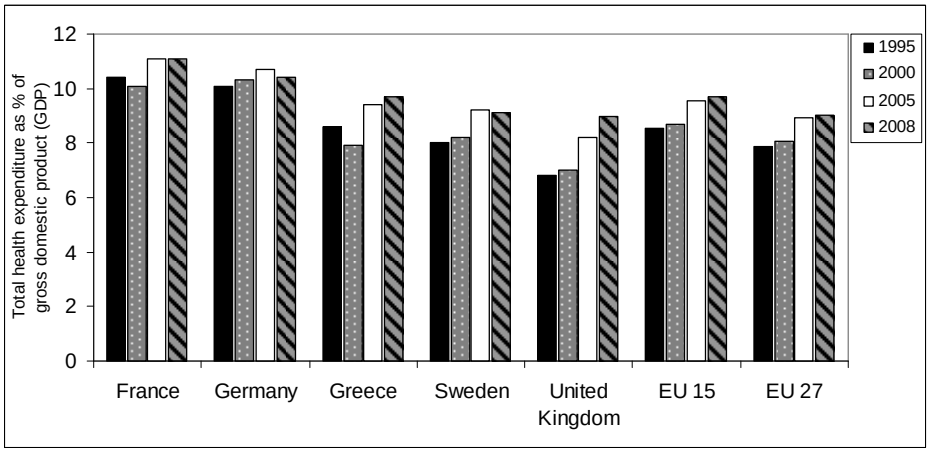
effectiveness of regulation depends heavily on the respective governance structure, the institutional set-up and impact of European pharmaceutical regulation is assessed. Special attention has to be given to the analysis of the EMA and the European approval regime created in 1995, as their establishment marked a watershed of European pharmaceutical regulation in many respects. Moreover, it will be discussed in how far regulation has been able to solve regulatory problems and contribute to the attainment of regulatory goals. Drawing on the results of previous chapters, the eighth chapter assesses the impact of pharmaceutical regulation on the realization of regulatory goals, by discussing regulatory outcomes. Given the previously mentioned data restrictions the chapter relies on previous studies of regulatory performance and proxy measures in assessing the outcome/output dimension. The ninth and final chapter summarizes the theoretical and empirical findings as well as discussing their relevance for the field of European pharmaceutical regulation and beyond. Moreover, further research needs, current political developments and some tentative conclusions for the advancement of regulatory effectiveness in the pharmaceutical sector will be presented.

2. The puzzle of European health policy

The role and competencies of national states and an increased influence of the European level has been the subject of a vital political and scientific discussion. While the debate has been particularly intense regarding economic policy (Müller, 1994), other fields have long been spared. The dominant role of national governments has largely remained uncontested in public policy such as defence, welfare, education and above all, the field of health policy (Alesina et al., 2005; Alesina & Perotti, 2004). Health policy represents a core policy field from the perspective of government since a close connection between the maintenance of public health and economic (and societal) performance exists (Bhargava et al., 2001; Bloom et al., 2004). A functioning health system plays an important role for political stability in general (Steffen et al., 2005: 1) and even though the role of the state in healthcare might be changing (Rothgang et al., 2005), European citizens still expect their governments to provide quality healthcare. Policy failures would thus most certainly result in a decrease of political support and potentially reduced legitimacy of their national governments. An explanation for the limited discussion of a supranational transfer of competences in health care may be the defensive if not protective stance towards a loss of authority in this field (Greer, 2006: 134). While health policy clearly represents a sensitive issue with high domestic salience and is of high political importance, the reluctance relates to the connected high costs of health provision. Since the delegation of competence would inevitably result in less national influence on financing, the Europeanization of health policy is perceived as an undesirable strategy. Health expenditure accounts for a significant share of gross domestic product. At the same time, healthcare in the majority of European countries is financed predominantly through public authorities (Thomson et al., 2009). Allowing the expansion of European competencies in this area would potentially reduce member states' discretion in deciding on resource allocation, which runs counter member states basic preferences. These national policy preferences are reflected in the current legal framework, with the European treaty providing nation states with exclusive competencies in the field of health policy (Hervey, 2005).[11] Notwithstanding the clear preference of member states and *judicial* protective measures, the clearly assigned roles and responsibilities between the national and European level seem to erode in the field of health.

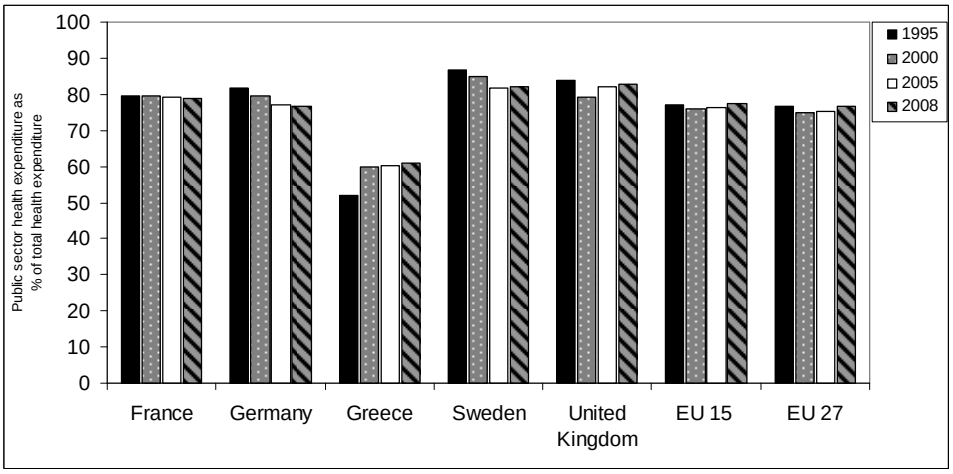
[11] See Article III-278 (7) TCE

Graph 1: Total health expenditure as % of gross domestic product (GDP)



Source: WHO health for all database

Graph 2: Public sector health expenditure as % of total health expenditure



Source: WHO health for all database

A rising number of studies assert the emergence of a European health policy (Gerlinger & Urban, 2007; Greer, 2006; Hervey, 2002; Lamping & Steffen, 2004; Randall, 2000; Steffen, 2005). This trend has been echoed in the official dialogue as well, as the Lisbon strategy explicitly advocates the modernisation of European social systems including health systems (Klusen, 2006).[12] The rise of European health policy seems puzzling, as it challenges the previously outlined relationship between member states and the European Union in the policy field. The question arises, how such assessments could emerge and how the political reality could be adequately described. Since concepts and definitions of as well Europeanization as health policy might be the reason for the controversial finding of a European health policy, a brief reassessment of previous studies serves as a starting point.

[12] Another health-relevant aspect of this strategy could be seen in the publication of EU health strategies by the Commission.

2.1 Europeanization of health policy – research, methods and definitions

The number of studies on the influence of the EU on health policy has been rising slowly but constantly. Comparing recent contributions, the methodological closeness of these works becomes apparent. In depth case studies form the mainstream analytical approach, relying heavily on the discussion of official EU documents and legislation (Gerlinger & Urban, 2007; Hervey, 2002; Lamping & Steffen, 2004; Randall, 2000; Steffen, 2005). This document-based approach is occasionally complemented by interviews with relevant European and national level actors (Greer, 2006). Turning to the underlying concepts of Europeanization and health policy, the different studies reveal significant differences. Hans-Jürgen Urban and Thomas Gerlinger (2007) for example, define Europeanization as, the gradual expansion of European regulatory competencies in the field of prevention and the increased trend towards a market-based organisation of health care systems built upon the four freedoms of the single market. The European Court of Justice (ECJ) is singled out as the main driver of this development, limiting member states' capacity in designing and reforming their national health care systems. In addition, Europeanization is seen in the establishment of European ideas and framing of problems. This trend becomes visible in the number of official publications lining out concrete benchmarks and targets for national reforms of health care systems increases. As the authors rightfully note, these publications have a non-binding character but still have an enormous leverage potential in context of the open method of coordination (2007: 136-137). Even though no clear definition of Europeanization is given by Urban and Gerlinger, the concept seems to be defined twofold: the increase of European competencies and the (harder to capture) emergence of a European agenda. Health policy is defined by two dimensions: prevention and the organisation of health care.

A significantly broader definition of health policy is offered by Tamara Hervey analyzing the process of Europeanization of health policy from a judicial point of view (2002: 69): „Health policy is defined broadly ,and thus a number of areas of Community law may contribute to such an EU 'health policy' [original emphasis]". As she highlights the contribution of other areas to health policy, the emphasis on spill over effects is evident. In line with the results of Urban and Gerlinger, Hervey stresses the connection between the realisation of the common market and the resulting limitations for national policy-making. Her analysis focuses mainly on changes in contractual frameworks and European competencies in the field of health, issued regulations and European case law. While no clear definition of Europeanization is provided by Hervey, the fragmented character of what is labelled European health policy

becomes evident: it is the sum of several spill over effects, including for example working time regulations which affect employees in the health sector (Hervey, 2002: 87).

In contrast to the previously mentioned studies, the book edited by Wolfram Lamping, Stefan Lehto and Monika Steffen offers a distinct discussion of European health policy. In the introductory chapter Lamping and Steffen (2004) start with a *non-finding*: from their point of view no real European health policy exists. Upon closer review, this non-finding can be qualified: it is based on the fact that there is no European competence for the provision of medical services: „the EU is not a provider of services or an agency of distribution and re-distribution, rather it primarily rules by regulation" (2004: 2). Using such restricted definition regarding the European level and its policy activities turns out to be rather problematic. If European policy were restricted to distributive and redistributive activities, European policy as a whole would be virtually nonexistent. The predominantly regulatory character of European policy has been acknowledged for quite some time, resulting in the much cited labelling of the European Union as a "regulatory state" (Majone, 1994b).

Instead of distributional activities, it is the occurrence of regulatory activity that should be perceived as a proof of European policy. Interestingly enough, Lamping and Steffen continue to identify exactly the same general trend previous studies identified when they highlight the indirect nature of European health policy:

> "Given the fact that health policy and health care is an intrinsic and considerable part of the European market of goods and services, it is not surprising that large parts of it have meanwhile been affected by European policy-making via single market compatibility, co-ordination, and harmonization" (Lamping & Steffen, 2004: 2).

The used definition of health policy is slender and consists of the two dimensions „'*public health'* (management of collective health risks) on the one hand and '*health care'* (treatment of individual illness) on the other [original emphasis]" (2004: 5). A useful distinction is introduced with these two dimensions. While Europeanization in the aforementioned meaning is traceable in the public health dimension, the authors point out that such influence or tendency is very limited in the area of health care and mainly results from European Court's activities (2004, 5). The authors identify the creation of the single market, public health crises as well as policy diffusion and European discourse as the main drivers of the development in public health (2004, 2).[13]

[13] This finding resonates with the definition and discussion of Gerlinger and Rosenbrock (2006).

While no clear definitions of concepts are offered in his study, Ed Randall (2000) views the emergence of transnational health crises, e.g. the case of BSE, as the trigger of a stronger European involvement in health matters. According to his research European activity is confined to the field of public health. As the previously cited authors, Randall stresses the piecemeal and haphazard character of Europeanization of health policy:

> "The development of the EU's role in health policy has – for the most part – been opportunistic and accidental, in some cases serendipitous, and, in public health terms, largely ineffective. Opportunism has, however, been an essential ingredient for getting the EU health policy show on the road and keeping it there." (2000: 139)

The contribution by Scott L. Greer does not identify a European health policy in the sense of direct and active European level steering. Again, the indirect character of European health policy manifested in spill-over effects is emphasized: „If something got into health service, it came via a market. That is the basis on which EU powers not originally directed at health come to shape the environments of EU health systems, despite the explicit refusal of member states to create EU health service competencies" (Greer, 2006: 145). The cited mechanism is exemplified by the impact of the Working Time Directive (93/104/EC) dating back to 1993. While the directive originally was drafted as an instrument for the completion of the single market regarding labour law, it had some serious consequences for national health policy. The main objective of the said directive was the improvement of working condition within the European Union in general, affecting employees in the health sector alike, expanding to doctors-in-training since 2000 (Sheldon, 2004). The negative consequences did not result from the original directive but from legal interpretation through the European Court of Justice (ECJ) (Nowak, 2008). As the court decided to use a limited definition of working time, maximal working time for doctors were reduced extensively, with severe consequences for the provision of medical care (Greer, 2006: 141).

Summing up the results of previous research, the finding of Europeanized health policy can be possibly attributed to the definitions used. There seems to be supportive evidence for the existence of European health policy claim as long as health policy is conceptualized as public health, and Europeanization is understood as an indirect spill-over rather than intentional process including the explicit transfer of competences. In light of such inclusive concepts, the controversial finding becomes less surprising. However, the evidence compiled by previous studies does not support a definitive conclusion concerning the question if a European health policy has emerged, is emerging or may start to emerge. Strictly speaking, no systematic

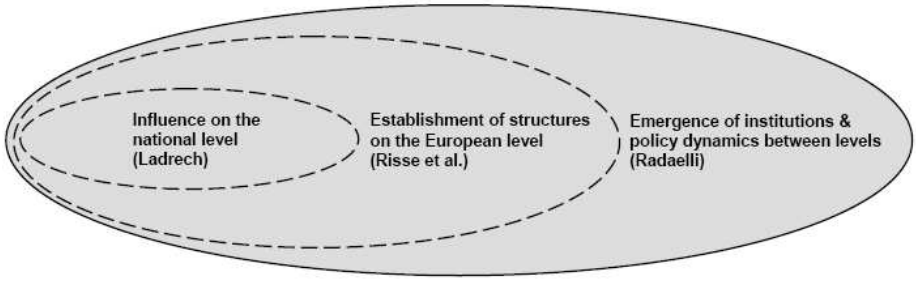
analysis of what could be understood as European health policy has been conducted by previous studies. To remedy this shortcoming, a more systematic analysis is needed. A precondition for such reassessment is a brief theoretical discussion of the key concepts Europeanization and health policy.

2.2 Concepts of Europeanization

The concept of Europeanization is a comparatively young and only partially established one within the wider field of research on the European Union (Jachtenfuchs & Kohler-Koch, 2003: 34). In contrast to the broader notion of political integration, Europeanization has a narrower but at the same time multilayered focus. Rainer Eising identifies three different notions of the concept in EU research, varying in focus and the respective object of investigation (2003: 393). While the focus of Thomas Risse, Maria Green Cowles and James Caporaso (2001a) in defining Europeanization is on the establishment of structures on the European level (1), Robert Ladrech (1994) focuses on the influence of European activity on domestic/national politics and the underlying logic of this development (2). The most complex and inclusive definition is offered by Claudio Radaelli (2000), including the emergence of institutions on the European level and the policy dynamics between the supranational and national under the term of Europeanization (3). In order to clarify the relation between the different notions one could organize the three perspectives on a common scale. While the influence on the national level (Ladrech) can be seen as the first step towards Europeanization, the emergence of structure (Risse and his colleagues) the final establishment of institutions on the European level and the resulting interaction between national and European level (Radaelli), can be understood as consecutive steps of this development. Understanding Europeanization in line with the concept developed by Thomas Risse and his colleagues, describing a process of emergence of specific structures on the European level, the finding of Europeanization of health policy seems to be supported by little evidence: There are no significant and established structures defined by a regulatory framework on EU level which would serve as a proof of such a process (Steffen et al., 2005: 5).[14]

[14] However, the establishment of the Commission's Directorate General for *Health and Consumer Affairs* (DG SANCO) in 1999 and several European agencies related to distinct health aspects might be interpreted as such a development. Considering the tasks of these agencies, with the notable exception of the EMA, they mainly engage in monitoring activities rather than adopting a steering function. The same holds true for the DG focusing on monitoring and the development of strategies.

Graph 3: Different notions of Europeanization



Source: author's own

Applying the concept of Ladrech, and in a more limited sense the concept of Radaelli, speaking of an Europeanization in health policy is at least theoretically possible. Even though the previously discussed studies do not explicitly refer to these authors, they seem to adopt their concepts. Europeanization is thus conceptualized as European influence on national policy even if no „distinct structure of governance" (Risse et al., 2001a: 2) exist. An alternative differentiation of Europeanization developed in context of European health policy is offered by Monika Steffen, Wolfram Lamping und Juhani Lehto (2005, 4-8). They propose at least five distinct perspectives on Europeanization:

- A *traditional* perspective, conceptualizing Europeanization as the emergence of institutions and directly binding political decisions at the European level.
- A *transformative* perspective which focuses on the changes in national institutional structures and policy styles caused by European influence.[15]
- A *political* perspective, viewing Europeanisation as the result of a complex interactive process of mutual alignment and shifting of topics between the two levels.
- A *constructivist* perspective which focuses on the transfer of ideas and framing of problems leading to a change in perception of issues on the national level.
- A *restructuring* perspective, identifying Europeanization as a change in national opportunity structures through European influence, which may change the national rules of the game and coalitions of actors.

The key difference of the presented perspectives can be attributed to the conception of the relationship between the national and the European level. While the second perspective conceptualizes the national level as a dependent variable, all other perspectives focus on the processes of transfer between the two levels. Conceptualizing interaction of the two levels this way seems to describe reality more adequate. A balance of power rather than a clear subordination between the member states and the federal European level exists, even though it

[15] The term transformative has not been used by Steffen and her colleagues, but was supplemented to increase consistency.

is a contested one (Haltern, 2005: 113). A second distinction can be based on the degree of institutionalisation with different levels of consolidation corresponding to a narrower definition of Europeanization. Conceptualizing Europeanization from such procedural perspective avoids the risk of mislabelling such tendencies as Europeanization. It is reasonable to assume that the emergence of a European discourse represents the *precursor* of Europeanization of a given policy field. The emergence of discourse might be interpreted as heralding signs of Europeanization, even though the next steps in the process might not follow automatically. To speak of European policy however, would presume that these consecutive steps actually have taken place. Therefore, Europeanization as defined in this study is limited to direct and targeted intervention of the European level. Using such a definition, the concept is able to discriminate between EU influences limiting national room to manoeuvre (even accidentally) and the explicit intentional intervention in a specific policy field.

2.3 Demarking European policy fields: the case of health policy

A fundamental conceptual problem for the analysis of European policy fields is the proper *demarcation*, depicting the conceptual clarification of what constitutes a *policy field*. Acknowledging this problem, Kennet Lyngaard (2007: 294) recently proposed a definition. According to his definition four main characteristics are relevant: Based on a common topic (1), a group of actors (2) operate within a distinct institutional and procedural setting (3) which could be distinguished from other (identical) systems (4). While offering a simple and comprehensive conceptualisation the contribution to reduce the problem of demarcation is limited. In the case of health policy, defining the common topic already proves to be complex. Looking at the public debate, the concept falls prey to two truncations (Gerlinger & Rosenbrock, 2006: 12). First of all, health policy is limited to the concept of (individual) health care. Secondly, the discussion is dominated by expenditure and cost cutting in health services while the larger implications of health policy on society and the measures taken to improve public health are neglected. To clarify the underlying common topic of health policy, existing definitions of health policy must be reviewed. A typology developed by Steffen, Lamping and Lehto (2005: 8-10) defines a concept which consists of five different characteristics or meanings of health policy.

1. „Policies that focus on the development of medical care, and the organisation of healthcare systems. [...] This part of the subject may be called *medical care policy.*“
2. „In a broader context, the focus tends to be on the social security system and the regime of social protection in the case of sickness. [...] This part of the subject may be called *social security policy covering sickness.*“
3. „Health policies may also be viewed from the perspective of health determinants such as work and living conditions, environment, traffic safety, nutrition, smoking and physical exercise, in addition to health education, vaccinations and screenings [...] this global public health approach could be called *health system policy*.“
4. „From the perspective of the economic interests related to this area, health policies may also be seen as *policies creating growth potential for health-related industry*.“
5. „Quite often, policies with other primary goals may also promote health. [...] In addition to policies, activities and institutions that have health as their primary goal, the concept could also cover those that have an impact on health, even if it’s only a secondary or tertiary goal or no goal at all of the considered policy, activity or institution [...] This dimension of health policy should be recognized as *policies with health impact*. [original emphasis]”

Against the backdrop of Lyngaard’s definition, the object of investigation can now be clarified. Following from this definition the policy field health would only include the characteristics of medical care policy (1) and health system policy (3) while the other three characteristics would fall outside a strict definition of health policy. Using a narrow definition seems to be of great importance, as one of the main problems of health policy research in the European context is the tendency to use elusive concepts.

Such conceptual stretching (Sartori, 1970) can result in impure definitions of the concept and runs the risks to include components which are not constitutive to the concept. Conceptual stretching constitutes a problem for the definition of national policy fields and European policy alike. While the argument of spill over effects may justify the usage of broader concepts, using a definition as broad as the one proposed by Steffen and her colleagues would include aspects of social policy (2), industrial policy (4) or, as in the case of policies with health impact (5), any political activity with an immediate influence on health policy. As a result, the concept would become useless as an analytical tool. This is not to say that spill over effects do not influence national policy discretion and the operation of health care systems. It is true that a lot of European influence happens indirectly, but the need to distinguish between the Europeanization of policy fields and European influence on national policy remains. While European influence in general is conceptualized in a broader way including spill over effects, Europeanization is treated as distinct in this context. If the

purpose of a definition is to grasp the conceptual core, a definition of health policy should be build upon the two core components of the term: the organisation of healthcare systems (medical care policy) and the safeguarding of public health (health system policy). It includes only those aspects aiming primarily at the common topic of health. Furthermore, it reduces the concept of health policy to direct (and intentional) intervention. In congruence with this concept, the health policy model of Gerlinger and Rosenbrock (2006) consists of two dimensions: prevention ("Prävention") and a system of medical treatment or health care ("System der Krankenversorgung").[16] The first dimension of prevention resembles the concept *health system policy*, while the second dimension entails most elements of the concept of *medical care policy*. In terms of sequence, prevention takes place before health is negatively affected. Health policy in terms of prevention therefore entails all societal or political efforts aiming at the protection of public health in general (Baggott, 2000). Turning to the definition of the second dimension of health policy, Gerlinger and Rosenbrock (2006) identify five relevant subfields: health insurance (Krankenvesicherung), ambulatory care (ambulante Versorgung), inpatient treatment (Stationäre Versorgung), supply of pharmaceuticals (Arzneimittelversorgung) and care (Pflege). According to this characterization, the dimension *organisation of healthcare systems* contains the provision and steering of the defined areas and services. In contrast to prevention, the second dimension predominantly deals with issues concerning the improvement of an already negatively affected health. This two-dimensional definition of health policy offers a clear-cut yet sufficiently complex concept. It allows for the differentiation between health policy in a narrow sense and political decisions in general which might influence health policy even though health policy is not their primary focus.

2.4 Quantitative re-analysis of the European health policy claim

As previously stated, the majority of studies on European health policy employ case studies and descriptions of single events. The qualitative focus represents a general tendency within the broader field of European studies comprised of detailed case studies in policy fields, European regulatory activity and the national reactions to these European influences (Majone, 1996b, 1992; Windhoff-Héritier, 2001; Windhoff-Héritier & Knill, 2000). Case studies are very useful to track short term developments and the testing of integration theories, but their

[16] The high congruence between the two concepts could as well be seen as an external concept validation.

usefulness is more limited in tracing general tendencies mainly consisting of incremental changes over a long period of time. In order to trace the existence and expansion of Europeanization of policy fields a quantitative analysis of European (legislative) activity seems to represent a more promising research design complementing qualitative research. Such an assessment can draw on the (economic) study of Alberto Alesina, Ignazio Angeloni and Ludger Schuhknecht (2005). While the focus of their study is the analysis of European activity regarding its responsiveness to public demands and preference their method of measuring European activity – a comparison of the number of issued documents and legal acts – can easily be transferred to the present research question.[17]

The following analysis tries to track the emergence of a European health policy operationalised through an increase in the number of legal acts directly linked to the issue of health. Health policy is defined as all activities aiming *primarily* at health. Activities that have an influence on health policy or the management of health in general, while being focused primarily on a different policy objective are excluded from this definition. It therefore excludes spill over effects, as they should not be considered as intentional policy intervention in a strict sense. Furthermore, an *exclusive* definition of Europeanization is applied, as only legally binding activities are included. The general advantage of such a definition is a higher discriminatory power between *actual* activity in the sense of legislation or judicial activity and all other activities that could be labelled as *soft* coordination and steering e.g. official communications and position papers. Even though these soft instruments may often serve as a pre-stage for later legislative activity in line with a gradual understanding of Europeanization, this is by no means an automatism. The previous considerations can be merged into two hypotheses which will be tested in the following analysis.

1. Europeanization of health policy should be traceable through an increase in European (secondary) law focusing primarily on health.
2. European health policy in a broader sense should be traceable in all relevant sub-dimensions of health policy.

2.4.1 Operationalisation of Europeanization

Logically, the attempt to quantify Europeanization starts on the most basic level: the level of the treaties. The treaties basically codify the competencies and responsibilities of the

[17] A general discussion on the usefulness and usability of the proposed approach can be found in Alesina, Angeloni and Schuhknecht (2005).

European Union and the respective institutions (Herdegen, 2007: 69). An analytical problem regarding the analysis of contractual competencies is that they are contingent upon the respective interpretation of the treaties and „if one takes an extensive interpretation of the Treaties, the EU seems to have some say in almost all policy areas“ (Alesina et al., 2005: 279). Furthermore, European activity is not confined to the laid down competencies in the treaties. In fact, the European Union is active in areas where its competencies are at best vaguely defined (2005: 279). What has to be developed is an analytical distinction between competencies and activities. If the focus of the assessment is to track the competencies of the Union, it has to be based on the treaties. However, if the focus is on factual activity of the European Union such analysis has to go beyond the narrow focus of the treaties. In order to track the degree of Europeanization in a given policy field, the research focus has to be shifted. Rather than focusing on the competencies codified in the treaties, the activities of the European institutions, especially the Commission and the ECJ, should be reviewed. Regarding their activities, analysis should focus on the different instruments of secondary law, non-binding declarations and case law. According to Alesina and his colleagues the following instruments should be differentiated and considered:

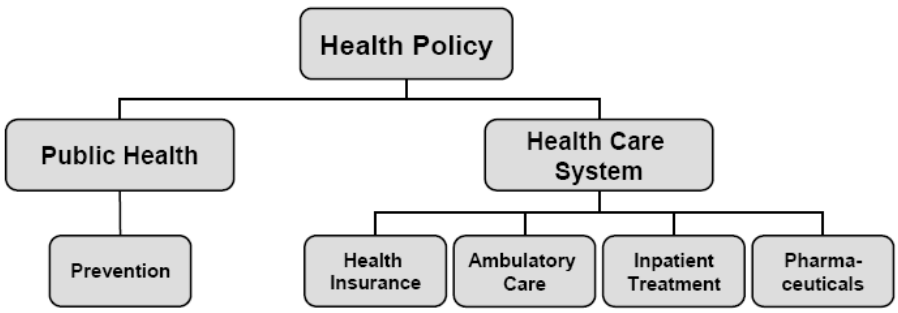
> ”1. *Regulations* contain general provisions, fully binding vis-a-vis all parties in all member states. They are directly applicable without need for national implementation;
> 2. *Directives* are binding vis-a-vis all member states addressed. They specify the results to be achieved but leave member states the choice of form and methods to implement them. They need not apply to all member states (although they usually do) and are rather general, often specifying outcomes that national measures are supposed to attain;
> 3. *Decisions* are binding vis-a-vis all parties addressed. They may be addressed to one, several, or all parties or member states. They can be very specific, like administrative acts, or rather general;
> 4. In addition, the EU Commission issues a number of *‘softer’ acts*, or documents, of non-binding nature. Occasionally, particularly when new policy initiatives are envisaged, the Commission publishes White Papers to outline their legislative strategies. [original emphasis]” (2005: 287)

In light of the previous discussion on the definition of health policy and Europeanization, non-binding documents and the *other instruments* mentioned in the fourth point should be excluded. Turning to the measurement, the number of relevant European documents is counted. More specifically, relevant legislation is counted. While this may only serve as a proxy measure, it provides a basic insight into European activity in particular policy fields. Compared to the predominantly qualitative approach used in European studies the presented method enables the tracking of changes over longer periods of time in an intuitive and

comprehensive way. This sensitivity regarding developments over time seems to be especially useful in order to trace the emergence of European policy fields.

Data was retrieved from the *EUR-Lex* data base (http://eur-lex.europa.eu/). The inbuilt search function can be used to identify previously defined documents. Based on the concept of Gerlinger and Rosenbrock (2006), two dimensions and five sub dimensions can be singled out, each representing a distinct feature of health policy. The originally developed sub dimension of *Care* was left out, as a search based on this term would yield results hard to interpret.[18] Furthermore, the concept of *Care* is partially covered in the dimensions of *ambulatory care*. The site search option provides two different search modes. Either, documents are identified based on the title or on title and text. Both methods are used in the following computation. Additionally, the search function for key terms can be limited to specific types of documents. The search of secondary legislation was conducted based on the three different types of documents: *Regulations, Directives and Decisions.* Another specification of the simple search is reached by organizing the results over time. To improve the usability and comprehensibility of the computation, the total period of examination spanning from the 1970 until 2008 was split into five year intervals. Thus the last interval includes only 3-years - a fact that has to be taken into account when it comes to the interpretation of the results.[19]

Graph 4: Specified concept of health policy



Source: author's own based on Gerlinger & Rosenbrock (2006)

[18] Using the search term results in a large number of *hits* not related to health policy.
[19] To ensure the *replicability* of the computation, the process is exemplified in the appendix (A.1).

2.4.2 Computation results

A first overview of the general development of European level legislative activity is given in the following table displaying the total number of documents *produced* between 1970 and 2008.

Results at this highly aggregated level already show a continuous expansion of overall European legislative activity. The expansion is especially evident in the case of regulations with the number of regulations issued between 1970-1975 doubling in the period between 1991 and 1995. Focusing on the initial research question, all relevant documents regarding health policy in general are counted.

Table 1: European legislative activity (1970-2008)

Period	1970-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2008
Total documents	33439	38505	51066	62772	73444	86211	83834	40581
Legislation								
Regulations	6246	8224	8659	10411	12114	16512	14186	6774
Directives	385	644	653	793	1011	1146	1144	936

Source: Eur-lex

The database is evaluated based on the outlined process using the search term *health*.[20] The results of the computation are shown in tables two and three. Both search modes support the first two formulated hypothesises. A clear trend towards more activity is traceable at least since the beginning of the 1980s. Changes have been most significant regarding regulations as the number of issued documents doubled in the period from 2001-2005. Generally speaking, European health policy measured in the broad sense of European activity obviously seems to exist. The trend manifests itself in a rise of legislation thus confirming the importance of the legislative actors in the expansion of European competencies beyond the contractual agreed competencies. However, the explanatory power of this highly aggregated analysis should not be overstated. This reservation holds especially true for the results of computations based on

[20] The search was run using both *full text* and *title* analysis, as the two possibilities reflect different premises: Using full text will naturally result in a higher number of counted documents, offering a stronger support for the general hypothesis that an expansion of European influence in the field of health policy has happened. Restricting search to the *title*, will result in a more exact result: if the relevant term is already mentioned in the title, the chance of a wrong classification of documents is reduced as one could reasonably expect that using the word in the title assigns greater weight and meaning to it.

title and full text and calls for a cautious interpretation of the results. The computation merely provides an overview of the growth of the usage of the term *health* throughout time. Nevertheless, the used approach offers an approximate quantitative analysis of the process of Europeanization. Using *title* search the results could be reasonably expected to represent a change in importance of health as a political issue for the European political actors.

Table 2: Legislation: health (title search)

	1970-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2008
Legislation								
Regulations	**6246**	**8224**	**8659**	**10411**	**12114**	**16512**	**14186**	**6774**
Health	1	0	2	5	9	6	20	28
Directive	**385**	**644**	**653**	**793**	**1011**	**1146**	**1144**	**936**
Health	25	23	26	47	80	49	32	23
Decisions	**2052**	**3485**	**3148**	**3448**	**4944**	**5950**	**6435**	**4568**
Health	9	63	109	90	197	175	265	108

Source: Eur-lex

Table 3: Legislation; health (title and full text search)

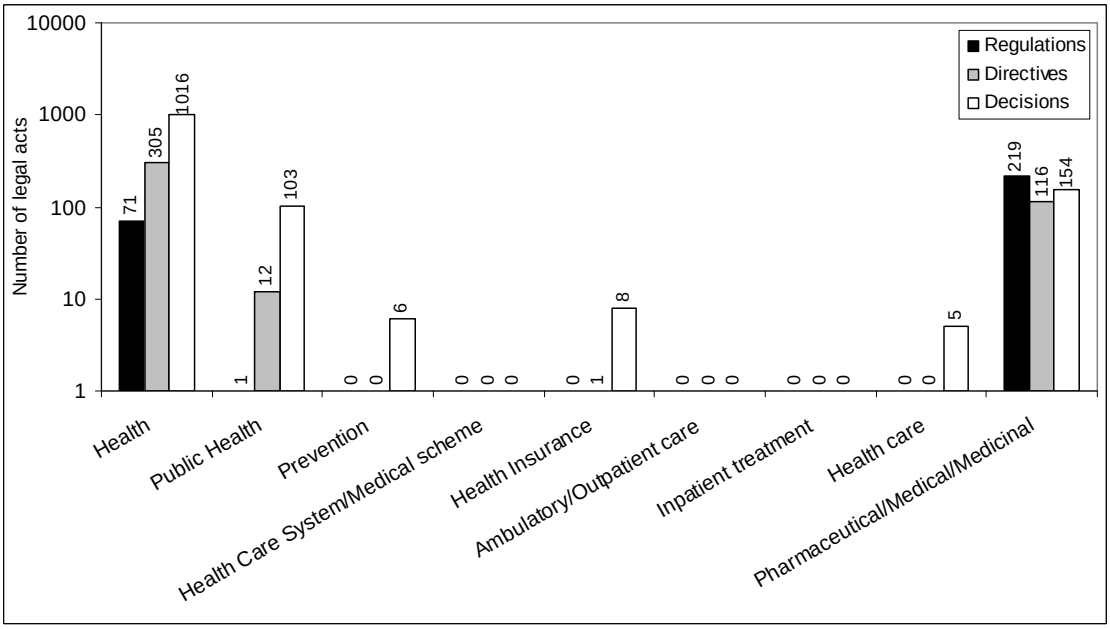
	1970-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2008
Legislation								
Regulations	**6246**	**8224**	**8659**	**10411**	**12114**	**16512**	**14186**	**6774**
Health	21	37	114	192	265	278	655	628
Directives	**385**	**644**	**653**	**793**	**1011**	**1146**	**1144**	**936**
Health	25	123	149	247	366	357	478	330
Decisions	**2052**	**3485**	**3148**	**3448**	**4944**	**5950**	**6435**	**4568**
Health	17	115	455	470	1075	1279	1762	1271

Source: Eur-lex

Since the previously identified trend is evident in this case as well, the initially forwarded claim of an increase in European activity seems to be supported. In order to verify the third hypothesis and investigate the form and content of the supposed Europeanization of health matters, the mode of analysis has to be modified and differentiated further. Differentiation is

achieved by combining the used approach and the concept of health policy as outlined in the previous sections. By conducting a detailed analysis, the claim of a European health policy can be tested.[21] Looking at the aggregated results of the restrictive computation, focusing on document titles, an interesting picture emerges: The dominant trend at the higher level of aggregation only incorporating the concept of health seems to disappear in the more detailed computation of legislative activity.[22]

Graph 5: Legislative activity: health dimensions (1970-2008) (title search)



Source: Eur-lex; Note: A logarithmic scale was used.

While there are virtually no results for most sub-dimensions, only the pharmaceutical sub-dimension yields results, hereby even outnumbering regulations that contain the term health in several periods.[23] The computation thus points to an increased *direct* involvement of the European level in pharmaceutical matters. The second hypothesis is obviously not supported by the data. Using the inclusive search, the results change only slightly. In addition to the trend within the sub dimension pharmaceuticals, a rising number of documents can be traced within the dimension of public health and the sub dimension of prevention. This pattern is unsurprising, as the search terms used are not limited to the field of health policy but represent

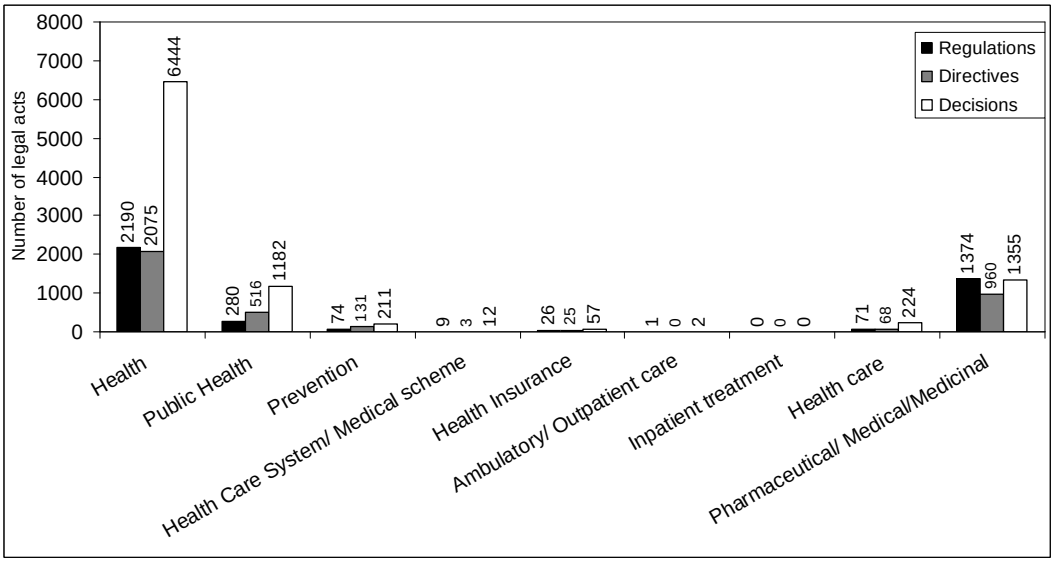
[21] The same method was used and the search was conducted using both the restrictive and the inclusive alternative. Based on the underlying logic of the health policy concept a *knotted* search was employed, counting documents, which addressed one dimension and one sub-dimension e.g. *public health* and *prevention*.

[22] For the detailed results regarding legislative activity see the appendix (A.2).

[23] However, the comparatively high level is at least partially explained by the use of three different terms to operationalise the same sub dimension.

issues familiar to a vast array of policy fields. It points to one of the major limitations of the proposed approach.

Graph 6: Legislative activity: health dimensions (1970-2008) (title and full text search)



Source: Eur-lex

While the method can be used to track the changes in frequency, the usage of words and their literal sense and meaning in a specific context cannot be traced by using single word search. This limitation is especially important in the case of a *full text* search as the matter of context becomes increasingly relevant.[24] In addition, the explanatory power of the inclusive search mode compared to the restrictive one is diminished by the higher basic probability to find the specific term in a given document. One possibility to remedy this shortcoming is the combination of search terms in order to reduce the number of wrong attributions. Furthermore, the quantitative approach could be supplemented by qualitative text-analysis of the respective legal documents to reconfirm and validate the results. However, such an approach is much more complex and the respective costs clearly exceed those associated to the presented quantitative approach. Since the main focus of this study is not on an in-depth discussion of European health policy the presented crude measure can be regarded as sufficient. Against this backdrop, the restrictive search seems to be the more appropriate approach, since the context seems to be of lesser importance in this case. The titles of specific legal documents consists of a limited number of words, the probability of a wrong attribution decreases significantly.

[24] The issue of context is a general problem of text based quantitative methods. See, for example, the discussion on the Wordfish approach (Proksch & Slapin, 2009)

2.5 Conclusion: Clarifying the puzzle of European health policy

As it was outlined at the beginning of this chapter, an increasing number of authors identify the emergence of a European health policy. These results were challenged based on the current legal framework as outlined in the treaties blocking the shift of competencies to the European level. Moreover, the field has been identified as a key area of state activity and has traditionally been treated as a *reserved domain* of member states. It turned out that the studies shared relatively broad concepts of health policy, including activities primarily from other policy fields while causing spill-over effects on health policy. A second common feature of the studies discussed is the approach used to support the basic claim. Researchers use case studies and discuss singular events in order to find evidence for the emergence of a long-term development. European health policy thus is deflected from single events and decisions. Against this backdrop, the true nature of what was called a European health policy could be delineated further. What is traceable is an increase of indirect European influence limiting member states' room to manoeuvre. The reduction of discretion for member states should, however, not be confused with the emergence of a European health policy. What is missing is direct and intentional activity on the European level, focusing exclusively on the issue of health. This perception has been confirmed by computation pointing to a rise of importance of the health topic on the European agenda. However, the existence of a European health policy, including all relevant dimensions of the concept was disconfirmed. Legislative activity regarding the topic of health increased considerably, yet the development is only traceable on a very general level and should not be confused with the emergence of a European health policy in a general sense. For most constitutive elements of health policy, no activity is measurable. Instead of a European health policy, a European pharmaceutical policy has emerged. While this finding helps to clarify the *puzzle* of European health policy, it is in itself puzzling. On first sight, a strong European influence in this field is less surprising since in contrast to health policy, pharmaceuticals are first and foremost tradable goods. The harmonisation and completion of the single market could be understood as a catalyst of European activity exempting the pharmaceuticals from the reserved domain of national health policy. While this explains the easier *access* of the European level, the expansion of competencies still needs some further clarification. As pharmaceuticals constitute one of the key levers regarding the financing of national health systems, simply accepting increased European influence interpreted as less national policy discretion seems to be counter inductive from a member states perspective.

3. Re-theorizing the delegation of pharmaceutical risk regulation

The discussion of the research on European health policy conducted in the previous chapter revealed an interesting finding: while no European health policy in broader terms is traceable, a European pharmaceutical policy has emerged over the last four decades. Considering the focus of pharmaceutical policy however, the emergence of European level policy activities, raises question(s) similar to the case of health policy.

3.1 Defining pharmaceutical policy

Pharmaceutical policy can be conceptualized by applying different approaches. One option to clarify the boundaries of the policy field could be seen in the different policy objectives influencing pharmaceutical policy. Govin Permanand distinguishes three policy objectives: "public health policy (drug quality, safety and efficacy); healthcare (financing and reimbursing medicines); and, in some countries industrial policy (ensuring a successful and productive pharmaceutical sector)" (2006: 4). All three objectives directly refer to pharmaceuticals as a product. While pharmaceutical policy is defined as a dimension of health policy, this definition point to the coeval notions of consumer *and* industrial policy. Pharmaceutical policy can be conceptualized either as drug safety policy, as drug financing policy or as competition policy. These different possibilities of interpretation reveal the possible tensions and potential tradeoffs within pharmaceutical policy, between the aims of safety and financing on the one side and the aim of industrial policy on the other (Valverde, 2006). An alternative approach is offered by Vittorio Fattorusso (1979) focusing on the aim of pharmaceutical policy. Based on the concept of a *pharmaceutical supply system*, including all activities regarding the supply of medicine to the population, pharmaceutical policy focuses on its' improvement. In essence, pharmaceutical policy should ensure "to render accessible to the whole population the most effective and safe pharmaceutical products of established quality at reasonable cost" (1979: 1-2). While the issue of industrial policy is excluded in this definition, the author highlights its importance, since: "it is not uncommon, to find that drug policies are directed mainly towards industrial and trade development and sometimes contradictory policies exist independently […] in different sectors of the government" (1979: 2). A third definition of pharmaceutical policy is provided by Rob Summers focusing on the purpose of pharmaceutical policy which "generally aims to make safe and efficacious drugs available and affordable to the entire population, and to ensure that they are used appropriately by prescribers, dispensers and

patients" (2004: 89). Summers emphasizes that the most important components of pharmaceutical policy are drug legislation and regulation, since privately organized and informal control of this sector is insufficient.[25] Such regulation ought to include "the manufacture, purchase, donation, import, export, distribution, supply, information, advertising and sale of drugs, and monitoring of adverse reactions" (2004: 98). While his definition can be rendered as rather inclusive, it reflects the same basic goals expressed in the previously cited definitions. Moreover, it points to predominant regulatory character of pharmaceutical policy.

Drawing on previous definitions, this study defines pharmaceutical policy as all (political) activities aiming at the provision of safe medicine to the public. Pharmaceutical policy is thus organized along the chain of production starting with the development of a medicinal product and ending with its consumption. Pharmaceutical policy therefore entails both aspects of *safety* and *financing*, revealing the political salience and societal importance of the policy field.

3.2 The political relevance of pharmaceutical policy: costs and risks

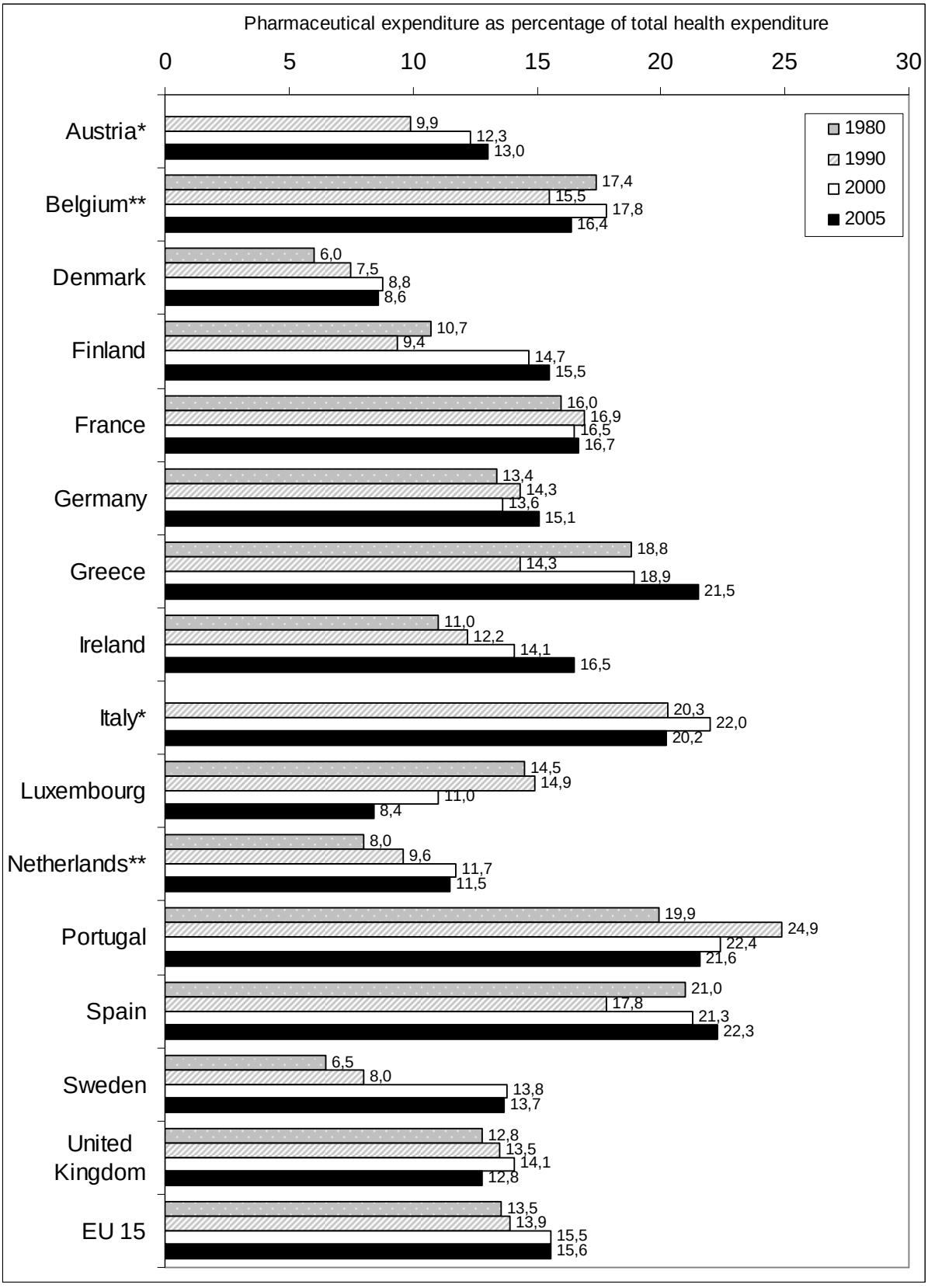
Governments take a key role in the pharmaceutical supply system, the financing of consumption and the provision of access to medicine. In the last decades, the majority of European member states were confronted with rising healthcare and pharmaceutical costs, growing faster than their gross national product (Ess et al., 2003: 90-91). As data by the World Health Organisation (WHO) indicates, the average share of pharmaceutical expenditure on the overall health budget in the EU 15 is growing, even though subject to variation on the member state level.[26] In fact, the data used is under-estimating the real dimension of expenditure, since it only includes expenditure on pharmaceuticals bought in pharmacies (WHO, 2006). Given the fact, that pharmaceuticals constitute a main component of inpatient treatment and inpatient care is mainly financed through public funds, the eventual public expenditure on pharmaceuticals can be expected to be much higher.[27] Looking at the per capita pharmaceutical expenditure within the EU 15, the increasing financial pressure on healthcare system emerges regarding pharmaceutical consumption becomes apparent.

[25] In line with former studies on the sector, the terms *pharmaceuticals*, *drugs* and *medicinal products* are used synonymously.

[26] Obviously, the fact that the pharmaceutical share of the health care budget is growing could be partially explained by cuts in other forms of health care. However, as it will be shown below, the absolute figures are rising in the countries as well.

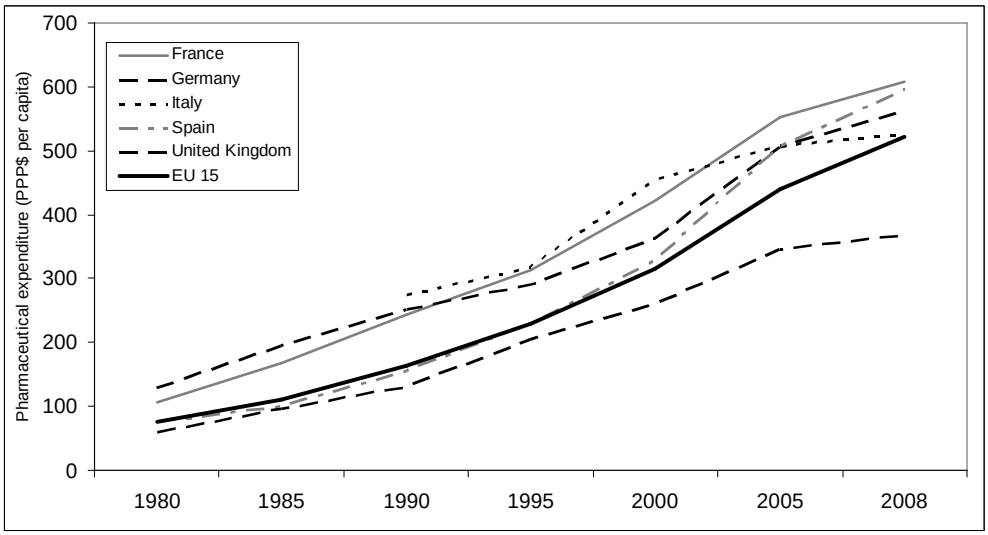
[27] In 2005, public expenditure of total inpatient expenditure in the EU 15 countries covered in the HFA-DB database was between 83,8% (Austria) and 97,1% (Sweden) (WHO, 2006). Moreover, treatments administered under surveillance (in hospitals) can be expected to be more expensive.

Graph 7: Pharmaceutical expenditure EU 15 (in % of total health expenditure)



Source: WHO European health for all database (HFA-DB); Note: * No data for 1980 was available for Austria and Italy. ** Since no value for 2005 for Belgium and the Netherlands was available, values from 2004 (Belgium) and 2002 (Netherlands) were supplemented.

Graph 8: Pharmaceutical expenditure in the five biggest European markets 1980-2008 (PPP$ per capita)



Source: WHO European health for all database (HFA-DB); Note: EU 15 has been calculated based on national values. In 1980 and 1985, no data was available for Austria, Italy and Luxembourg. Data for Luxembourg and for the Netherlands was also missing for 2005 and 2008. In several cases data was supplemented by drawing on preceding years.

Both in the largest five national pharmaceutical markets and the EU 15 as a whole there has been a continuous rise in per capita consumption. In light of decreasing tax revenues and rising health expenditures, governments in Europe developed individual strategies to provide medicine at reasonable costs and keep health budgets balanced.

Table 4: EU 15 public pharmaceutical expenditure as % of total pharmaceutical expenditure (1980-2005)

	1990	1995	2000	2005
Austria	52,2	58,4	66,7	64,3
Belgium*	46,8	43,0	48,9	54,2
Denmark	34,2	48,6	48,7	55,8
Finland	47,4	47,6	48,1	52,3
France	61,9	63,0	66,9	69,4
Germany	73,1	71,0	72,5	73,6
Greece	56,7	70,9	62,9	72,9
Ireland	64,8	62,8	63,9	70,5
Italy	60,5	38,5	44,6	49,7
Luxembourg	84,6	81,7	81,6	83,5
Netherlands**	66,6	88,8	58,3	57,2
Portugal	62,3	63,3	56,2	57,5
Spain	71,7	71,1	73,5	72,0
Sweden	71,7	73,4	70,0	60,4
United Kingdom	66,6	63,5	78,4	83,3
EU 15 average	61,4	63,0	62,7	65,1

Source: WHO European health for all database (HFA-DB); Note: * data for 2000 was not available for Belgium. An estimate was calculated based on the values from 1997 and 2003. ** Data for 2005 for the Netherlands represents 2002.

Despite the common interest in cost-containment, national health authorities have adopted different supply and demand based mechanisms to achieve these goals, representing a major obstacle to European integration (Hutton, 1994). The national interest and measures taken may at times conflict with European priorities as in the case of cost containment versus market liberalization (Permanand & Altenstetter, 2004: 41).

Given these divergent interests, the willingness of member states to grant European influence in the field of pharmaceutical policy ought to be very limited. Beyond the autonomy of financing a second reason for the sensitivity of pharmaceutical policy flows from the specific characteristic of pharmaceuticals as potentially harmful products. While the regulation of cost represents an important activity to ensure access for their citizens, governments must engage in activities to protect their citizens from the potential adverse effects and risks connected to the consumption of pharmaceuticals as one of the key responsibilities of governments is to protect its citizens from harm. Clearly, this task goes well beyond the field of pharmaceutical policy. It relates to the responsibility of governments in more general terms and its crucial role in the field of risk regulation (Hood et al., 1999; Scheu, 2003). Even if this might be a dramatization, the prime *raison d'être* of the state is to guarantee the safety of its citizens. It thus represents the basis of its legitimacy, conceptualizing the state as a guardian and "Schutzstaat" (Stoll, 2003: 5). Obviously, this concept conceives the state as a sovereign, primarily keeping individuals from harming each other rather than saving them from more abstract risks threatening society. Therefore, the function of the state providing safety rather than (only) peace seems to be limited. Nevertheless, the principle idea has been adopted in contemporary constitutional law, viewing the provision of safety as one of the key functions of the modern state, while at the same time expanding the notion of safety beyond its initial meaning (Stoll, 2003: 4). Today, citizens in *risk societies* (Beck, 1996) expect their governments to protect them from the multitude of risks and uncertainties that modern life provides. The modern state is thus confronted with a more complex task. Governments have to react to public demands by providing adequate policies. Given the central importance of protection as a core task of the state, the fulfilment of these demands is directly linked to the legitimacy of the state and government more specifically. If legislators fail to provide adequate policies, public support and therefore state legitimacy are most likely to erode (Majone, 1999). Since democratic governments need legitimacy and public support in order to survive in the political *game*, shifting powers to the European level could result in a reduced room to manoeuvre. The choice of policies to achieve safety and therefore generate legitimacy will be

effectively reduced by European influence and harmonisation measures, as this has been the case in other areas (Börzel, 2002; Risse et al., 2001b; Scharpf, 2002). Considering the implications for national autonomy both from the perspective of financing and regulation of risk, Europeanization of pharmaceutical policy should be rather improbable. First, a higher degree of Europeanization promoting free markets would render state intervention in pricing and cost containment as market distortions.[28] Second, the provision of safety represents one of the key functions of the modern state and its realization serves as an important source of legitimacy. Constituencies preferring national over European regulation serve as an additional reason for this position. While the influence of the European level grew constantly in many areas, public trust in the capabilities of the European Union to govern effectively did not (Hooghe, 2003; Kaase, 1999; Lubbers & Scheepers, 2005). As voters could be expected to oppose deeper integration in some areas, member state governments should adopt a reluctant stance towards such decisions.

3.3 The puzzle of European pharmaceutical policy

Given the identified implications for member states, the Europeanization of pharmaceutical policy comes as a surprise. A closer look at the results of the computation conducted in the second chapter, clarifies this paradox from the perspective of *financing*. While legislative activity regarding pharmaceuticals was high compared to other aspects of health policy, European activity focuses almost exclusively on *safety* aspects while leaving the issue of *financing* of pharmaceutical consumption untouched.

The identified *regulations* mainly addressed general questions related to the trade in pharmaceuticals and questions regarding market authorisation. Released *directives* mainly cover the approximation of testing standards regarding pharmaceutical safety, good manufacturing and clinical practice and market authorisation. The only notable exception in this regard has been directive No. 89/105/EEC, addressing the transparency of measures regulating the prices for medicinal product. As in the case of health policy, European pharmaceutical policy must therefore be described as fragmented rather than holistic. In fact, it would be even more precise to characterize European pharmaceutical policy as safety or risk regulation in the first place. This might explain why member states at least not actively oppose

[28] European governments can draw such conclusions from other regulatory and policy fields, for example environmental policy (Jordan, 2002) or economic policy (Schmidt, 2002b), where Europeanization has been more advanced.

European activity since it does not interfere with the national autonomy regarding the financing of pharmaceutical expenditure. However, the question why member states would be willing to give up their autonomy in the area of pharmaceutical safety still remains unanswered. As previously stated, the importance of this question is going beyond the narrow field of pharmaceutical regulation. The general question is, why states delegate competencies in *sensitive* regulatory fields especially in the field of risk regulation, a trend that has not gone unnoticed(Alemanno, 2008a, 2008b; Klinke et al., 2006; Vogel, 2001, 2003; Vos, 2008). In order to derive an answer to this question one can turn to the rich body of literature on the subject starting on the most general theoretical level of European Integration.

3.3.1 Explaining delegation and shifting of competencies in the European context

European integration constitutes a research field of its own within European studies and is characterized by constant evolution. Most of the theories originated from the field of international relations and therefore do not exclusively focus on the European development. Nevertheless, they all share a common cognitive interest in describing the European integration process. Especially in the case of the two main schools of European integration *neofunctionalism* and *intergovernmentalism*, this interest focuses on the larger developments and integration steps on the European level.

Classical studies on the European integration process offer two competing explanations, why integration and a shift of competencies to the European level take place. While neofunctionalist accounts stress the importance of the European institutions as driving factors and characterize integration as a self-sustaining process, intergovernmentalists view the member states in the driver seat of further integration (Pollack, 2000). Unfortunately, due to the procedural focus neither of the two theories provides an (explicit) explanation for the reasons of initial integration.

While Ernst B. Haas (1958) as the most prominent representative of neo-functionalism focuses on the interdependency of nation state rather than on their interests and motivation for integration (Wolf, 2006: 67), representatives of intergovernmentalism focus on the state. Accordingly, at least a functional explanation is offered by intergovernmentalism. Integration and collaboration takes place, “when joint actions produce better results, for each member, than ‘uncoordinated individual calculations of self-interest’.[original emphasis]” (Hoffmann, 1982: 33-34). However, the preferences of the state and how these preferences are formed

remain concealed in this explanation. This *blind spot* of European integration was remedied soon after. Starting from the premises of intergovernmentalism and liberal theory Andrew Moravcsik introduced a model of preferences underlying state action. In his view, integration could be explained by a combination of member states' preferences and interstate strategic interaction (1993: 482).[29] The basic dynamics of preference formation on the domestic level are easily traceable:

> "The primary interest of governments is to maintain themselves in office; in democratic societies, this requires the support of a coalition of domestic voters, parties, interest groups and bureaucracies, whose views are transmitted, directly or indirectly, through domestic institutions and practices of political representation. Through this process emerges the set of national interests or goals that states bring to international negotiations." (Moravcsik, 1993: 483)

But how does this mechanism serve as an explanation beyond economic integration, the main focus of Moravcsik's enquiry, for example regarding sectoral integration and the growth of European regulation? He emphasizes the need for collective action as a reason for the Europeanization of regulation. If domestic policies are not capable to solve domestic problems because of interference from foreign governments, incentives for coordination arise. Such coordination will most likely involve the transfer of certain powers to a supranational actor (1993: 492). The preferences for coordination result from societal pressure, pushing governments into a certain direction. In some way liberal intergovernmentalism could be seen as precursor of the shift from the neofunctionalist/intergovernmentalist divide towards a rationalist/constructivist debate.

With this shift in debate the question of *how* was replaced by the question of *why* integration, or – to use a term central to rational choice theory – *delegation* to a supranational actor takes place. Rational choice approaches, especially rational institutionalism, therefore gained popularity among scholars of European integration.[30] One advantage compared to previous *grand theories* can be seen in the higher degree of sensitivity. Rational choice can be applied to both large integration steps as well as to incremental change at the European level and in different sectors. Within rational choice theory, *Principal Agent* theory (P-A) serves as a "common anchoring" (Tallberg, 2002b: 24) of existing literature, studying delegation. Member states act as principals delegating power to an agent, in this case the institutions of the

[29] Even though Moravcsik rejected the underlying concepts of neo-functionalism, the basic mechanism of preference formation can be found in supranationalist theories. Societal groups are perceived as the main factor *shaping* nation states and European institutions preferences for further European integration (Nölke, 2006).

[30] For an excellent overview and critical discussion of prominent rational choice approaches in European integration research see Kassim & Menon (2003).

European Union. The basic explanation for delegation resembles the explanation put forward by Stanley Hoffmann. According to P-A theory, delegation takes place, when expected benefits outweigh expected costs. In essence, this explanation is purely functional (Pollack, 1997a: 102) since, as Hussein Kassim and Anand Menon put it: "institutions are chosen or created because of their intended effects" (2003: 123). Based on this functional argument, several scholars attempted to differentiate explanations why states delegate powers either internally e.g. by establishing national independent agencies, or externally to supranational actors. Drawing on the works of Pollack (1997), Tallberg (2002b) and Kassim & Menon (2003), distinct benefits of delegation can be singled out. The first and probably most striking one is delegation in order to overcome problems of collective action. A supranational agent is installed to act as a monitor on contractual parties capable of convincing politicians to "jointly tie their hands" (Tallberg, 2002b: 26). Delegation serves as a mechanism to ensure policy stability safeguarding long-term instead of short term interests. Furthermore, the creation of an agent can help to solve the problem of inconsistent policy-making as an agent is granted agenda setting powers to deliver relatively unbiased policy proposals (Pollack, 1997a: 106). Closely connected to these arguments is the issue of incomplete contracting: No contract can take into account all factors, which have an impact upon the durability and effectiveness of the contract. Thus, an agent is installed ensuring contractual flexibility and adaptation. Furthermore, delegation can have a positive effect on policy quality. This argument is connected to the issue of asymmetric information. While principals would need to devote time to gather policy-relevant expertise, an agent designed exclusively for such a task represents a more efficient solution. As agents become experts in a certain policy field, policy efficiency increases. Adopting a more pessimistic view, delegation can be abused to *lock in* distributional benefits. Delegation in this context can be used to secure certain gains by exporting them to an agent. Finally, delegation can be employed for blame-shifting. As Morris P. Fiorina (1986: 39) regarding legislative behaviour rightfully notes: "risk acceptance is not a standard assumption; indeed, risk aversion is standard". Government's main motivation is to stay in office. This is why they probably would shy away from political decisions, which carry a high risk of policy failure or, to put it into more general terms, little gains compared to possible high costs. As Christopher Hood highlights: "politicians seeking to claim credit and avoid blame from voters face a choice of direction or delegation in any policy domain, while voters or citizens choose between praising or blaming those who direct responsibility in public policy". (2002: 17) Under such circumstances, politicians delegate in order to shift the blame and escape from being held responsible. The identified reasons outlined above surely help to enhance the

understanding of delegation. On the downside, they are still extensions of the basic functional argument (Flinders, 2008). Therefore, they are affected by the same problem that Hussein Kassim and Anand Menon formulated regarding liberal intergovernmentalism:

> "Functional explanation is itself inherently problematic owing to its *ex post facto* attribution of motives without empirical investigation, its stress on interests that remain unelaborated, and its lack of precision in identifying the mechanism that links cause to effect" (Kassim & Menon, 2003: 127).

This criticism touches upon the issue of insufficient micro-foundation of rational choice and P-A theory. While both theories provide a rationale explanation for action, they do not discuss preferences underlying state action beyond the obvious. They do not necessarily advance the understanding of states' motivation to delegate since the reason for delegation is explained by what is (rationally) expected from the act of delegation itself. While rational choice based theories do provide a broader perspective on integration, especially compared to earlier theories, their *explanatory power* therefore depends on what is under scrutiny. Turning to the field of regulatory policy, the theoretical accounts do not offer convincing and holistic explanations for the development of (risk) regulation in the EU (Kelemen, 2004). Going back to the underlying subject of this study – pharmaceutical policy – most reasons put forward by rational choice theory offer little explanation for supranational delegation. If pharmaceutical policy is perceived as risk regulation, Moravcsik for example would argue that the traceable integration resulted from incentives to cooperate in the first place: effective problem-solving could only be achieved by collective action and therefore delegation to a supranational field. Yet, it can be argued that national governments – out of legitimacy considerations – still prefer to keep regulation under their control, even if it would be rational and efficient to delegate. Ensuring a credible commitments or policy stability, there is no reason why they would have to delegate the issue to a supranational actor. It would suffice to delegate horizontally, for example by establishing a regulatory agency on the national level. Moreover, the explanatory value in case of pharmaceutical regulation is diminished by the partial character of delegation. While, member states did delegate pharmaceutical risks, financial aspects of regulation, despite being subjected to the same potential efficiency gains, remained on the national level. The second reason forwarded by Moravcsik identifies societal pressure as an alternative reason for the delegation of national competencies to the European level. European integration is thus explained by power struggles on the national level, pushing rational governments to legislate in favour of dominant interest groups in exchange for vote margins. Business interests try to dominate these struggles, and due to their specific interest structure and resources available

mostly succeed in this endeavour (Moravcsik, 1993: 483-485). State preferences thus are a function of societal power struggles, and the Europeanization of pharmaceutical regulation can be explained by a dominance of pharmaceutical industry's interests (Abraham & Lewis, 1999; Abraham & Reed, 2001; Krapohl, 2008; Permanand, 2006). Pharmaceutical industry favours European regulation, since it is connected to a lower level of complexity. While this explanation of state preferences is convincing, it tends to oversimplify and exaggerate the power of business interests. Certain industries have an enormous influence on political actors and the pharmaceutical industry - given the importance as an employer and taxpayer - surely resides amongst the most influential ones (Abraham, 2002a). Nevertheless, politicians need to satisfy the interests of their voters, not necessarily favouring European integration in general. While governments will have to account for economic and industrial interests, their focus will be on the preferences of the wider public as well.

Summing up the previous discussion, integration theories offer unsatisfactory explanations for the integration of risk regulatory activities in general and more specifically for the pharmaceutical sector. Blame avoidance might however be exempted from such theoretical objections. While the explanation put forward is functional as well, an individual rationale underlying action is implicitly provided: politicians delegate to avoid blame. If a lack of micro foundation is perceived as the key theoretical shortcoming and reason for reduced explanatory power of rational choice theory, such a micro foundation has to be established and blame avoidance – being the only explanation focusing on individual political behaviour – serves as the starting point.

3.3.1.1 Delegation, regulation and blame avoidance

The modern theory of blame avoidance is based on the work of Kent Weaver. In his seminal article *The Politics of Blame Avoidance* (1986), Weaver develops his basic argument. The notion *modern* is used in this study since Weaver himself notes that the idea of blame avoidance is traceable throughout political history. A quote by Louis XIV reflects the basic logic underlying the avoidance of blame: "Every time I fill an office, I create a hundred malcontents and one ingrate" (Weaver, 1986: 371). Initially, Weaver discussed the trend of *automaticity* in modern government, depicting a tendency of "self-limitation of discretion by policymakers" (Weaver, 1986: 371). This voluntary reduction of room to manoeuvre comes as a surprise, since politicians normally would be expected to pursue a strategy that maximizes their political options. If the assumption that the main interest of any politician is to stay in

office is correct, politicians need strategies to achieve this goal. Generally speaking, in order to "claim credit" (Fiorina, 1977) politicians need to take action.[31] The more options he has to take action, the easier it will be to achieve credit maximization. But the tendency to limit these options becomes comprehensible as soon as the assumption of credit claiming as the only motivation of politicians is modified. While credit claiming might be the dominant interest of politicians, it is not the only one. Weaver singles out several *non-electoral* motivations underlying political action (Weaver, 1986: 372). First of all, political behaviour can be determined by *vote trading*. Politicians may for example exchange votes for issues with low salience to them or their constituency. Second, politicians can simply be motivated by *good policy intentions*: acting because they (personally) believe that it is worthwhile. The third motivation might be seen in *power considerations.* Action in this case is guided by the motivation to improve ones' position within a respective institution. While these alternative motivations do influence politicians' decisions, Weaver plies for a realistic perspective according to which the electoral motivations clearly dominate politicians' behaviour. Despite these non-electoral motivations, Weaver introduces a more important concept into the discussion:

> "even choices that appear to offer substantial opportunities for credit-claiming can also create ill will from constituencies who feel themselves relatively or absolutely worse off as a result of a decision. Politicians must, therefore, be at least as interested in *avoiding blame* for (perceived or real) losses that they either imposed or acquiesced in as they are in 'claiming credit' for benefits they have granted. [original emphasis]" (Weaver, 1986:372)

Instead of simply maximizing vote margins, politicians need to include the minimization of risk into their respective utility function. As Weaver notes, the calculation of benefits is far form an easy task for politicians. Besides differences in how political decisions convey into constituency losses or gains, based on the importance of single constituency groups, credit claiming seems to be the dominant strategy only under certain conditions. That is, if constituencies "respond symmetrically to gains and losses" (Weaver, 1986: 373). In reality, there is an uneven perception of gains and losses. Constituencies react more sensible to losses than to comparable gains. The implications of this asymmetry are obvious: "the concentrated losses to constituents need not outweigh benefits for a policymaker to have strong blame-avoiding incentives; it is enough that those costs are substantial" (Weaver, 1986: 373).

[31] There are several examples that might prove that *doing nothing* can be a strategy to stay in office as well, e.g. the German example of Gerhard Schröder and his strategy in economic policy during 2001-2002 (*Politik der ruhigen Hand*) (Hasel & Hönigsberger, 2007). However, even if doing nothing can serve as a short-term strategy it can potentially backfire in the long run.

While the line of argumentation put forward by Weaver is stringent, avoiding blame should not be misinterpreted as a dominant strategy *per se*. In specific situations, political decisions can be dominated by non-electoral reasons while the dominance of electoral motivation is *taking a backseat*.[32] In addition, the assumption of politicians as risk-averse actors might be challenged as well. There are politicians willing to take risks. Weaver is aware of this fact as well. However, these objections do not change the validity of the blame avoidance claim itself, rather they are a reminder that there is no *one size fits all* approach in explaining behaviour and that the explanatory power of any approach will be highly contingent on its' context. In deciding on the right strategy and in the face of potential losses for their constituency, risk-averse politicians may consider the delegation to *independent regulatory commissions* as the best solution to avoid blame (Weaver, 1986: 388). Human (and political) risk aversion thus provides a *micro foundation* for the delegation of competencies based on blame avoidance theory. Since the concept of blame avoidance is developed in context of the US political system, the transferability to the European context and to the issue of supranational delegation could be challenged. Yet, further support for the general applicability of blame avoidance arguments is provided by the concept of *depoliticisation* developed by Peter Burnham in the European context, sharing its basic assumptions. Based on a study of New Labours economic policy, Burnham describes an underlying mechanism that dominates the work of governments: "In short, governments must appear to be competent, as a way of gaining market confidence, to create credit or leeway in policy terms." (Burnham, 2001: 128). Confronted with high expectations of their constituencies and an even growing number of problems, governments may struggle to promote their governing competence in order to ensure political support. Therefore, they might employ a strategy of *depoliticisation*, depicting "reducing the political character of decision-making" to absorb the negative effects resulting from heightened (voter) expectations (Burnham, 2001: 128-129). Based on the works of Burnham, Jim Buller and Matthew Flinders offer a more precise definition of depoliticisation:

> "*Depoliticisation* can be described as the range tools, mechanisms and institutions through which politicians can attempt to move to an indirect governing relationship and/or seek to persuade the demos that they can no longer be reasonably held responsible for a certain issue, policy field or specific decision"(Flinders & Buller, 2006: 295-296).

[32] Budget consolidation might serve as a policy example for such behaviour, since consolidation implies losses for many societal groups and therefore limited potential to claim credit. For a in-depth study see Wagschal & Wenzelburger (2008) and Wenzelburger (2010).

As the authors note, the term Burnham coined is imprecise since depoliticisation does not mean that an issue is not political any more. Rather, the term depoliticisation should be understood as a special mode of governance, which seeks to reduce the direct control and intervention of the state. It substitutes it with a *depoliticised* mode of governance, characterized by "the adoption of an relationship (institutional, procedural or ideological) that seeks to establish some sort of buffer zone between politicians and certain policy fields" (Flinders & Buller, 2006: 297). While the issue of governing competence is forwarded as the main reason, the use of depoliticisation can be based on the motivation to avoid blame in order to stay in office as well. Depoliticisation "can help to insulate politicians in office from the adverse consequences of policy failure." (Flinders & Buller, 2006: 296). This explanation is convincing especially in the case of *institutional depoliticisation* taking the form of a principal-agent relationship and thus delegation.

In contrast to previously discussed theoretical accounts the concepts of blame avoidance and depoliticisation seem to provide a more advanced understanding of European integration regarding risk governance in general and the regulation of pharmaceuticals more specifically. But how does delegation of competencies to the European level contribute to the claim of competent governance and the deflection of blame? It can be argued, that governments given a heightened level of scepticism of constituencies towards the European capabilities would be *better off* in keeping such fields under exclusive control. However, as Flinders and Buller argue a different logic does apply since "some problems will be either controversial or intractable (or both), so much so that any decision runs the risk of making matters worse rather than better" (Flinders & Buller, 2006: 296-297). Such risks *push* governments to delegate, even if this means that future opportunities to claim credit are forsaken. If a precondition for staying in office is to appear *competent*, governments need to take the right political decisions from a public point of view. Knowing what the public wants can be a tough task in certain policy (and regulatory) areas. This holds especially true for areas marked by a high level of complexity. In this case politicians do not only struggle with understanding the preferences of their voters, but with the fact that actual decisions have to be taken under the condition of uncertainty. This is not to say, that there are policy areas where perfect information exist. According to Ulrich Beck: "certainly, ultimate security is denied to us human beings" (1992: 96) and this holds true for politicians as well. Yet the level of uncertainty decision-makers are confronted with varies between policy fields. It will be higher in fields which present a new challenge, confronting politicians with a lack of experience and policy expertise. The

respective level of uncertainty thus seems to be the underlying reason or rationale to delegate risk regulation.

It is important to clarify the distinction between uncertainty and risk at this point (Renn, 2008; van Asselt & Vos, 2006). While many authors view both concepts as dichotomous, such a separation seems to be inappropriate, since uncertainty and risk are connected rather than distinct concepts. Risks can differ in their level of uncertainty, which is determined by the possibility to calculate and control them (van Asselt & Vos, 2006: 315). While this clarifies the connection between uncertainty and risk, it leaves risk to be defined. *Risk* can be defined as the "possibility that an undesirable state of reality (adverse effect) may occur as a result of natural events or human activities" (Renn, 2008: 1). Uncertainty is primarily connected to the occurrence of the event, but in addition might be thought as impacting on the definition of an effect as adverse. When talking about the modern form of risk, such risks are distinct from risks, which could be labelled as strokes of fate. Modern, or as Ulrich Beck calls them, *industrial* risk "presumes techno-economic decisions and considerations of utility" (Beck, 1992: 98). The risks we are facing are no longer caused by some higher power or nature, but could be traced back to human activity. This causes a change in the perception of risk and automatically triggers the question of who is responsible.

> "For with the origin of industrial risks in decision-making the problem of social accountability and responsibility irrevocably arises, even in those areas where the prevailing rules of science and law permit accountability only in exceptional cases. People, firms, state agencies and politicians are responsible for industrial risk." (Beck, 1992: 98)

From this perspective, the modern risk is no longer viewed as something abstract or *from above* but something that is caused by decisions made by organizations and finally individuals, who can be held responsible. As Beck (1992: 103) notes, the attribution of responsibility is complicated by the rise of *organized irresponsibility*: sources of risk intermingle and with the number of possible root causes, it gets harder to pinpoint a single cause or the combination of several causes for the damage done. Despite this problem, *risk societies* engage in the "calculus of risk" (Beck, 1992: 99); by using statistical description of risks, the issue is elevated from the individual to the aggregated level. Through this procedure, risk seems to be controllable, since numbers can express the probability that individuals will encounter such a risk. Risk *becomes* a societal phenomenon and the responsibility for the control of these risks is handed over to the political actors (Beck, 1992: 99). The initial uncertainty connected to risks is not diminished but only transformed: probabilities replace the diffuse concept of

uncertainty regarding the occurrence of events. Despite the shared responsibility for risks, government can be expected to be the first actor society turns to. The state becomes a *risk regulatory state* responsible for these industrial risks, even though it faces the same level of uncertainty regarding the appropriate regulatory intervention. Politicians are thus faced with another meaning of uncertainty. While they are aware, that voters want regulation, the right form of regulation is unclear. The situation leaves the rational politician with a decision: either to adopt a specific regulatory policy, or to delegate the decision. Going back to the argument of Fiorina according to whom "risk acceptance is not a standard assumption" (1986: 39) adopting the second option becomes highly likely. Delegation to circumvent a tough decision under uncertainty, stimulated by the identified risk aversion of political players finally does offer an explanation why risk regulation is delegated.

Delegation of risk regulation may therefore not be viewed as a *blame avoiding* strategy in the first place. The underlying reason for the act of delegation in *uncertain* policy fields is not to avoid blame but uncertainty. The relation between blame avoidance and uncertainty is a hierarchical one: uncertainty may lead to blame avoidance. Delegation of risk regulation can be explained by the fact that uncertainty is high regarding the aim of regulation, making the certainty of political gains hard to compute.[33]But if this explanation is true, how do risk aversion and the avoidance of uncertainty of national governments explain European integration in the field of regulation? As most theories of delegation mainly cope with the national level, the question arises, why delegation to a national regulatory agency does not suffice. An answer is provided by Christopher Hood noting that delegation to avoid blame presupposes the willingness of the *delegatees* to accept their role in the *blame game* (Hood, 2002: 27-28). European institutions seem to differ from those in the national setting in this regard. The need of national actors to shift blame coincides with the preference for *more Europe* of supranational institutions (Tallberg, 2002b: 27). While national regulatory agencies might be reluctant in taking the blame, European institutions accept the blame in exchange for more competencies.[34] A second reason for the Europeanization of risk regulation can be seen in the way such a regulatory structure maximizes the potential for blame avoidance:

> "the ideal design for a regulatory regime is one in which standards are set by international experts, monitored by autonomous agencies and enforced by local authorities – leaving those politicians in the

[33] The principle advantage of this explanation is the sound micro foundation based on the concept of human risk aversion. Moreover, uncertainty has been identified as a constituting characteristic of risk regulation (Breyer, 1993; Fischer, 2009).

[34] Another argument could be seen in the fact, that the delegation to the European level maximizes the distance and *buffer zone* between national governments and the delegated policy field.

> happy position of being able to blame everyone else rather than being blamed themselves when things go wrong." (Hood, 2002: 20)

Moreover, the delegation of risk regulation to Europe often happened after delegation and *levelling up* of regulatory standards on the national level already took place.[35] Therefore, it can be conceptualized as the *second step* in the blame avoidance strategy. If blame avoidance and underlying uncertainty are perceived as driving forces for delegation in the field of risk regulation, the emergence of such diversified structures should be traceable in the respective "regulatory regimes" (Hood et al., 2004).

Summing up the theoretical discussion of the previous sections, Europeanization of risk regulation and the fragmented integration of pharmaceutical regulation can be theorized as a consequence of the tendency of governments to avoid uncertainty. This explanation should not be seen as opposing previous accounts of European integration and delegation. Daniel Kelemen and Annand Menon have recently emphasized that "the nature of EC regulatory activity is shaped by a myriad of - not least political - forces." (2007b: 188). In other words, no single cause and explanation may be able to account for all aspects of EU regulatory integration, let alone the European integration process as a whole. Nevertheless, uncertainty avoidance offers an explanation based on a sound micro-foundation circumventing the "functionalist fallacy" (Krapohl, 2008: 25). It thus provides an alternative and more specific explanation for the Europeanisation of regulatory activities regarding risks.

3.3.2 Re-theorizing the rise of the European (risk) regulatory state

While the topic of pharmaceutical policy is a rather specific case, the general growth of regulatory competencies on the European level has been analyzed extensively (Kelemen, 2005; Kelemen & Menon, 2007b; Majone, 1999; Moran, 2002). The research on European regulation is deeply interwoven with the concept of the *regulatory state*. The concept popularized by Giandomenico Majone focuses on national developments. Modern states ought to fulfil three different types of functions: redistribution, stabilization and regulation (Moran, 2002: 402). The first meaning of the regulatory state can thus be seen in the simple demand for state led regulation. The "rise of the regulatory state" (Majone, 1994b), which in essence describes a shift in the balance between the three functions of the modern state, is seen as a "paradoxical consequence of the international debate about privatization and

[35] The case of pharmaceutical regulation is exceptional in this regard, as the levelling up of national standards was mainly caused by a harmonization of European rules (Collatz, 1996).

deregulation"(1994b: 77). As regulation by public ownership became unpopular in the late 1980s, European states started to privatize their key industries. This shift in regulatory tools from ownership to the control of now private ownership through regulatory policy, explains the rise of the regulatory state on the national level. It would be probably more exact to speak of a *shift* towards the regulatory state, since the main change should be seen in a change of tools, not in a change of basic activity. The rise of regulation as a preferred tool of state activity on the national level is matched by a similar development on the supranational, European level. The preference for regulatory policy-making can be explained by the constraints Brussels has to deal with:

> "Because the Community budget is too small to allow large scale initiatives in the core areas of welfare-state activities – redistributive social policy and macroeconomic stabilisation – the EU executive could increase its influence only by expanding the scope of its regulatory programs: rule making puts a good deal of power in the hands of Brussels authorities, in spite of the budgetary constraints imposed by the member states" (Majone, 1999: 2).

While offering a convincing explanation for the strong reliance of the European level on regulatory policy the question of delegation from the national perspective is still open. Answering this question is of central importance, since Majone views the delegation of regulatory competencies itself as one of the driving forces of the changes discussed on the national level. The shift from the positive to the regulatory (national) state is accelerated by the need of national regulatory systems to meet European requirements (Majone, 1996a). As Majone notes, delegation is a tool to enhance the credibility of regulation in order to satisfy business needs (Majone, 1999: 6). This explanation is convincing in the field of economic regulation. Indeed, a strong growth of regulatory output in the pharmaceutical field can be witnessed in relation to the establishment of the common market, namely the adoption of the *Single European Act* (SAE). Even today, market completion serves as a driving factor as "most EC regulation […] has been linked, either directly or indirectly, to the drive to 'complete' the Single market [original emphasis]" (Kelemen & Menon, 2007a: 176). What could be considered as a paradox in the first place is actually quite the opposite. The creation of a single market did not lead to a race to the bottom, but to re-regulation. While the single market advocates freedom of trade, such freedom cannot be sustained without any rules. What was instilled instead was the replacement of "the patchwork of national regulations with harmonized measures at the EC level" (Kelemen & Menon, 2007a: 176). In order to realize the benefits of the single market, the shift of regulatory competencies to the European level seems to be a necessary step from the perspective of member states. However, this explanation fails

to explain the large amount of European regulation that is not connected primarily to the realization of the single market for example environmental protection, health, food and pharmaceutical safety. Moreover, most of these regulatory policies were developed initially without a proper legal mandate or better yet legal competencies on the European level (Majone, 1994b: 85).[36] This raises the general question how the growth of European regulation in fields not primarily linked to the establishment of the single market can be explained. What is offered by the prominent scholars of European regulation comes close to the reasons offered for delegation in general: more stringent regulation at the European level, higher willingness for innovative regulatory solutions on the European level and the relentlessly pushing European bureaucracy eager to get more and more regulatory competencies in order to expand its powers (Majone, 1994b, 1999). While these arguments certainly are convincing, they supersede the question, why member states did not block the expansion of regulatory competencies in such *sensitive* fields as health, and environmental issues. What is ignored by such functional explanations is the politics involved in such decisions, especially in politically *sensitive* fields since "functional pressure rarely translate seamlessly into corresponding allocation of regulatory authority" (Eberlein & Grande, 2005: 90). However, delegation should not be seen as an automatism, but will depend heavily on the fact, how political gains and losses are related in the specific field. In line with the discussion in previous sections, the willingness to give up competencies regarding risk regulation can be largely explained by the occurrence of uncertainty. It can be reasonably expected, that the level of uncertainty will be distinct in fields of high complexity and, due to insufficient policy knowledge, in novel policy fields. Policymakers are confronted with regulatory demands by the public, and must take the decision if they regulate themselves or decide to delegate regulatory power. This decision becomes even more important, given the relative weight that constituencies assign to questions of (risk) regulation in comparison to other policy decisions. In light of the general risk-aversion of policy makers (Cox & McCubbins, 1986; Weaver, 1986) the most reasonable strategy is to delegate the decision in order to avoid negative consequences of wrong regulatory decisions. While this decision led to the emergence of regulatory bodies on the national level, the same basic mechanism can serve as an explanation for the rapid growth of European risk regulation. In an attempt to reduce uncertainty, national legislators try to distribute the policy field between as much actors as possible. This willingness is met by an

[36] As David Vogel (2001: 9-11) notes, subsequent revisions of the treaty expanded regulatory competencies of the EU for example in the field of environmental regulation and established the protection of health, safety, environmental and consumer protection to be considered in all regulatory measures taken.

European Commission seeing "regulatory activity as a means of enhancing the EC's popular appeal by demonstrating its ability to address areas of great public concern, such as social, consumer and environmental regulation" (Kelemen & Menon, 2007a: 177).

Accordingly, a combination of several factors resulted in the emergence of European risk regulation. On the level of preferences, national governments are reacting on the increasing demand of the public for risk regulation by delegating regulatory power to a European Commission with the willingness to take the regulatory burden. A shift in public preferences as the initial trigger is especially striking in the case of risk regulation:

> "In sum public support for stricter health, safety and environmental standards is no longer confined to northern Europe. Rather in recent years, much of western Europe appears to have developed a common civic culture, one which is more risk-averse than in the past, especially with respect to issues of public health and which shares higher expectations about the role of governments in protecting both consumers and the environment" (Vogel, 2001: 9).

This change in public preferences can be linked to the previous discussion of the risk society. The reaction of governments is understandable: while the potential of credit claiming is high given the salience of the issue, the risk to fail is high as well. With public perception turning towards a more risk-averse stance supposedly punishing regulatory failure even harder, governments' preferences should be to delegate these issues. Thus, delegation to the European level seems to be a strategy to combine the *benefit of distance* with the potential of claiming credit at least indirectly. The discussed theoretical connection between uncertainty, risk regulation and delegation is indicated by several developments in the European context providing further evidence for the outlined theoretical claim.

3.3.2.1 Uncertainty, national regulatory failure and delegation

A first supportive observation is provided by elucidating the relation between national regulatory failure and the decision to delegate. The connection is evident in the field of pharmaceutical regulation, as the first European directive dealing with pharmaceutical safety was agreed upon during the aftermath of the *Thalidomide* disaster.[37] In the case of pharmaceutical regulation the explanatory value of uncertainty seems to be of even greater significance, since the first steps in delegation were taken, even before a single market for pharmaceuticals was created (Krapohl, 2008: 8). The explanation of growth of regulation as a

[37] *Thalidomide* was a sleeping aid pill originally released in 1957 in West Germany under the imprint *Contergan*. It caused peripheral neuritis in pregnant women and lead to prenatal death and the birth of babies with congenital anomalies in several thousand cases (Permanand, 2006).

logical consequence of the single market does not fit in this case, even though in most fields of European regulation it served as a critical juncture. The discussion about harmonized European regulation for pharmaceutical products would have been inevitable in connection with completion of the common market, but the tragedy "kick started the process" (Permanand, 2006: 2), at a time when a single market for pharmaceuticals was not at the centre of political negotiations. In this particular case, it was not the well-funded pharmaceutical lobby urging governments to regulate in favour of the industry or the need for credible regulatory commitment. Instead, a mixture of political strategy and public pressure calling for the establishment of effective regulation to prevent another tragedy stimulated policy developments. Besides the massive changes in national laws and systems for drug testing that resulted from the *Thalidomide* disaster (Permanand, 2006: 2), limited delegation constituted an exit option from the regulatory *dead end* national regulatory systems had obviously reached. Confronted with uncertainty how the safety of drugs should be regulated in the future and the failure of previous regulatory decisions in mind, risk averse governments did decide to at least pool resources in determining regulatory decisions.

While the case of pharmaceuticals constitutes a special topic, with a European regulatory history spanning more than forty years, the BSE crisis serves as an additional example for the causal link between risk aversion and delegation. Caused by the announcement of the British government that cases of *Creutzfeld Jakob disease* in humans were linked to the exposure to the cattle disease BSE, regulatory crisis shook the national and European level (Frewer & Salter, 2002; Moran, 2001). It lead to drastic measures as the Commission issued a global ban but even more important "dramatically exposed the gap between the single market – which exposes all European consumers to products produced anywhere within the EU – and the inability of European institutions to assure the safety of the products sold within that market" (Vogel, 2001: 12). On first sight, there are few parallels between the two examples: While delegation of pharmaceutical regulation more or less started from scratch, since effective pharmaceutical safety regulation was not in place in most European countries in the 1960s, a well established European regulatory regime was in place in the case of food safety.

However, upon closer review the same basic mechanism of adaption to uncertainty can be identified in the latter case, despite an additional shift on the European level. Not only did the crisis accelerate the shift of more regulatory competencies to the European level, but changed the regulatory architecture as well, calling into question the formerly used advisory boards (Thatcher, 2002a). The scandal caused a massive loss of public confidence in European and

national regulatory capacities alike, leading to the creation of the *European Food Safety Agency* (EFSA) subsequently to the Nice summit and several institutional repercussions at the national level (D. Vogel, 2001: 14). Acknowledging the functional pressure that was present at that time, the act of delegation can be interpreted as a response to regulatory failure, and thus at least partially connected to the high level of uncertainty at that specific point in time.

3.3.2.2 Uncertainty and European regulatory architecture

Underlying uncertainty in risk regulation is not only traceable in the delegation of competencies but impacts on the European regulatory architecture as well. As in the case of the pharmaceutical sector and in the field of foodstuff, community agencies were set up in several fields of risk regulation at the European level.[38] This "agencification" (Christensen & Laegreid, 2005) on the European level can be explained by the risk aversion of national and European officials. Beyond the functional arguments that were employed to justify their creation (Kelemen, 2002: 99-109), the decision reflects the distributed irresponsibility highlighted by Beck (1992), leading to the emergence of several actors occupied with the same regulatory subject. Risk aversion thus explains the emergence of ideal regulatory regimes, consisting of a multiplicity of actors, as Hood (2002: 20) suggested. This line of reasoning supports the claims put forward by regulatory federalism (Kelemen, 2004) and the research on the emergence of transnational regulatory networks as the dominant structural feature of European (risk) regulatory regimes (Dehousse, 1997; Eberlein & Grande, 2005). Regulation is based on a division of labor: while federal government will engage in policy making, implementation will remain on the state level drawing on national regulatory resources, mostly organized within national regulatory agencies (Kelemen, 2004: 9-15).

3.3.2.3 Uncertainty, the impact on risk regulation and the precautionary principle

While the notion of uncertainty provides a rationale for the decision to delegate and provides and explanation for the resulting architecture of European risk regulation, it finally impacts on actual regulatory policy-making. As federal regulators try to expand their regulatory competencies, they have to take into account the preferences of the public at large and the

[38] Beyond the EMA (pharmaceuticals) and the EFSA (foodstuff), several additional agencies have been created, for example the European Environment Agency (EEA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECA). For a general discussion of the agencies and their functions see Geradin and Petit (2004).

preferences of the state governments as well. Only if the resulting policies are compatible with their preferences, state governments will grant leeway to the federal level. Remember however, that given the rise of risk aversion in public opinion (Vogel, 2001), state governments probably adopt an even more cautious approach regarding risk regulation. If risk aversion influences state level preferences, it can be expected to impact on the general federal risk regulatory style. To assess this claim the general characteristics of the regulatory process and principles of risk regulation in the European context must be considered.

Starting with the regulatory process and the regulatory structure a tendency towards functional separation of tasks should be traceable. In clearly distinguishing regulatory process steps between the actors involved, responsibilities are assigned in a clear-cut way increasing the accountability of the regulatory system and reducing uncertainty within the regulatory regime. In addition, officials can be expected to prefer a science-based approach to risk regulation, relying heavily on scientific expertise. Indeed, one of the defining features of European regulatory policy-making, the strict separation of risk assessment and risk management on the European level (Vogel, 2001), represents a way to reduce regulatory complexity. The production of information on which regulation is based and the actual decision are clearly separated. At the same time, this separation leaves politicians with more actors to blame publicly: European agencies increasingly taking over the role of risk assessors, while decisions are finally taken in a member state committee. Second, the motive of uncertainty will lead to stricter regulation regarding the level and the degree of specification. As clear rules are crafted, expectations regarding regulatory outcomes can be deducted. As clearer rules give clearer guidance, state governments should be in favor of such provisions. Accordingly, European risk regulation can be expected to be rather detailed and judicialized (Kelemen, 2006). Evidence for the stricter character of European risk regulation is provided by the comparison with regulation in other jurisdictions. Comparing European and US risk regulation, David Vogel (2001, 2003) identifies a European trend towards stricter limits and tougher benchmarks. Besides tendencies towards stricter regulation the process of implementation becomes increasingly dominated by the issuance of “enforceable goals, deadlines, and transparent procedural guidelines” (Kelemen, 2006: 102) from the federal level. A second feature of the European regulatory style is the tendency or shift towards adversarial legalism amplifying the legalistic style of regulation. This tendency results in longer and more detailed European directives, as the research by Fabio Franchino (2006) indicates. While the emergence of a more *legalized* regulatory approach is heavily influenced by the fragmented

nature of the European polity, it is also influenced by the mistrust of governments regarding the stringent implementation of their peers (Kelemen, 2006). Again, the urge to reduce uncertainty serves as driving force for this development. As the degree of detail increases, national discretion gets reduced and transforms the former "cooperative, informal, and opaque approaches to regulation at the national level" (Kelemen, 2006: 105). This unintended consequence is accepted by member states, as stringent implementation serves as a valuable tool for avoiding regulatory arbitrage. The result of the transformation is a more adversarial instead of cooperative relation between regulator and regulatee as a constituting feature of European regulatory style, possibly reducing the flexibility of regulatory approaches. Paradoxically, the shift to a more legalized approach led to an open rather than a closed mode of regulation. As the old model of closed door bargaining gets pushed back, the increased emphasis of European regulation is on procedural formality and transparency (European Commission, 2001). This change is probably most significant compared to the former national regulatory systems, but could be seen as well in the evolution on the European level: As regulation by committee is increasingly supplemented by broader participation and European agencies take over more and more tasks in regulation, higher transparency is the unavoidable outcome.

The third and probably most important consequence of the discussed development is the preference for safety over scientific certainty. Risk regulation that is influenced by the motive of uncertainty thus will be characterized by the desire to be better safe the sorry. In light of this guiding regulatory ideal, the emergence of the precautionary principle as a new risk regulatory principle in the European context becomes understandable. Officially adopted at the Nice summit In 2000, it marks a clear European commitment to risk-averse policies (Vogel, 2001: 16). Its emergence can be seen as a late-arrival answer to the general mistrust the public developed towards the culture of expertise as the dominant regulatory model in deciding what level of risk is acceptable (Renn, 2008: 55). Developed in the context of environmental regulation, the principle can be generally applied to all areas of risk regulation. The connection between uncertainty avoidance and the principle is obvious: it can be invoked to legitimize regulatory activity, before the negative impact of risk has been established.[39] Despite the contested perception of the principle (Feintuck, 2005; Majone, 2002), the European Union and Commission more specifically, advocated its usage as the basis for risk regulation, giving the principle a high political relevance. Drawing on the previously discussed characteristics, the

[39] In this sense, "uncertainty is the essence of the precautionary principle" (van Asselt & Vos, 2006: 314).

European risk regulatory approach can be described in broad terms. Considering its structure, it is characterized by a clear separation of tasks, with the different areas of regulation assigned to different players in the regulatory regime. Separation is both traceable in the use of regulatory networks and the separation of policy-making and implementation, leading to the description of the European mode of regulation as a two-tier concept (McGowan & Wallace, 1996). Turning to the European regulatory style, a detailed and judicialized style characterizes the current European approach emphasizing clarity of rules and procedures. Finally the precautionary principle, underlying European risk regulation leads to a more cautious – and potentially politically charged approach to regulation. Instead of granting access to markets unless there is a proof of harm, regulation tends to be based on the logic of guilty until proven innocent.

3.3.3 European regulation and the logic of efficiency

Drawing on the previous discussion, uncertainty avoidance proves to be a valuable and complementing explanation for the delegation of risk regulatory competencies, the resulting regulatory architecture and the European risk regulatory approach. At the same time, it calls into question the capacities of the European regulatory state. If regulation is delegated to avoid uncertainty and not because European regulation is considered to be better than purely national arrangements, it must be questioned in how far European regulation proves to be superior. The described European regulatory approach and the tendency towards stricter and more risk averse regulation, can be considered as positive from the public perspective, serving as a mechanism to protect citizens from harm. Yet, while the Europeanization of risk regulation has lead to stricter regulation, this does not necessarily mean that it conveys into better regulation (Vogel, 2001). Doubts regarding the claim of European regulatory superiority are amplified further, when the focus and development of debates on governance and regulatory quality on the European level is considered. When the Santer Commission jointly resigned in 1999, the European political project had reached a watershed. Triggered by rising public concerns regarding the expansion of European regulatory responsibilities, the permissive consensus for further integration shifted to a more critical stance towards the European vision (Hooghe & Marks, 2009; Hurrelmann, 2007) resulting in a public and scientific discussion of legitimacy (Majone, 1999; Scharpf, 1999, 2009) and the democratic

deficit of the European Union (Follesdal, 2004; Follesdal & Hix, 2006).[40] As a response to the political crisis, the Commission decided to engage into a campaign to restore the European (regulatory) image and the confidence into the European Union. The so called better regulation debate started in 2000. As the Commission's White paper on European governance, released in 2001 stated:

> "Today, political leaders throughout Europe are facing a real paradox. On the one hand, Europeans want them to find solutions to the major problems confronting our societies. On the other hand, people increasingly distrust institutions and politics or are simply not interested in them. […] It is particularly acute at the level of the European Union. Many people are losing confidence in a poorly understood and complex system to deliver the policies that they want. The Union is often seen as remote and at the same time too intrusive." (European Commission, 2001:3)

Starting off as a promising project to overcome the identified shortcomings, the debate took a rather disappointing route leaving the fundamental challenges from the perspective of European citizens aside. Instead, it shifted towards the question of efficiency and the framing of regulation understood as regulatory burden (Radaelli, 2007).[41] While such an understanding has its merits in the area of economic regulation, it seems to misinterpret the purpose of regulation: the debate framed it as costs instead of an instrument for correcting market failure and unwanted externalities, reflecting a clear business perspective. Such perspective proves to be too limited when the European Union is understood as an economic and political project. Given that there are two main stakeholders in European regulation – businesses and citizens – these two groups could be thought of as representing different preferences and perceptions regarding regulation. For example, these two groups most probably will assign a different weight to the improvement of regulation, which is either more efficient (1) or more effective (2) regulation. Both parties surely are interested in both aims but nevertheless could be thought of as valuing one over the other. Businesses will be more interested in the efficiency or better yet cost-effectiveness of regulation. As businesses are first and foremost interested in maximizing gains, regulation represents a cost factor, which ought to be minimized in order to maximize the total gain. This is not to say, that business is always favouring less regulation or is against regulation in general.[42] However, if their main

[40] At the heart of legitimacy debate seems to be, what Anthony Arnull has defined as *social legitimacy*. Social legitimacy depicts "the extent to which the allocation and exercise of authority within it commands general (is) acceptable." (2002:4).

[41] For a critical assessment of the white paper and the *better regulation* debate, supporting the general argument of lacking social legitimacy, see Arnull and Wincott (2002a) as well as Eriksen (2001), Hoereth (2001), Kohler-Koch (2001) Scharpf (2001) , Schmitter (2001) and Steinberg (2001) .

[42] Regulation might not only represent a burden but a competitive advantage for example entry barriers protecting (existing) producers from new competitors.

concern is to maximize profits, it is plausible to assume a focus on efficient regulation while the effectiveness at least might play a subordinate role.

In contrast to businesses, citizens or consumers can be thought of assigning a higher weight to the effectiveness of regulation (Radaelli, 2004: 10). This holds especially true for regulation referred to as social regulation and consumer protection. As the costs of regulation are mainly borne by the companies, the question of efficiency from a customer perspective might play a subordinate role. Turning to economic regulation, efficiency would be the first priority of consumers only if this would impact on the price one would have to pay. However this direct connection is not apparent in most cases. Even though this argument might run the risk of making a generalization, one could say that business focuses on the efficiency while customers focus on the effectiveness of regulation. In the case of BSE, for example, citizens do not criticize the European Union for too much regulatory burden, but for the lack of regulatory effectiveness (Fischer, 2009; Krapohl, 2003). The dominant regulatory logic on the European level focusing on efficiency is problematic, as it does not advance the legitimacy of the European regulatory state from the perspective of citizens. If the regulatory focus is more efficient regulation, this may advance the legitimacy of the regulatory regime towards the business community. However, it does not ensure that improving regulation automatically translates into more effective regulation. A regulatory state dominated by efficiency considerations may secure the support of business but not necessarily public support resulting in a further erosion of social legitimacy. In light of delegation in order to avoid uncertainty and the European regulatory logic, the superiority of European regulation must be questioned. Challenging the common knowledge that European regulation is efficient, effective and its problem-solving capacities live up to their expectations (Skogstad, 2003), a reassessment of European regulation seems to be necessary. Strikingly, little effort has been made to analyse regulatory quality beyond efficiency considerations even though the European Union "is before anything else a political system that regulates (and not a system that taxes and offers social protection), the first priority of single market governance concerns the quality of regulation." (Radaelli, 1998: 17).[43] Only if the European mode of regulation satisfies the conditions of effectiveness and efficiency, it will be legitimized from the perspective of European citizens. What is needed is not only a proper functioning internal market, but "an internal market for the citizens and the firms of the Union" (Radaelli, 1998: 18). This

[43] A notable exception has been the study on consumer safety by Christopher Hodges (2005). A (limited) discussion of the efficiency/effectiveness divide of European regulation could be found in Skogstad (2003).

necessitates analysis based on a broader understanding of regulatory quality complementing existing studies focusing on the quality of regulation in the sense of processes and efficiency (Radaelli, 2004, 2007). It must consider the performance and the outcomes of the European regulatory structures, considering that the legitimacy of European regulation and the European Union primarily rests on output regulation (Krapohl, 2004b; Majone, 2000; Scharpf, 2009).

3.4 Conclusion: uncertainty avoidance, delegation and regulatory quality

This chapter started with a puzzle: an increased European influence in a policy field that is highly sensitive, namely the safety of pharmaceuticals. The political sensitivity stems from the fact that the provision of safety constitutes one of the core tasks of modern states and thus contributes to its legitimacy. Delegation in such fields seems to oppose states' vital interests. The review of European integration theories provided only unsatisfactory explanations, since they focus on European integration at large. Starting from the premises of blame avoidance theory, risk aversion as a general human and thus political trait was identified as a micro foundation for the delegation of regulatory competencies. As national politicians are confronted with regulatory demands by their constituencies while at the same time facing a high level of *uncertainty* regarding the appropriate way of regulation, delegation becomes a rational strategy. Since politicians want to stay in office, their main aim is to maximize vote shares.[44] In order to secure support, he is confronted with policy choices. While choosing certain policies in order to claim credit for political action, seems to be the appropriate strategy in many policy fields, in some policy fields choosing the right policy is complicated. Policy fields can be marked by a high level of uncertainty that is, insecurity about the impact of policy decisions on constituencies. As it was shown, adopting an alternative strategy, namely delegation of the decision seems to be appropriate in such policy fields, considering the underlying risk aversion of rational politicians. This micro-founded explanation provides an complementing approach to the delegation of regulatory competencies within the European Union. The dominance of uncertainty and thus risk-averse behavior does not only provide an alternative explanation for delegation of risk regulation, but offers some insight regarding the emerging regulatory architecture. As it has been shown, the current approach to European risk regulation is influenced at least partially by the avoidance of uncertainty. While this has

[44] Of course the exclusive focus on vote seeking represents a generalized assumption and could be challenged in light of the extensive research on different motivations, for example office and policy seeking. For an overview see Jäckle (2010).

implications for the architecture of the European risk regulatory state as the number of regulatory actors involved increases, for example by creating new regulatory agencies, it impacts on the actual regulatory policy reflecting an increased tendency towards stricter and more risk averse regulation. The Europeanization of risk regulation has lead to stricter regulation in general, but this does not necessarily mean that it conveys into better regulation. While the regulatory superiority of the European level has been taken for granted, the discussion throughout this chapter calls for a critical reassessment of this assumption. The understanding of what constitutes good regulation remains limited on the European level, focusing on business rather than public preferences. Therefore, rather than assuming that European regulation works in effective ways, an analysis of regulation adopting an effectiveness perspective is necessary. Accordingly, a framework for the assessment of regulatory quality beyond efficiency will be developed in the following chapter.

4. The assessment of regulatory quality

A broader understanding of regulation going beyond the limited scope of efficiency is necessary to fully assess the quality of European regulation since only if European regulation meets the standards of both key stakeholders (businesses and citizens alike), the European regulatory state can be understood as legitimized sufficiently. The chapter will proceed in five steps to develop a more holistic understanding of regulatory quality. First, existing concepts of regulation will be discussed briefly to derive at a sound theoretical foundation of core concepts. Subsequently, the idea of regulatory quality beyond efficiency considerations will be discussed. Drawing on a redefined concept of regulatory quality, existing principles of good regulation will be synthesized from previous research. In the next step, the realization of regulatory quality within regulatory systems is discussed. In addition, the section will address common problems of regulation and their potential negative impact on the realisation of regulatory quality. In a fourth step, the implications of risk regulation as a specific type of regulation and the European context have to be included to derive a more specific understanding of regulatory quality applicable to the field of European pharmaceutical regulation. Finally, a general framework for the analysis of regulation in the European context is presented.

4.1 Defining regulation: review of previous theory

Defining regulation is a complex task, given the vast number of distinct definitions used in regulatory studies. In addition, the usage of regulation in law, sociology and political science context differs tremendously.[45] However, it should be at least possible to derive a definition that grasps the mutually accepted features of the concept. The first attempts to classify regulation from a political science perspective, date back to the studies of Theodore Lowi (1964). He identifies regulation as a form of policy, which can be distinguished from *redistributive* and *distributive* policies. The distinction between the different policy types is based on their level of conflict: redistributive policies will naturally create winners and losers, while distributive and regulatory policies might do so only to a limited extent (1964a: 690-692). This dichotomy proves to be problematic: regulatory policy might create winners and losers as well, rendering the used differentiation as meaningless (Fischer, 2009: 68). While it

[45] For a general theoretical discussion of regulation and comparable definitions see for example (Baldwin & Cave, 1999; Ogus, 1999; Quirk, 1981; Wilson, 1980).

is justifiable to identify regulation as a specific type of policy, the distinction has to be based on other criteria than conflict potential. An alternative definition is provided by John G. Francis: “regulation occurs when the state constrains private activity in order to promote the public interest” (Francis, 1993: 1-2). Following from this, regulation can be understood as an instrument to regiment actors’ behaviour. Compared to distributive and redistributive policies, regulation is conceptualized as a more indirect way of achieving certain outcomes. Regulation therefore is rather about prohibiting and permitting than taking and giving. In other words, regulation is about “social control” (Jordana & Levi-Faur, 2004: 3). Moving beyond this rather broad conceptualization of regulation as social control, Robert Baldwin, Colin Scott and Christopher Hood synthesize two alternative meanings based on the discussion of regulatory studies. The second notion of regulation covers all modes of state intervention in the economy. The third and most specific notion renders regulation as a form of governance based on the setting of authorative rules (Baldwin et al., 1998: 3-4). Rather than simply limiting the second notion of regulation to the economic sphere, interventions in the social sphere could be included into the concept as well. Social regulation, as opposed to economic regulation mainly aiming at the protection of citizens from high prices and price discrimination, covers interventions in order to protect consumers from health and other risks (Francis, 1993: 2-3). While actual regulation contains elements of both economic and social regulation, the distinction is useful as it differentiates between regulation as a market intervention and regulation that tries to reduce the externalities a market might produce. The classification of Baldwin, Scott and Hood points to a twofold meaning of regulation. First, regulation can be defined as a rule-based intervention into private conduct in both the economic and social sphere. Regulation is thus defined as a specific form of policy or more general political activity. Second, regulation can be thought of as a specific form of *governance*. The second form of conceptualization implies an institutional perspective on regulation. The need to define regulation as a specific form of governance structures is obvious in the European context. As regulation takes place in a multi-level system, the functioning of regulation will depend on the regulatory system in place and the interaction of different stakeholders and levels. Drawing on the concept of Arthur Benz and Burkard Eberlein (1999: 331), distinguishing *vertical* and *horizontal* governance, all actors within a regulatory field on a level (horizontal) and the interaction of different levels on which regulation takes place (vertical) have to be considered. This twofold conceptualisation of regulation provides a broader and more focused definition, going beyond the definition of

regulation as regulatory burden and costs. Based on this concept the next section will try to deflect a fitting definition of good regulation or better yet regulatory quality.

4.2 Redefining regulatory quality

Starting from premises of regulation as a policy, a tentative idea of regulatory quality can be drawn. As Francis noted, regulation has to be carried out in order to fulfill the public interest (1993: 1-2). Only if the regulation will serve such a higher purpose, the intervention is considered as legitimate. Regulatory quality can thus be linked to sufficient justification of regulation. A typology is advanced by John G. Francis, distinguishing four general justifications: the reduction of risks (1), regulation based on moral grounds (2), setting reasonable limits (3) and the provision of stability or an equilibrium (4) (Francis, 1993: 10-21). However, justifying regulatory intervention does not serve as a sufficient definition of regulatory quality. It rather represents a precondition of good regulation and is directly linked to the legitimacy of regulation or regulatory activity. Shifting from regulation understood as policy, to regulation as a mode of governance, regulatory quality can be defined in a more functional way. Given that regulatory intervention in a specific case is legitimized (and therefore viewed as a rightful intervention), the quality of regulation will depend on the realisation of the underlying regulatory goal (the initial reason for regulatory activity). From the perspective of regulatory governance, a "regulatory regime" (Hood et al., 2001: 9) does not only serve the public interest, but has a problem-solving and coordinating function.[46] While the European better regulation discourse frames the issue of good regulation as a question of regulatory efficiency, the more decisive and preceding question is, if a given regulation is able to reach the underlying goal(s). Put differently, regulatory quality depends first and foremost on the achievement of effectiveness. A useful definition of effectiveness developed in the context of regime theory, is offered by Marc Levy, Oran Young and Michael Zürn:

> "Broadly speaking, effectiveness has to do with the contributions institutions make to solving the problems that motivate actors to create them. […] A more applied or policy-oriented definition, which appeals to many economists as well as practitioners, focuses on well-defined goals and asks what policy adjustments will prove effective in attaining these goals" (Levy et al., 1994: 28-29).

[46] This function has been highlighted by *rational choice* approaches linking the emergence of regulatory institutions to social and economic necessities (Knight, 1992).

Linking the definition to the prior thoughts on rational institutionalism, the quality of regulation and respective institutions will depend on a set of clear goals and their achievement. Reconciling the relationship between regulatory effectiveness and the concept of efficiency, the latter should be understood as *subordinate*. Regulation needs to fulfil the requirement of effectiveness in order to be considered as legitimate in the first place.[47] The criterion of effectiveness does provide a basic *yardstick* for the assessment of regulatory quality focusing on the achievement of regulatory goals. However, besides this principal criterion, additional and closely connected criteria of regulatory quality can be identified. While effectiveness represents the final goal of regulation, some comprehensive criteria related to the regulatory process can be thought of as supporting the achievement of effectiveness.[48]

4.2.1 General principles of good regulation

Based on public and scientific acceptance and their significance for the European regulatory debate, the criteria developed by the European Commission in its white paper (2001), principles developed by the OECD (1995) as well as those advanced by the *Better Regulation Task Force* (2003) can be singled out.[49] As the table shows, the criteria developed by the Commission and the Better regulation task force are largely congruent. Therefore, a detailed discussion of the principles developed by the better regulation task force can be limited to the criteria *consistency*, *targeting* and *proportionality*. Before the chapter turns to the discussion of these principles, it must be made clear, that the principles were initially developed in the context of regulatory policy and policy design. However, as the present study understands regulation as a twofold concept, the principles can mainly be understood as principles of *policy-formulation* but some of them can help to improve *institutional design* of the regulatory regime as well.

[47] If regulation satisfies the criterion of effectiveness, efficiency needs to be considered to fully assess the regulatory quality. While the efficiency of European pharmaceutical regulation is beyond the scope of this study, it is argued that the introduction of a European regime necessarily translates into more efficient regulation (Majone, 1994a, 1996b; Pelkmans, 2007).

[48] Moreover the adherence of regulatory processes to certain commonly accepted criteria can increase the social legitimacy and trust in regulatory regimes (Grimes, 2006).

[49] The *Better Regulation Task Force* has been included, since it represents a key actor both in the British and European discourse on regulatory quality.

Table 5: Criteria of good governance and regulation

EU Commission White paper on governance (2001)	Better regulation task force (2003)	OECD (1995)
1. openness 2. participation 3. accountability 4. effectiveness 5. coherence	1. proportionality 2. accountability 3. consistency 4. transparency 5. targeting	1. Is the problem correctly defined? 2. Is government action justified? 3. Is regulation the best form of government action? 4. Is there a legal basis for regulation? 5. What is the appropriate level (or levels) of government for this action? 6. Do the benefits of regulation justify the costs? 7. Is the distribution of effects across society transparent? 8. Is the regulation clear, consistent, comprehensible, and accessible to users? 9. Have all interested parties had the opportunity to present their views? 10. How will compliance be achieved?

Source: adapted from EU Commission (2001), OECD (1995), UK Better regulation task force (2003).

4.2.1.1 The white paper on governance

Starting off with the criteria entailed in the white paper on European governance, five general principles of European governance are offered: *openness*, *participation*, *accountability*, *effectiveness* and *coherence*. To clarify the contribution of these principles to the effectiveness of regulation, a closer look at the remaining four principles as defined in the white paper is necessary. The principles are defined as follows:

"- **Openness**. The Institutions should work in a more open manner. Together with the Member States, they should actively communicate about what the EU does and the decisions it takes. They should use language that is accessible and understandable for the general public. This is of particular importance in order to improve the confidence in complex institutions.

- **Participation**. The quality, relevance and effectiveness of EU policies depend on ensuring wide participation throughout the policy chain – from conception to implementation. Improved participation is likely to create more confidence in the end result and in the institutions which deliver policies. Participation crucially depends on central governments following an inclusive approach when developing and implementing EU policies.

- **Accountability.** Roles in the legislative and executive processes need to be clearer. Each of the EU Institutions must explain and take responsibility for what it does in Europe. But there is also a need for greater clarity and responsibility from Member States and all those involved in developing and implementing EU policy at whatever level.

- **Coherence**. Policies and action must be coherent and easily understood. […] Coherence requires political leadership and a strong responsibility on the part of the Institutions to ensure a consistent approach within a complex system. [original emphasis]" (European Commission, 2001:10).

While the paper explicitly aims at the formulation of governance principles, the underlying definition of regulation as a mode of governance renders them applicable to regulation as well. Based on the previous discussion, effectiveness should not be treated as on the same *logical level* as the other four principles. In fact, the four principles support the realisation of effective regulation. The first principle *openness* represents a reference to *transparency*.[50] To be effective, regulation has to be understood. Besides making the relevant regulation available to those concerned, the specific policy needs to be written in a comprehensive manner and entail further information on the reasons for regulation. Turning to its meaning for the regulatory regime, openness has to be ensured by clear roles and responsibilities and the access to information used within the regulatory governance structure.[51] While the second principle, *participation*, mainly aims at the input dimension of regulatory policy, it can be applied to the implementation phase as well. Effective regulation depends on the ability of a regulatory system to mediate between different interests and *tie in* stakeholders. While this will depend on the balanced inclusion of respective preferences during the process of policy-making, participation remains relevant as well during the implementation stage to increase compliance and trust in regulatory capacities (Braithwaite & Makkai, 1994) Moreover, its effectiveness will depend on how regulatees perceive regulatory conduct and the governance structures (Nielsen & Parker, 2005). The third principle, *accountability*, is closely connected to the principle of *openness*. The basis of accountability is the clear identification of actors taking decisions. It thus raises the level of organisational transparency. Accountability is closely connected to the idea of *legitimacy* (Papadopoulos, 2007; Riekmann, 2007), as those actors affected by regulation want to know who is responsible for regulatory decisions.[52] The principle can be applied to the policy-making process. However, the resulting policies should include clear definitions of responsibilities as well. Regarding the design of governance structures, defining roles and responsibilities has some important implications for the implementation of regulation. As it was outlined regarding the inclusion of relevant stakeholders, it should be made clear who is responsible for which task in the regulatory process.

[50] Accordingly, the study will use the terms of *openness* and *transparency* synonymously.

[51] The establishment of transparency has to be understood as relative rather than total (Lodge, 2004). There are good reasons to limit transparency regarding certain information within the regulatory process.

[52] The connection between accountability and legitimacy is especially striking in multilevel governance structures as mechanisms of input legitimacy are insufficient to legitimate increasingly complex and *seemingly* detached systems (Papadopoulos, 2010).

Finally, the principle of *coherence* calls for the alignment of different but intertwining regulatory policies and all relevant actors in the regulatory system. Additionally, the principle can be applied to the specific regulatory task: regulation is coherent if it manages to integrate all aspects of the underlying problem in need of regulation and thus addresses the problem adequately (internal coherence). Coherence can be defined in an external sense as well. Regulation is neither developed nor carried out in a *political vacuum*. New regulation can impact on different areas and has to take into account previously drafted regulation. Fitting new regulation into these complex existing structures will impact on its effectiveness as well.

4.2.1.2 Better regulation task force

Beyond the four relevant principles developed in the white paper the *Better Regulation Task Force* identifies three additional principles:

> "*Proportionality:* Regulators should only intervene when necessary. Remedies should be appropriate to the risk posed, and costs identified and minimised. […] *Consistency*: Government rules and standards must be joined up and implemented fairly. […] *Targeting*: Regulation should be focused on the problem, and minimise side effects.[original emphasis]" (Better Regulation Task Force, 2003: 4-6).

The principle of *proportionality* both addresses the need for the well-founded justification of regulatory intervention and the appropriateness of actions taken. In addition, it links regulatory intervention to the concept of efficiency: regulation has to be limited to the minimal intervention in order to reach a specific regulatory goal. The principle of *consistency*, calls for the consideration of other rules in applying regulation, basically sharing the idea expressed by the European Commission within the principle of *coherence*. Therefore, it does not have to be considered separately. Finally, *targeting*, while sharing some features of proportionality, represents a unique criterion of regulatory quality. It contributes to effectiveness by asking for the focused intervention regarding a specific regulatory problem. Regulation thus needs to be designed in a way that avoids *collateral damage* and unintended effects on other areas not within the regulatory scope.

4.2.1.3 OECD criteria of good governance

In contrast to the previously discussed contributions, the criteria developed by the OECD represent a *checklist* for regulatory activity and regulatory policy making rather than normative criteria. The review of the ten questions proposed by the OECD, reveal at least

partial coherence with the previously discussed criteria. However, the first four questions addressing the formulation of a regulatory goal (1), the justification of government intervention (2), the use of regulation (3) and finally the legal base of regulatory intervention (4) do not represent criteria of good regulation itself but *preconditions* of regulatory intervention. Accordingly, they should be included in a discussion of regulatory quality, and assessed upfront.[53] The fifth question addresses an issue of regulatory system design, extremely important in the European regulatory context. It touches upon the principle of *subsidiarity*, which will be discussed in further detail below. The sixth question addresses the issue of regulatory costs, which is represented within the principle of *proportionality*. The seventh question deals with the impact of regulation on the different stakeholders. While the equal distribution of regulatory costs and benefits is not connected to regulatory effectiveness itself, it represents a unique value of good regulation and should therefore be included in the assessment under the concept of *fair distribution of regulatory burden*. The following two questions represent aspects covered within the identified criteria. The last question addressing the issue of compliance reflects the principal concept underlying both the criterion of *proportionality* and *coherence*.

Following from the review of regulatory principles, seven specific criteria of good regulation can be deducted*: openness, participation, accountability, coherence, proportionality, targeting* and *fair distribution of regulatory burden*. These criteria serve as additional benchmarks in assessing regulatory quality and will be integrated into the still to be developed assessment framework. Linked to the primary criterion of effectiveness, the seven principles can be understood as enforcing and supporting its realisation. However, as the study focuses on the regulatory quality in the European context, a specific criterion of regulatory quality, *subsidiarity* needs to be integrated.[54]

4.2.1.4 The principle of subsidiarity and regulatory quality

As the focus of this study in on European regulation, the analysis of regulatory quality has to account for its specific characteristics. The European regulatory system is essentially a federal one (Kelemen, 2004, 2005). Therefore, an additional criterion for the quality of regulation in the European context has to be seen in the justification to regulate on the European level. The

[53] The four questions complement the pre-assessment beyond the criteria of justification introduced by Francis (1993).

[54] The need to consider the principle of *subsidiarity* is highlighted in the white paper on European governance (CEC, 2001: 10).

quality of regulation in the European context will thus depend on the satisfaction of the *subsidiarity* principle. The principle is of high importance considering the issuance of European regulation as it represents the basis for the coordination of European regulatory activity. The principle was introduced in Article 3b of the Maastricht treaty in the year 1992.[55] The article states:

> "The Community shall act within the limits of the powers conferred upon it by this Treaty and of the objectives assigned to it therein. In areas which do not fall within its exclusive competence, the Community shall take action, in accordance with the principle of subsidiarity, only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States and can therefore, by reason of scale or effects of the proposed action, be better achieved by the Community. Any action by the Community shall not go beyond what is necessary to achieve the objectives of this Treaty."

European regulatory activity can be justified, if the scope of the problem necessitates supranational activity. The principle can be interpreted as twofold. First, it serves as precondition broadening the principal requirement of justification for regulatory action. Beyond justifying the respective regulatory intervention, the necessity of European regulatory intervention has to be established. Second, subsidiarity represents a design principle for regulatory systems. Action has to be taken on the appropriate level, which might lead to the division of regulatory activity e.g. the setting of standards and their implementation. In addition, the said activity should be as limited as possible in achieving the desired regulatory outcome.

4.2.2 Intermediate results: effectiveness and principles of good regulation

Summing up the previous discussion, eight principles of good regulation can be defined in the European context: *openness, participation, accountability, coherence, proportionality, targeting, fair distribution of regulatory burden* and *subsidiarity.* These principles should be traceable within the respective regulatory policies and, depending on their applicability, within governance structures. In addition to these principles, the discussion revealed several *preconditions* for regulatory quality. Initially, a clear goal advancing the public interest must be defined. Subsequently, a public (and legal) mandate to regulate on the European level has to be established. If these preconditions are met, the actual assessment of regulatory quality based on the eight principles can be conducted. While the principles have their own normative

[55] Now article 5 (TEC).

foundation and advance the *good conduct* of regulation they first and foremost serve the achievement of effectiveness.

4.3 Achieving effective regulation

Based on the underlying twofold definition of regulation as a type of policy and form of governance the implementation of the outlined principles and the realisation of regulatory effectiveness is achieved on at least three levels. Defining regulation as policy, the outlined principles can be applied both to the policy making process (1) and to the resulting policy (2). Yet, an analysis of the realisation of the identified principles in the policy-making process does not seem to be of key importance for the assessment of regulatory quality. In fact, analyzing the policy-making process would allow for an assessment of law-making quality rather than the quality of the law. Following from this, such an assessment will not be conducted in this study. If the policy-making process is not considered, regulatory quality has to be achieved via policies. Limiting the discussion to regulatory policy however would be too narrow: while the inclusion of principles within the policies underlying regulation ensures good regulation de jure, this does not ensure the realisation of these principles de facto.[56] Only if the regulatory practice during the implementation stage reflects the underlying principles, real effectiveness can be achieved (Croley, 1998: 6). This shifts the focus to the realisation of regulatory principles through regulatory governance (3).

From the governance perspective, good regulation has to be achieved by institutional (and process) design supporting the implementation of the policy itself.[57] The outlined principles can thus be understood as design principles, which should be reflected in the resulting institutional set up governing a specific regulatory field. However, not all of the principles seem to be applicable to regulatory system design. Therefore, the discussion of principles in the context of governance can be limited to openness, participation, accountability and subsidiarity.[58] Beyond assessing the existence of principles within institutions, the analysis of regulatory quality must focus on the analysis of regulatory institutions and the performance of these systems contributing to the effectiveness of regulatory institutions themselves. In fact,

[56] The issue of de jure and de facto realisation has been discussed extensively regarding the measurement of democracy (Lauth, 2004, 2000).

[57] This conceptualization accounts for the significance of institutional arrangements on regulatory outcomes, presupposing that (conscious) institutional design is possible and that the design of institutions will have a significant impact on the behaviour of actors and outcomes.

[58] The other principles have been excluded since they do not seem to be applicable to governance structures.

the implementation stage is viewed as more critical in achieving regulatory effectiveness, highlighting the importance of effective institutions for regulatory effectiveness.

4.3.1 Regulatory effectiveness and institutional effectiveness

Adopting a functional perspective, the effectiveness of an institution depends on the realisation of the underlying regulatory goal. If the developed principles of good regulation are perceived as important in achieving the regulatory goal, they have to be traceable in the resulting institution. While this provides a first idea of an effective institution, there are additional factors, which ought to be considered in the design of effective regulatory institutions. Institutions do not exist in a vacuum but in a given political and social context (Radaelli, 2004: 4). Only if regulatory institutions consider the requirements flowing from this context, they will be able to deliver fitting regulatory answers. In contrast, the ignorance of these requirements might lead to common and often criticised problems of regulation.

4.3.1.1 Evaluating the common critique of regulation

Using a classification developed by John G. Francis (1993), four different strands of criticism can be distinguished: ineffectively delivered or inability of state regulation (1), the potential of regulatory capture (2), the negative impact of regulation on economic performance (3) and overregulation (4).[59]

The first strand of criticism addresses the structural inability of (state) regulation to realize its goals. Regulation is drafted as a response to a specific problem at a specific point in time. As time goes by, the regulatory response to a problem might simply go out of date with changes in economic and social conditions. Obviously, this critique is not confined to regulation but to all legal-based forms of governance. What is criticized is the heavy reliance on inflexible regulatory tools. This perception is traceable within the European better regulation debate, as it highlights the need for smart regulation and alternatives to legal regulation (Héritier & Eckert, 2008; Radaelli, 2004).

The second strand addresses the much discussed problem of *regulatory capture* and has first been described by George Stigler (1971) and Richard A. Posner (1974), even though Sam

[59] While the categories introduced by Francis are used to structure the next section, they are supplemented by addressing respective solutions for the criticism.

Peltzman (1976) popularized the concept.[60] As stated previously the final goal of regulation is the protection of public interest. However, as Stigler proposes such an altruistic view of regulation is not capturing reality adequately. In fact, the creation of regulation is the *product* of private rather than public interests: "as a rule, regulation is acquired by the industry and is designed and operated primarily for its benefit." (Stigler, 1971: 4). Such benefit could be seen for example in the regulation of market entry, effectively protecting those in the market from those who want in. Capture becomes possible because the political mechanism enables companies to exert pressure on officials by offering votes and financial support. Politicians in turn either exert influence on the respective regulatory agency to *produce* regulatee-friendly regulation or do so themselves. Even though Stigler developed the concept of capture focusing on economic regulation and more specifically the regulation of monopolies, the idea of capture is applicable to all forms of regulation and often works in a more direct way than Stigler proposes. It is the close relationship between regulatory bureaucracies and regulated companies that breeds capture: as regulators lack their own basis of information for judgment they gradually become the allies of the industry (Francis, 1993: 27). This is even more the case, where regulatory activity depends heavily on industry support, for example on the provision of certain information or industry funding (Owen & Braeutigam, 1978). Often, regulators will face a situation of asymmetric information, making them dependent on information provided by regulatees (Baron & Besanko, 1984a). The idea of private interests capturing the regulators' behavior should not be viewed as limited to companies. While it is true that businesses have a competitive advantage in influencing regulators through information dependencies, other interest groups e.g. environmental or health activists can capture them as well (Banks & Weingast, 1992; Calvert et al., 1989; Greer, 2008; Sabatier, 1975). It will depend on the general political climate, towards which private interest a regulator is more open.[61] From a theoretical point of view, one could argue that *public* regulatory capture can be perceived as less problematic, since regulators are captured by the constituency (Sabatier, 1975: 325-326). While regulation in such a situation could be labeled as highly responsive, it should not be confused with effective regulation. Using the example of risk regulation, citizens might prefer excessive levels of protection from a certain threat inevitably leading to overregulation. Public capture should thus be viewed with the same

[60] Bernstein (1961, 1972) and Sabatier (1975) both contributed to the political science perspective on capture theory. For a more detailed economic discussion of the capture argument see Ernesto Dal Bo (2006).

[61] At the same time, the research on the impact of business interest on regulation seems to justify the perception of a stronger position of businesses in the regulatory arena as advanced by Stigler especially in the European case (Braithwaite & Drahos, 2000; Broscheid & Coen, 2003; Coen, 1998, 2002; Eising, 2007).

skepticism as industrial capture. Furthermore, public capture might take an indirect route as politicians try to influence the work of regulators. Given the fact, that in most European member states (risk) regulatory tasks are pre-dominantly carried out by special regulatory agencies (Elgie, 2006; Thatcher, 2002a), governments or concerned ministries will try to influence these agencies in ways conducive to their interests and priorities, for example the maximization of vote shares (Calvert et al., 1989: 589).[62] Finally, regulation can be distorted by capture from *within*. It is unrealistic to assume that regulators do not have interests. As companies try to preserve their competitive advantage and citizens publicly demand stricter regulation, bureaucracies seek to keep and expand their regulatory mandate. As Gordon Tullock (1976) stressed, regulators are *utility maximizers*. Regulation therefore will be influenced by bureaucratic preferences as well (James, 2000; McKenzie & Macaulay, 1980).

A third strand of critique addresses the connection between (extensive) regulation and economic decline. In comparison to the issue of regulatory capture this critique stems from empirical observation rather than theoretical claims. Again, this critique is not directed at regulation in general but addresses the possible inefficiency that certain forms of regulation promote. While such critique has led to the emergences of massive deregulation programs in most OECD and European countries (Blanchard & Giavazzi, 2003; Crafts, 2006), Dieter Helm, suggests that "the link between regulation and economic performance is tenuous and complex and there is no *a priori* reason to expect a tight negative causal relationship between them" (Helm, 2006: 177). A second problem not addressed by Francis could be seen in the negative effect on innovation (Bassanini & Ernst, 2002; Fai & Morgan, 2007). As in the case of economic performance, a general negative correlation between regulation and innovation is hard to prove. Nevertheless, possible negative effects of regulation have to be considered in respective regulatory decisions in order to avoid such effects.

The fourth strand of critique can be characterized as a combination of the capture critique and those commentators questioning the general efficiency of government or public regulation in contrast to private self-regulation. First, regulators might be simply overburdened with regulatory tasks, therefore lacking the ability to regulate in an efficient way. A second problem could be seen in *over-regulation*. Either regulatory objectives are expanded beyond the initial goal of public interest and the regulatory mandate (Wiener, 2006), or the level of regulation is raised based on the perceptions and preferences of the regulator, beyond the

[62] On the other hand, the delegation argument developed in the previous chapter suggests, that in risk regulation this influence will only be traceable in the policy-making process, while regulatory governance understood as the daily regulatory operations will be left to the regulators.

social optimum (G. Banks, 2006; Littlechild, 2008). One central problem in claiming over-regulation and the gathering of supportive evidence is the fact that it is extremely hard to trace.[63] While a low level of regulation might result in insufficient problem solving, overregulation can be expected to ensure that the problem is solved, however at costs exciding the benefit of regulation. While the reason for too much regulation can mainly be seen in regulator's interests and the public demand, it might result as well from the over- or underestimation of a specific thread to the public interest. The wrong valuation of a regulatory problem undermines reliable cost-benefit analysis, enabling the right level of regulatory intervention (Francis, 1993: 31).

4.3.1.2 Ensuring effectiveness by addressing common problems of regulation

As the synopsis of regulatory critique illustrated, several problems can affect regulation. Consecutively, the effectiveness of regulatory institutions will be negatively influenced if the identified challenges occur. Reassessing the identified strands of criticism, two more fundamental underlying issues can be identified. The first issue underlying the regulatory critique is a misfit of regulatory problems and regulatory answers. While this problem is not connected to the capture argument, the three remaining strands of regulatory critique are based on the perception that regulation fails to address the respective problem in an adequate way. This might either be the result of wrong problem perception or the wrong choice of regulatory answers. Accordingly, avoiding such problems depends on adequate analysis and even more important the choice of adequate *regulatory strategies*. The second underlying issue can be seen in the conflict between regulatory goals and affected preferences of stakeholders. As stakeholders try to alter the regulatory structures to maximize their utilities, regulatory effectiveness will be influenced. While this issue is clearly traceable in the case of regulatory capture, preferences play a (subordinate) role regarding the other issues as well. Rather than solving the issue by choosing appropriate regulatory strategies, the solution has to be based on *institutional design*. Accordingly, the next two sections will address how the two identified sets of problems can be solved focusing on the contribution of regulatory institutions.

[63] The risk of over-regulation will increase over time and in case of public regulatory crisis (Aizemann, 2009).

4.3.1.3 Regulatory needs and regulatory strategies

With regulation criticized as an inflexible and ineffective form of intervention, the deliberate choice of regulatory strategies and mechanisms represents the appropriate lever to ensure institutional and therefore regulatory effectiveness. This can imply the shift from the state as the main conductor of regulation or a change of regulatory mechanisms. These two options are not isolated from one another. In most cases the change of mechanisms will have an impact on the role of the state as well: legally based regulation, for example, was used to replace state ownership as the most drastic (and inflexible) form of state regulation (Baldwin & Cave, 1999; Egan, 1998). Opposed to this model of regulation, one could think of self-regulation organized by the regulatees: regulation is left to the market, while the state retains a very limited role (Gunningham & Rees, 1997; Haufler, 2001). Between these two poles, several arrangements based on a varying mixture of private and state influence over regulation are possible (Sinclair, 1997). The second lever of improvement is closely connected to the right choice of actors within a regulatory regime. In achieving regulatory goals regulatory regimes might resort to different regulatory strategies. Based on the typology introduced by Baldwin and Cave (1999), two sets of strategies can be distinguished. The first and more intrusive set of strategies can be clustered under the heading of command and control regulation.[64] This strategy is essentially based on legal regulation and is characterized by "the exercise of influence by imposing standards backed by criminal sanctions" (Baldwin & Cave, 1999: 35). The state retains a strong position in this regulatory set up by granting rulemaking power to a specialized agency and delegating enforcement to the judicial branch. Due to the heavy reliance on law, this approach is characterized by less flexibility and might take different forms. For example regulation might be realized through market-harnessing controls: competitive law, the use of franchising (granting licenses and product approval), specific contract agreements with companies instead of state provision of services and the issuance of tradable permits (1999: 44-47). A less intrusive option can be seen in the usage of incentives instead of punishment. Furthermore, the disclosure of information – naming and shaming – can be used as a regulatory strategy to influence market participant's actions. The second set of strategies is the employment of rights and liabilities. Rather than being involved directly, the state resorts to a basic market mechanism: the allocation of rights. The enforcement of specific market rules is effectively delegated to the courts: In addition, public compensation

[64] For a detailed discussion of *command and control* regulation, see Braithwaite (2002) and Braithwaite & Drahos (2000).

and social insurance schemes can be used to deal with unwanted externalities (1999: 51-54). In contrast to the conceptualization of Cave and Baldwin (1999), the outlined strategies should be thought of as sub strategies of command and control regulation, rather than an alternative regulatory approach since law remains the basis of the different strategies. While it is theoretically possible that these strategies could be set up and run by private actors, the state will remain involved (Jordana & Levi-Faur, 2004). Even if it is not directly involved as in the case of the allocation of rights, the court will remain the enforcer of last resort. Opposed to command and control strategies, self-regulation can be identified as a distinct second regulatory strategy. The respective regulatory regime is either operated and enforced by the regulatees, or the state decides to retain a structuring and supervisory role (Baldwin & Cave, 1999: 39). Instead of being based on law, regulatory regimes will be built upon soft law and voluntary commitment. From a theoretical perspective, self-regulation can represent an optimal regulatory strategy, resulting in a higher flexibility of the regulatory regime able to adapt quickly to new requirements (Black, 2002a). On the other hand, self-regulation depends largely on the trust that the public and the political actors have in its abilities (Gunningham & Rees, 1997; Ogus, 1995). Regulators will have to choose based on the underlying issue for regulation, which role the state should resume in the resulting regulatory regime. Effective regulatory institutions depend on the appropriate choice of strategies and the appropriate distribution of tasks between private and public actors in order to realize regulatory goals.

Given that regulation in any event will be based on some sort of rules, another important decision is the selection of an appropriate level of *precision* (Diver, 1983). Regulators might decide to create highly precise rules to reduce discretion and uncertainty in rule application but at the same time this implies decreased flexibility. In contrast, they could decide to issue a very general rule granting some leeway but at the same time leaving regulatees with little guidance how to comply with regulation (Ogus, 2002: 640).[65] A second issue is the right method to assess the regulatory problem. Only if regulators are able to assess the regulatory problem appropriately, they will be able to choose the fitting regulatory tools and take (informed) regulatory decisions. This is especially important in the area of risk regulation as the (right) assessment of the risk represents the foundation for effective risk regulation (Noll, 1996: 167; Renn, 2008). Before this issue is discussed in further detail, the next section discusses the conflict between regulatory effectiveness and private interests.

[65] Furthermore, *general* regulatory rules run the risk of being too generic and not targeting the regulatory problem effectively.

4.3.2 Conflict of interests: regulatory goals and stakeholder preferences

After highlighting the connection between regulatory strategies and (institutional) effectiveness, the discussion now turns to the second source of institutional ineffectiveness: conflicts of interests. As regulatory effectiveness is based on the achievement of regulatory goals, conflicting interests can affect its realisation. Internal and external stakeholders will try to alter regulation (or the respective agency) in ways conducive to their own preferences. In order to protect regulation and regulatory institutions from capture, political, institutional self and private interests have to be controlled. A key concept for safeguarding institutions from political interests and self-capture can be found in P-A theory (Kassim & Menon, 2003; Pollack, 2002; Ross, 1973). After delegation, agents may fall prey to certain forms of unintended behavior. Martin Lodge identifies three forms of drift, which can affect the agent and the regulatory regime as a whole:

> "These involve *agency drift* by the regulated actor(s) through the evasion of control in the pursuit of self-interested action […] *bureaucratic drift* by regulatory and bureaucratic authorities enforcing regulation through selective or biased attention, budget- and turf-maximization strategies, and finally *coalitional drift* where the governing coalition seeks to move beyond the policy preferences established by the enacting coalition.[original emphasis]" (2004: 126)

Regulatory effectiveness can be negatively affected by delegation in several ways. First, the regulated industry might refuse to comply with regulation. A second possibility beyond the problem Lodge identifies can be seen in the attempt to alter regulation and regulators' behavior in ways more conducive to a private agenda. Second, the regulator might pursue his (own) agenda. Third, the (political) principal might want to relinquish long-term goals of regulation in order to pursue short-term interests to claim credit (e.g. react to a regulatory scandal by enacting stricter regulation). To prevent these problems, the agent has to be subjected to certain measures of *control*. The principal can clearly define the agent's scope, task and procedures to adhere to (ex ante) and use oversight mechanisms (ex post) monitoring the behavior of the agent (Geradin & Petit, 2004: 50-55). Besides including control mechanisms within the rules establishing the agent, external review will ensure his compliance, for example by employing judicial review (Ogus, 2002: 644). While principal-agent theory stresses the importance of avoiding self-inflicted capture – describing a regulator pursuing his (own) agenda – the presented measures can be thought of as limiting undue influence of the principal and private interests over the regulator. If the agent's scope is clearly defined, it will be harder for the principal to push for regulation more conducive to

short-term political interest. Accordingly, delegation can serve as a form of credible commitment. Furthermore, the risk of subjective assessment of regulatory problems e.g. based on political considerations is reduced. As clear rules guide the assessment of regulation, the risk of a subjective bias in regulators' assessment is minimized (Gehring et al., 2005). While the creation of an independent and controlled regulator will help to remedy the negative influence of political and self-inflicted capture, the risk of private capture is reduced as well. If regulators are subjected to clear rules and procedures governing regulatory decision-making, their remains little leeway to rule in favor of certain private interests (Elgie, 2006). Without undue simplification, the safeguarding of regulatory effectiveness necessitates the creation of a regulator, respecting the principle of transparency and accountability. Anthony Ogus (2002: 643-644) provides a detailed concept of accountability in regulation. First, regulators (or agents) should respect their respective regulatory budgets. Using budgetary constraints could thus serve as an incentive to ensure financial accountability. Second, regulators have to ensure procedural accountability by including principles of due process and publicly justifying regulatory decisions. In other words, the requirement of procedural accountability calls for the realization of participation and transparency within the regulatory process. Finally, substantive accountability forces the regulator to justify their regulatory interventions based on its costs and benefits. Following from this, the transparency of the regulatory system serves as a precondition for accountable regulation. It is tempting to believe that by maximizing accountability and transparency, regulatory effectiveness is maximized as well. However, the relationship between regulatory effectiveness, accountability and transparency should not be perceived as linear. As Martin Lodge notes, a more reflected understanding is necessary accounting for the fact that: "accountability and transparency are not 'good things' in their own right of which we should simply have 'more', but that particular choices […] invite particular tradeoffs [original emphasis]" (2004: 128). While a high level of accountability and transparency are obviously necessary to safeguard the loyalty of an independent regulator to regulatory goals, there is a downside to it. With greater spans of control, the agent's effectiveness might decrease while costs on the principal's side increase (Huber & Shipan, 2000; Pollack, 1998). Institutional design of a regulatory system has to strike a balance between the need for control and avoidance of drift and the need for flexibility in order to regulate effectively. While accountability and transparency are detrimental to ensure such control they might negatively impact on the latter. First, a (too) high level of transparency might lead to regulatory behavior overemphasizing compliance and regulation by the book. If regulators are subjected to rigorous control and transparency, this

might lead to a heightened awareness of public perception on the regulators' side. Rather than focusing on his regulatory task, the regulator might thus become preoccupied with the external perception.[66] This will prevent the regulatory system from developing more fitting regulatory strategies and can cause institutional gridlock, leading to rigid and thus suboptimal regulatory outcomes (Lodge, 2004: 140).

Second, opening up the regulatory black box can result in the publicization of regulatory decision-making (M. Flinders & Buller, 2006). Regulation in most cases will involve the assessment of experts (Brint, 1990; Pollak, 1996). Due to the complex nature of most regulatory problems and the resulting uncertainty, experts will have to engage in scientific reasoning about the best advice to inform regulatory decision-making. Making these discussions transparent can have some unintended consequences. The unfiltered presentation of arguments and different view points might be misinterpreted by the lay public, leading to further erosion of trust in scientific assessment, increase public uncertainty, and the re-politicization of a regulatory field. Again, this could lead to regulatory answers influenced by public perception rather than effective problem-solving as well as a prolonged decision-making process (Lodge, 2004). While the issue of public influence is even more pressing regarding the participation of lay people in regulatory decision-making in order to advance its accountability (Joss, 1999), it has to be discussed in the case of transparency as well. Beyond these rather theoretically founded reasons, there might be a third legitimate reason to limit transparency to a certain level: to protect legitimate private interests of citizens and companies. A recent report by the *International Risk Governance Council* (IRGC) reviewing common failures of risk regulatory regimes argues:

> "Likewise, the protection of business secrets in competitive markets, where innovations can be the subject of piracy, is also seen as necessary for a well-functioning, innovative economy. […] a desire to avoid public panic may justify a prioritisation of confidentiality over transparency"(2009: 48).

Referring to the discussion on the critique of regulation, the limitation of transparency can be viewed as necessary in order to reduce the distorting effects of regulation on economic growth. However, while a certain level of confidentiality is necessary to safeguard regulatory effectiveness, it calls for deliberate consideration.

[66] This would factually undermine the intent of delegation and the intent to depoliticize certain regulatory fields (Buller & Flinders, 2005; Burnham, 2006).

As in the case of too much transparency a secretive mode of regulation:

> "may reduce trust in risk management and in decision-makers by raising suspicion that the shield of confidentiality is being used as a power lever (e.g. by government and/or industry) to advance or protect particular interests without adequate justification" (IRGC, 2009: 48).

Companies and regulators might overemphasize the need for confidentiality in order to protect their position rather than enabling effective regulation.[67] Summing up the previous discussion, the design of regulatory institutions obviously faces a crucial trade-off. To ensure effectiveness an institution (agent) shielded from external influence and kept from pursuance of his own goals while at the same time granting the agent enough discretion and leeway to pursue the regulatory goals must be created.

4.3.2.1 Regulatory institutions and equilibrium theory

While the avoidance of drift and capture by a carefully designed zone of discretion and the safeguarding of accountability and transparency form major building blocks of effective regulatory activity, the need to keep regulatees and other affected stakeholders out of regulation seems to be overemphasized and impractical. Such conceptualization ignores the broader meaning of a regulatory institution in a functional sense: social coordination (Knight, 1992). Institutions have a structuring function, as they can be "thought of as part of what embeds people in social situations" (Shepsle, 1989: 134). This assumption is valid in the case of regulation as well. A regulatory institution brings together stakeholders affected by regulation. Since these groups have their own goals and preferences, they can be expected to have altering views about the institution itself. This will affect their perspective on the respective institution and the respective institutional outcomes. In some (rare and ideal) instances, preferences and goals of affected parties might eventually coincide, rendering the emergence of conflict as improbable. However, such constellation seems to be detached from reality. What will emerge most likely is a conflict of interest regarding the institution and its workings. Given the fact that institutions can be altered, actors will try to do so in order to create an institution meeting individual preferences. This clash of interests will obviously impact on effectiveness since regulatory institutions need credibility and mutual trust to carry out their task effectively (Nielsen & Parker, 2005; Shimshack & Ward, 2005). While regulatees often depend on the regulator, as for example in obtaining market approval, a

[67] This has been a well-researched and discussed topic in the field of pharmaceutical regulation. See for example (Abraham & Sheppard, 1997; Kesselheim & Mello, 2007; Lexchin, 1999).

higher level of trust in the abilities of the regulator will lead to increased performance of the regulatory system.[68] What has to be achieved in order to reach a certain level of effectiveness is a state of balance, between the regulator and stakeholders. Put differently an (institutional) *equilibrium* has to be created. The concept of equilibrium has been initially developed within economics based on the workings of Léon Walras (1954) and developed further by Kenneth Arrow and Gerard Debreu (1954) focusing on the institution of markets.[69] In context of regulatory governance the idea of an equilibrium can be understood as institutional stability. Without undue simplification, stability primarily relies on the rules that enable change of institutions (Shepsle, 1989). Even if competing interests exist regarding the individually preferred regulatory outcome, institutions will depend on its acceptance by affected stakeholders and how easy the institution can be changed. The higher the barriers and transaction costs for change, the higher the robustness of an institution will be. In line with P-A theory, regulatory capture is minimized by shielded institutions.

While this ensures that affected stakeholders will not be able to alter the regulator in the future, it does not tackle the root cause of capture. An institution needs to be robust vis-à-vis the goals and regulatory interests of the concerned actors in order to fulfil the regulatory goal, but at the same time able to change if such changes would be necessary to realize the regulatory goal more effectively.[70] Accordingly, a (limited) congruence between regulatory goals and private interests has to be achieved, expanding the initial meaning of equilibrium. Regulatees need to perceive the regulatory situation as an equilibrium of interests, fulfilling their preferences at least partially. First, minimal consensus regarding what should be achieved by regulation must be achieved (Gilliland & Manning, 2002). If the parties involved share a common understanding of the regulatory problem despite their respective preferences, an institution can be effective. Second, the institution itself has to have some degree of acceptance, depending mainly on its performance. If the regulatory institution manages to analyze the regulatory problem appropriately and will develop fitting regulatory answers, regulatees can be expected to accept the institution. Furthermore, the acceptance will depend on the building of mutual trust in regulatory relations.

[68] While the argument focuses on the relationship between regulator and regulatee, the reputation of a regulator in the public perception impacts on his effectiveness as well (Guehlstorf & Hallstrom, 2005). In any case it will have an impact on its perceived *social legitimacy* (see chapter 3).

[69] The underlying idea of an equilibrium representing a specific and stable set of the preferences of the actors involved, can be transferred to political science and institutions in general (Pierson, 2000; Shepsle, 1989).

[70] For a critical account on the possibility to design institutions and structure outcomes see Pierson (2000).

4.3.2.2 The building of institutional trust versus regulatory capture

While (institutional) governance structures play a crucial part in achieving regulatory goals, this perspective neglects the importance of relationships and interaction in achieving regulatory effectiveness. As research on regulatory compliance has shown, forms of *informal* control like sharing of information and interaction enhance compliance of regulatees supporting the conceptualization of trust as crucial for regulatory effectiveness (Axelrod, 1984; Gilliland & Manning, 2002). Unsurprisingly, trust is of vital importance regarding the (lay) public acceptance of regulators as well (Poortinga & Pidgeon, 2003). Before the discussion turns to the implications of trust for the relationship between regulators and the public, the relation between regulators and regulatees has to be explored further. While there are some regulatory areas, where no *direct* regulatees exist, industry or businesses will constitute the target audience of regulation in most cases. As previously discussed simple *control and command* strategies and an adversarial regulatory style in pursuing regulatory goals might be ineffective. Most regulatory relationships are characterized by some sort of asymmetric distribution of information in favour of the regulated industry (Baron & Besanko, 1984b) and a more cooperative approach towards industry might ensure the disclosure of information necessary to enable effective regulatory decision-making. While this does not imply that regulators should resign from control as a vital component in achieving regulatory compliance, it highlights the importance of *reputation* and *goodwill* in the relationship between business and regulators (Black, 2002b; Coen, 2005a). While regulators should be expected to be primarily interested in compliance, the regulated industry will be mainly interested in clear communication of expectations, guidance regarding compliance and predictability of regulatory decision-making. The establishment of resilient *regulatory relations* will be based on long-term experience and repetitive interaction between the firm and the regulator (Willman et al., 2003). Good relations between the regulator and the regulated will be necessary to ensure effective regulation, but there is an obvious downside to it. As indicated in the life-cycle model of regulation developed by Marver Bernstein (1955), regulators will progressively subordinate the public interest to the interests of the regulated interest and fall pray to industry capture. The repetitive interaction between regulators and regulatees does not only breed trust but might result in too close relations.[71] While a distinction between legitimate ties and undue closeness has to be drawn, even the former

[71] This development is amplified by the phenomenon of *revolving door* (Quirk, 1981) describing the transition of former regulators to the regulated industry. However, research indicates that the phenomenon of revolving doors does not lead to more industry friendly regulation (Makkai & Braithwaite, 1992).

could be seen as a problem as the growing literature on regulatory relations specifically in the pharmaceutical sector indicates (Abraham et al., 2002; Abraham & Lewis, 2000). Beyond the scientific discussion, the (necessarily) closer relationship between regulators and regulated industry, could lead to a decline in public trust in the regulator's integrity. In a broader sense, the acceptance of the regulatory institution will depend, on how opposing interests are absorbed and incorporated in institutional change. There might not only be a conflict between personal interests and the regulatory goal, but between competing private interests as well. If the regulatory institution will establish a too close link to one of the stakeholders, this will lead to the demise of acceptance of other stakeholders. If regulators would favour public perceptions over industry interests, this can lead to lower levels of compliance and imperfect disclosure of information on behalf of the regulated firm.[72] If regulators constantly favoured the industry, this could lead to severe political repercussions and the decrease of public trust in regulatory competencies. Unfortunately, this problem can never be fully excluded as regulation can never be made fully egalitarian (Lodge, 2004). Regulation as a distinct type of policy necessitates a close(r) relationship between the regulator and the regulated. At the same time this necessity should not be misunderstood as a justification for the exclusion of other stakeholders. Drawing the line between legitimate close ties and favouritism of stakeholders is contingent upon the situation and must be assessed individually. However, such analysis can be based on the assessment of regulatory principles in the regulatory work: the inclusion of the different groups as well as the general level of transparency and accountability characterizing the regulatory regime. The closer the conduct of regulation resembles a *black box*, the higher the chances that regulation favours industrial interests (Abraham & Davis, 2007).

4.3.3 Intermediate result: regulatory institutions and effectiveness

Summing up the discussion to this point, the effectiveness of an regulatory institution will not only depend on its ability to realize the regulatory goal and incorporate principles of good regulation, but its ability to adequately define regulatory problems, the right level of cooperation between private and public actors, the right regulatory strategy and finally the implementation of fitting regulatory answers. In addition, regulatory institutions will have to avoid any form of capture by retaining a certain degree of independence. By establishing clear

[72] This conceptualizes the regulatory arena as a game-type situation, with different private interests as opposed to each other competing for regulatory relations (Owen & Braeutigam, 1978).

rules for the regulatory decision-making process the problem of self-inflicted and private capture is reduced, as the discretion of regulators to pursue other instead of the public interest is limited (Lodge, 2004). The effectiveness of regulation will mainly depend on the pursuance of the public interest, but total isolation of the regulator from external influence has to be avoided. In order to realize regulatory goals, acceptance of the regulator and mutual trust between the regulator and the regulatees is vital as well. While a certain level of congruence between regulatory goals and private interests serves as a precondition for such relations, experience and repetitive interaction between the parties serves as a key lever to establish trust. Good relations between regulators and stakeholders will support the realization of effective regulation, but they have to stay within the limits of cooperation, Furthermore, regulatory systems need to engage in balanced stakeholder management, minimizing the negative effects that the focus on singular interests in regulation might have. While the developed requirements represent generally applicable criteria to assess regulatory quality, the chapter now turns to the specification of the framework, accounting for the specific challenges connected to risk regulation and the European context.

4.3.4 Risk regulation and regulatory effectiveness

The previously developed criteria for the assessment of regulatory effectiveness can be applied to risk regulation as well, but the distinct features of risk regulation have to be accounted for in regulatory analysis. A specific feature of risk regulation is the complex process of defining the underlying regulatory problem. Compared to other forms of regulation, the regulation of risk is fundamentally characterized by uncertainty about the form, nature and severity of risks (Renn, 2008). The regulation of monopolies, for example, could be understood as minimizing the emergence of monopolies and this regulatory task rests upon (relatively) sound evidence and knowledge regarding monopolies and their market-distorting effects (Sherman, 1989). In contrast, risk regulation in most cases lacks a sound basis and therefore qualifies as regulation under uncertainty. While the degree of uncertainty might differ between types of risk, uncertainty can never be fully excluded. This has implications for the choice of regulatory strategies and institutions and the concept of risk regulation has therefore been increasingly substituted by the concept of risk governance (Hutter, 2006; Renn, 2008) and (risk) regulatory regimes (Eberlein & Grande, 2005; Hood et al., 2001; Vogel, 2001). The concept of risk governance accounts for the general tendency of de-centred regulation and a “move to state reliance on new forms of fragmented regulation”

(Hutter, 2006: 215). Instead of focusing exclusively on the regulatory aim, the state increasingly engages in regulation of the stakeholders and in meta-regulation by monitoring performance and increasingly shifting implementation to regulatees (Jordana & Levi-Faur, 2004: 6-7; Morgan, 2003: 490). The tendency towards risk governance should not be viewed as a simple account of the erosion of state centred regulation. It also stresses the increased importance of regulatory structures in delivering fitting regulatory policies. This perspective is closely connected to the notion of regulation as a form of governance. Since risk regulation represents regulation under uncertainty, a heightened meaning has to be attributed to the institutional setting in which regulation takes place (Renn, 2008: 9). As valid information forms a precondition of effective regulation, the assessment of risk becomes a focal point of risk regulation and its effectiveness. While the *production* of information on which regulation is based is relatively uncontested in many regulatory fields, the situation in risk regulation is different. First, certain risks can never be pinpointed, since they can only be estimated but never measured exactly (Gould, 1988). Second, these assessments will be subjective to some degree as they have to be made by experts. Different experts might come to different conclusions as humans in general might err in deciding on the severity of risks (Kletz, 2001). While the *risk to err* affects all forms of delegated decision-making, the potential negative implications connected to risk regulatory failures amplify these concerns leading to distinct models of risk regulation.

4.3.4.1 Models of (risk) regulatory decision-making

Even though the options for the design of regulatory systems are numerous, consensus regarding a basic process of risk regulation seems to exist. The process of *risk analysis* should include *risk assessment*, *risk management* and *risk communication* (CEC, 2000; Fischer, 2009; Renn, 2006).[73] Linking the discussion of these process steps to the more general discussion of regulatory effectiveness, several requirements regarding the evaluation of risk regulation can be derived.

Risk assessment: the role of expertise in regulatory decision-making

Risk regulation necessitates decisions about the nature, severity and impact of a certain risk. The model of *science-based* risk assessment can be thought of as the general approach in the

[73] It should be noted, that there has been a detailed a heated debate on the right risk regulatory model. For an overview see for example Robert Fischer (2009) and Ortwin Renn (2006).

European context: scientific experts assess risks in order to subsequently inform political decision makers, who take appropriate political action to manage the risk (Gehring et al., 2005; Löfstedt & Fairman, 2006). The reason for delegation to experts is comprehensible as "elected political officials,[…] face the same information imperfections as do the citizens exposed to the risk" (Noll, 1996: 168), reflecting the argument of uncertainty avoidance. The *science-based* approach has been exposed to heavy criticism (Abels, 2002; Boswell, 2008; Liberatore & Funtowicz, 2003; Shrader-Frechette, 1995). What has been criticized is the heavy reliance on experts in the process: scientific considerations potentially dominate resulting political decisions, as decision makers have to rely on the evidence that science produced. This would constitute a minor problem, if the scientists providing scientific input could be expected to do so in an objective and unbiased way. The objectivity of science and the need for independence of experts from political and private influence, has been highlighted and used as a legitimization of science based regulation (Majone, 2000). While the isolation of experts reduces the potential of external influence it does not address the inherent problem of subjectivity in regulatory science. Experts are humans and therefore their decisions will always be influenced by subjective assessment to a certain degree. A more decisive problem regarding the science based model, stems from the underlying uncertainty of risk regulation. Considering that some risks and their effects are more uncertain than others (Fischer, 2009), the superiority of experts is called into question in the latter case.[74] If experts are not sure how to assess a complex risk, they no longer could claim a more important role than anyone else. More specifically, science-based risk regulation is challenged on four grounds (Shrader-Frechette, 1995: 117). First, the scientific character of risk assessment is challenged. As in risk management, value judgements are influencing the risk assessment process. If there is no certainty about how to assess the risk, science can no longer claim an exclusive position in decision-making, as authors advocating the "social robustness" (Nowotny, 2003) of science stress. Instead of limiting assessment to scientific facts, it is proposed that some claims about the nature of risk could be made on democratic grounds. No longer does the meeting of scientific standards suffice, but assessment has to meet social (or better yet societal) criteria as well to be perceived as legitimate (Nowotny, 2003: 155). Second, the model is challenged on ethical grounds. Since risk regulatory decisions have an impact on individual welfare and in some cases the individual property, there is a need to involve the affected parties in risk assessment. The third objection is of ontological nature.

[74] For a classification of different risk types and the respective level of uncertainty see, for example, Renn (2006).

Since risk regulation has an impact on many areas of human live and in some cases even an impact on future generations, the involvement of the public (interest) is advocated. Finally, the fourth reason challenges the role of experts on democratic grounds. As it has been discussed in a previous chapter regulation will be based on certain goals. These goals ought to be based on democratic consent: if regulation has an impact on the constituency, the constituency should be allowed to have a say in it. While the reasons forwarded by Kristin S. Shrader-Frechette might have high face validity, even though not entirely distinguishable from one another, the need of public participation in risk assessment does not seem to be mandatory in all cases. Going back to the initial idea of separating risk assessment and risk management, a concept that Shrader-Frechette challenges as well, risk assessment ought to provide a mere assessment of a risk. Including lay perception would be reasonable in case of a respective risk characterized by a high level of uncertainty. In this case, the superiority of expert knowledge as well as the superiority of scientific assessment and scientific methods can be challenged to a certain degree. The assessment phase of risk regulation is resolved. It would be justifiable to open up the assessment of risk to all participants affected by the regulation. However, if the risk under scrutiny is a known risk, the benefit of opening up the assessment process is questionable. In fact, the raised criticism misinterprets risk assessment as a sub-phase of risk management. Risk assessment is about the assessment of a risk in order to inform political decision-making through evaluation of scientific facts. Often, the information that will result from the assessment will chart the path of political decision and in some cases will take the form of a policy proposition. However, the actual regulatory decision remains a political (and value based) one, possibly dissenting from the results of risk assessment. If the objectivity and superiority of experts is challenged, solving the problem by opening up the risk assessment and the inclusion of value judgements, will hardly improve the overall objectivity of the assessment. Instead, scientific reasoning is replaced by value-laden discussions, slowing down the process reducing the regulatory effectiveness and efficiency alike (Lodge, 2004). The critique raised by Kirstin S. Shrader-Frechette (1995) has to be accounted for in the risk management phase: Surely, there is a need for the inclusion of peoples' perceptions in the management of risk, but this is not challenged by science-based models of regulation. If the underlying risk can be framed as a known risk, the science-based model can be seen as a practicable solution and the role of experts seems to be at least tolerable. Nevertheless, the problem of objectivity and the need for accountable experts in risk assessment remains. Objectivity has to be shielded against undue external influence and the scientific experts have to be controlled in order to minimize subjectivity. The solution to this

problem must be seen in institutional design: subjective or privately biased assessment can be reduced by introducing clear criteria for assessment, while external influence has to be minimized further by isolating those conducting the assessment. While this argumentation supports the claim that risk assessment of known risks should be delegated to experts, additional qualifications have to be introduced. If experts conduct risk assessments, there is a heightened need for transparency, accountability and clear rules guiding the decision-making process. This is necessary in order to avoid subjective scientific assessment. In addition, the provision of information on how a decision was derived supports the "informedness of citizenry" (Noll, 1996: 174), educating the public to understand and evaluate risk in a more rational way.

Risk management: weighing the costs and benefits of regulatory intervention

The second step in risk analysis, *risk management*, focuses on the "design and implementation of actions and remedies necessary to cope with the specific risk" (Renn, 2006: 16). It focuses on the political management of risks by developing a regulatory answer, considering the broader societal implications as well as its costs and benefits. Risk management should not be understood as simply transforming the scientific assessment into a political decision within a given bureaucratic structure, resulting in a regulatory *black box*. While such an approach to risk management can be found in many risk regulatory regimes, it represents a suboptimal risk management strategy. First, it ignores the fact that "science can provide crucial information, but cannot determine correct policies"(De Marchi & Ravetz, 1999: 755). Second, taking political decisions in secrecy runs the risk of ignoring public perceptions on risk and how to react to it. It can result in insufficient cost benefit analysis, inadequate consideration of different options and a lack of anticipation of regulatory effects and impacts (IRGC, 2009). While risk assessment has to be isolated from public reasoning, the opposite seems to be true for the second phase of risk analysis. Affected stakeholders must have the possibility to state their case and provide information to enable better regulatory answers (Renn, 2006). Despite creating the opportunity to involve stakeholders in (political) decision-making, the principle of transparency and the establishment of clear rules guiding the process play an important part during risk management. As in the case of risk assessment, the decision has to be based on a clear process to create understanding for the decision itself and allow for independent external scrutiny.

Risk communication: ensuring the transfer of risk knowledge

Communication obviously represents a prerequisite for the effective regulation of risk and interaction during the risk management phase. According to Ortwin Renn, the aim of risk communication is twofold:

> "Not only should risk communication enable stakeholders and civil society to understand the rationale of the results and decisions from the risk appraisal and risk management phases when they are not formally part of the process, but it should also help them to make informed choices about risk, balancing factual knowledge about risk with personal interests, concerns beliefs and resources, when they are themselves involved in risk-related decision-making" (Renn, 2006: 15).

The aims of risk communication can be rendered even more precisely. First, risk communication is about the announcement of the regulatory decision, including the facts and reasons leading to the decision. Second, risk communication should be understood as a tool to advance the general public understanding of specific risks. Third, risk communication can and should be understood as a mechanism to establish trust in the regulatory system as whole (Poortinga & Pidgeon, 2003). While risk communication for a long time was *reduced* to the first aim, its meaning and importance for the effectiveness of risk regulation as a whole grew significantly over time, leading to a more holistic approach considering all three aims of risk communication in a more focused way (Leiss, 1996). In realising these aims, regulators face some key challenges. First of all, there is a disparity "between risks assessed by experts on the one hand and as understood by the general public, on the other" (Leiss, 1996: 86). Regulators have to understand what causes these differences in perception as "the experience of risk therefore is not only an experience of physical harm but the result of processes by which groups and individuals learn to acquire or create interpretations of risk" (Kasperson et al., 2003: 15). Risk communication has to be sensitive to these dynamics in order to enable effective knowledge translation. Some practical implications for risk communication have been synthesized by John Maule (2004). Risk communicators have to be aware that the lay public might interpret risk estimates differently (Dake, 1991; Sjöberg, 2000), especially concerning statistical information. Three implications can be derived regarding effective risk communication: the uncertainty of any formulation of risk has to be recognized (1), methods to determine how different audiences will react to the use of estimates have to be applied (2) and risk communication has to be organized as a *two-way* process (3). Especially the last point is of high importance. Rather than just passing out information, doing so in the form of a dialogue with the stakeholders will help to establish a common understanding of the risk at hand, reducing the risk of misinterpretation. In order to establish better communication,

understanding the target audience and what influences their perceptions plays an important role as well. Maule identifies individual factors shaping the perception of individuals regarding risk. In order to account for the individual factors, he suggests that regulators should focus on the usage of words instead of numbers in risk communication, present statistical info in more understandable ways and finally train risk communicators to be more sensitive to the meaning of individual perception. Besides individual factors, perceptions of risk are shaped by societal factors. Maule distinguishes cultural differences as well as stakeholder specific perceptions as the two main differences. The implications for better risk communication are obvious: Risk communicators need to be aware of their target audience. Finally, Maule identifies trust as a key concept for effective knowledge transfer in risk communication. As it was discussed with regard to the effectiveness of regulatory institutions, trust and reputation is important for effective regulation. However, trust itself depends on perception of the regulatory structure. Based on the work of Levine and Renn (1991), Maule identifies five facets associated with the perception of a communicator as trustworthy [75]:

> "the communicator is competent (has the appropriate expertise), objective (messages are free from bias), fair (all points of views are acknowledged), consistent (in terms of behaviours and statements made over time) and acting in good faith (a perception of good will)." (Maule, 2004: 25)

Compared to the aforementioned concepts, trust cannot be achieved by simply applying different risk communication techniques. Rather, trust has to be developed over a long period of time, depending on past experience with the respective institution. Given a perceived decline of trust in regulatory agencies and governments, establishing trust in risk communication is becoming even more complicated. Acknowledging the complexity of the task, Maule (2004) recommends two basic strategies for communication. Risk communication should draw on concepts of two-way communication, to establish repetitive interaction between the regulator and stakeholders. As interaction deepens over time, regulatory reputation, mutual understanding and eventually trust can be built. A second and more short-term oriented tool can be seen in using trusted communicators. Regulators might, for example, use physicians in order to communicate the risks involved in using novel drugs, as they are considered more trustworthy.[76]

[75] Their importance is amplified in a situation of high uncertainty and time constraints (Siegrist et al., 2000).

[76] This assumption is valid in the European case, as the public perceives doctors and health associations as the most trustworthy sources regarding health information (DG Sanco, 2003a).

4.3.5 The impact of Europe on effective regulation

Since regulation is carried out in a system of multilevel governance in the European context (Coen & Thatcher, 2008) the peculiar characteristics and the impact on regulatory effectiveness must be considered. Starting with a general assumption, the Europeanization of regulation can be framed as amplifying most of the problems addressed in former sections. The amplification of regulatory problems in the European context stems mainly from the specific *regulatory architecture*. Regulation in Europe is exercised in a multilevel governance system spanning different regulatory levels and even more important different regulatory phases. As the European level engages in regulatory rule-making, the implementation of regulation is carried out by the national level or even below (Haverland & Romeijn, 2007; Versluis, 2007). The introduction of different regulatory levels expands the number of stakeholders in regulation. In the simple (national) model of regulatory institutions the group of stakeholders consist of regulatees, (other) private groups and the public. In the case of European involvement, the set of stakeholders is expanded to national regulators and the interests of member states as well as additional European level political stakeholders. As a consequence, regulatory institutions on the European level face an expanded set of (public/political and private) stakeholders. And as the number of stakeholders expands, the number of conflicting preferences expands as well. Realizing effective regulation in the European context is thus complicated by the fact that national regulators, assuming a pivotal role in implementation and in most cases having a large *zone of discretion* in applying European regulation, will have a fundamental interest in keeping up their respective regulatory approach.[77] In light of national regulatory styles, the creation of alignment of national regulators with the overarching European regulatory goals is of crucial importance. As the regulatory system or network in most cases will depend on the regulatory resources on the national level (Geradin & Petit, 2004; Kelemen & Menon, 2007a), circumventing national regulators and their interests is simply impossible. Following from that, European regulatory structures have to ensure alignment, compliance and support of national regulators beyond legal commitments. As in the case of regular stakeholders, this necessitates the creation of opportunity structures convincing national regulators that compliance and cooperation will pay off. Furthermore, the safeguarding of regulatory independence becomes an even greater challenge in the European context. While the principle mechanisms developed in this chapter

[77] National regulators will try to maintain their regulatory approach, since an alternation would clash with ingrained regulatory styles (Howlett, 2002; Meidinger, 1987) and imply adaptation costs.

are applicable in the European context as well, the multiplicity of interests involved will translate into higher pressure on regulators and European regulatory agencies more specifically. In addition, the two-level character of the regulatory system has implications for the implementation of regulation. Even though this notion seems to be trivial, the timely and homogenous implementation of European rules has emerged as a real and prevailing problem in reality and sparked an intense scientific debate on the compliance of European member states (Börzel, 2001; Falkner et al., 2007; Falkner et al., 2005; Toshkov, 2007). While compliance with European regulatory policy is essential for the according implementation on the national level, this again would only ensure the *de jure* effectiveness of European regulation.

What is even more important considering the implementation phase seems to be the fit between national regulatory structures and the European requirements. What is needed to ensure a well functioning regulatory system is an institutional fit between the different regulatory levels (Bailey, 2002). The fit and internal coherence of the overall regulatory system can be expected to have a considerable impact on the implementation of regulation. While good transposition of European regulation (in the sense of policy) will depend heavily on political will to comply, the institutional fit represents a measure of compliance costs or adaptation costs in an institutional sense. The mere similarity of regulatory structures on both levels will however not suffice to ensure effectiveness. Beyond institutional fit the personal fit of national bureaucrats and their willingness to accept European rules has to be considered. In more general terms, national regulatory cultures will impact on the effectiveness in the implementation stage. In the case of risk regulation, for example, national regulators might have a different risk perception or general risk awareness concerning a certain issue, reflecting specific national cultures of risk (Douglas & Wildavsky, 1982; Viscusi & Hamilton, 1999).[78] Besides national regulatory culture, the organisational culture of the respective regulatory agency can impact on perceptions and behaviour of agencies and individual regulators (Deily & Gray, 2007). The implications for the regulatory system are obvious. If national regulatory cultures are very distinct and hard to align, national regulators will almost certainly oppose deeper integration to protect their own (national) regulatory beliefs and culture. Their opposition could refer to the general framework developed on the European level, as well as to the opinions and techniques of other national regulators. The latter will be

[78] While cultural differences have been discussed regarding risk perception and risk awareness (Hofstede & McCrae, 2004; Walls et al., 2004), it could be applied to all types of regulation serving as an important tool for understanding differences in regulatory assessment and decision making (Meidinger, 1987).

especially problematic if the *new approach* based on mutual recognition is considered in regulatory integration (Higgs, 2000; Schmidt, 2002a, 2007). If regulatory competition between national regulatory agencies is stimulated to derive the best regulatory strategy, reservations towards concurring frameworks are likely to create a gridlock. As a consequence, a regulatory system in the European context will have to deal with the diversity of cultures and find a way to isolate the distorting effects of cultural disharmony. This is achieved by offering certain incentives for national regulators to cooperate and probably more important by setting up procedures to effectively tie in national regulators. Mutual trust in regulatory competencies is crucial in this regard, but at the same time very hard to achieve. Regulatory cultures are build around deeply held believes. The acceptance of concurring concepts, especially when it comes to the perception of risk, could be seen as a major challenge in this regard (Schein, 2004). The alignment of national regulators can be seen as the key lever to ensure effective regulation in the European context. Again, the development of a fitting regulatory structure respecting the principles of participation, transparency, accountability and subsidiarity proves to be crucial in this regard.

4.4 Conclusion: Assessing the regulatory quality of European risk regulation

The main objective of this chapter was to develop a general framework for the assessment of regulatory quality in the European context and the regulation of risks more specifically. The concept of regulatory effectiveness rather than the prevailing concept of more efficient regulation has been singled out as a yardstick against which regulatory quality can be assessed. Beyond the core concept of regulatory effectiveness, eight principles of good regulation have been deducted. In addition to effectiveness, defined as the realisation of regulatory goals, these eight principles provide further criteria to assess regulatory quality in a general sense. Turning to the realisation of regulatory quality, four main levers based on the twofold conceptualization of regulation as a type of policy and mode of governance can be identified. First of all, regulatory quality will depend on the proper (legal) mandate and the legitimate reason for regulation, forming a set of preconditions. Regulatory policies represent the second lever to ensure regulatory quality. As policies represent the foundation on which the regulatory framework, understood as the sum of all policies governing the respective sector, rests, several requirements can be drawn. First of all, the regulatory goal must be specified properly and the framework should cover all its relevant aspects. Second, the identified regulatory principles should be realized within the framework. Third, in light of the

specific structure of the European regulatory context, the transposition of European regulation must be considered. The third lever consists of the governance structures and the regulatory regime set up to implement the regulatory policies. The implementation stage could be seen as critical in ensuring de facto regulatory effectiveness. Drawing on the previous discussion of effective institutions, risk regulation and the European context, a set of requirements can be synthesized. First, the design of governance structures must ensure that fitting regulatory strategies, covering the regulatory problem as a whole, can be developed and that the probability of regulatory capture is effectively reduced. Therefore the principles of participation, transparency and accountability should be traceable in the regulatory design and conduct. Moreover, the application of the principle of subsidiarity should result in a balanced distribution of tasks between the European and national level. Second, the regulatory regime should reflect an equilibrium of interests, accounting for the different stakeholders. Third, the regulatory regime must ensure the creation of a regulatory network, tying in national regulators and isolating the distorting effects of national regulatory preferences and culture. Fourth, the regulatory regime must reflect the different stages of risk regulation including risk assessment, risk management and risk communication. The fourth lever in assessing regulatory quality and effectiveness relates to *regulatory outcomes*. Since the achievement of regulatory goals represents the conceptual core of regulatory effectiveness, considering the impact of regulatory governance on these goals represents a vital component of analysis.

Graph 9: Integrated framework assessment of regulatory quality

Lever	1 Preconditions	2 Regulatory Policies	3 Regulatory Governance	4 Regulatory Outcomes
Lead Question	*Are the preconditions for effective regulation met ?*	*Does the regulatory framework allow for effective regulation?*	*Does the regulatory regime support effective regulation?*	*Are the regulatory goals accomplished?*
Identified Requirements	• Mandate • Justification • Regulation as the right tool	• Goal clearly defined • Integration of regulatory principles • Transposition of EU rules	• Deliver right regulatory answer • Avoid capture • Balance of interests • Ensure regulatory network • Integration of risk regulation process	• Achieve identified regulatory goals

Source: author's own

The proposed framework based on the four different levers is used to structure the following empirical part of the study focusing on the regulation of pharmaceuticals in Europe. Depending on the realisation of the developed requirements, the degree of regulatory quality and effectiveness can be approximated. Moreover, such qualitative assessment will allow for

the identification of possible weak points of the regulatory framework. Before the study turns to the analysis of European pharmaceutical policy, the next chapter will introduce the specific characteristics regarding the pharmaceutical sector and its regulation. As certain unique features characterize the pharmaceutical policy field and needless to say the market itself, such digression is necessary as it provides the basis for the analysis of pharmaceutical regulation in the subsequent three chapters.

5. The pharmaceutical sector: characteristics and regulatory aspects

The pharmaceutical sector is frequently described as an exceptional case (Schweitzer, 2007). The reasons for such an assertion must be seen in a combination of different factors. First, pharmaceutical products as well as the unique development and production process contribute to this perception. Second, the characteristics of the pharmaceutical market and the peculiar constellation of supply and demand forces represent a distinct feature of this sector. Third, the high level of regulation clearly distinguishes the sector from others. Since any attempt to analyse pharmaceutical regulation requires an understanding of these distinct features, this chapter provide a comprehensive overview of the pharmaceutical sector covering the product and its production process, the dynamics of the pharmaceutical market and the resulting need for regulation.

5.1 Pharmaceuticals: a special product

Pharmaceuticals can be distinguished from most other goods based on their peculiar characteristics. Despite their intended effect, pharmaceuticals can have additional yet unintended (side) effects leading to so-called *adverse drug reactions* (ADR), with possible lethal consequences. This qualifies the consumption of pharmaceuticals as a risk and mandates a general risk-benefit assessment prior to their consumption. The evaluation of risk in the case of pharmaceuticals presupposes medical and pharmaceutical knowledge and the majority of consumers cannot be expected to conduct such assessment themselves. Considering the severity of consequences treating this issue as a normal risk of consumption, regulating it through consumer protection law and the possibility to claim personal damages does not seem to be a feasible regulatory approach. Moreover, applying a private regulatory approach by delegating the said assessment to the industry is not considered as sufficient (Bührlen et al., 2003).[79] Given these reservations, the state traditionally engages in the regulation of pharmaceuticals. While the control of pharmaceuticals initially was limited to the registration of new products in most European countries, the regulatory approach was changed radically after the Thalidomide crisis in the nineteen sixties, marking the beginning of modern pharmaceutical regulation in Europe. In the aftermath of the tragic event, the requirements for the marketing of pharmaceutical products were expanded to protect

[79] Leaving regulation entirely to the private sector is perceived as problematic since pharmaceuticals, as well as the provision of healthcare in more general terms are considered as ethical products.

consumers from unsafe medicines. Instead of simply registering a pharmaceutical product, producers were now expected to demonstrate the quality, safety and efficacy of their products prior to market approval (Breitenbach, 2010; Maynard, 2005). The quality of pharmaceuticals mainly relates to manufacturing and the adherence to specific standards (Hefendehl & Muazzam, 1999). Safety mainly refers to the risk of adverse drug reactions: producers are obliged to assess the risk of occurrence of such events, conducting a risk-benefit analysis (Aigner, 2010: 88). Finally, the efficacy of pharmaceuticals relates to the performance of the pharmaceutical in improving the treated condition (Röhmel et al., 2005). Beyond defining approval criteria, (modern) pharmaceutical regulation covers (almost) the entire development process of new pharmaceuticals.

5.2 The pharmaceutical development process

The product development process is commonly divided into four mayor process steps: the search for new active pharmaceutical ingredients (1), pre-clinical development (2), clinical development (3) and registration (4) (Breitenbach, 2010: 36). While the first stage of pharmaceutical development remains unregulated, the remaining three phases follow strict procedural requirements.[80] The aim of the first stage is the identification of a so-called drug development candidate (DDC), an active ingredient (AI) intended for a specific indication (Breitenbach, 2010: 39). Based on the DDC, the second stage of preclinical development begins. The main aim of this stage is the identification of a fitting and stable formulation depicting the composition of ingredients for the pharmaceutical product, the analysis of interactions between the different ingredients comprising the pharmaceutical and the scale-up of a small development sample to mass production. During this stage, the manufacturer collects data on the intended manufacturing process and the supply chain of the specific pharmaceutical product. The second stage is critical in realising the quality criteria. In addition to these tasks, producers will need to analyse the toxicology and the pharmacokinetics of the respective product. While the toxicology of a pharmaceutical refers to the occurrence of unintended effects distinct from ADRs, pharmacokinetics pertains to the concentration of an active ingredient within the organism and its degradation over time (Boroujerdi, 2002; Lemmer & Brune, 2007). These assessments are carried out in animal experiments. The completion of the second stage marks a focal point in the drug development

[80] The following paragraph intends to provide a general overview of the development process. For a detailed description of the drug development process, see for example Aigner (2010), Breitenbach (2010), Lee, Lee & Lü (2003) and Welling, Lasagna & Banakar (1996).

process, as the clinical studies in the subsequent stage are conducted by using human test subjects. Therefore, it is quite common to treat the beginning of the third stage as the starting point for the pharmaceutical development in a more narrow sense. Within the third stage, three different phases of clinical trials are distinguished in general.[81] Phase I trials try to establish the safety and tolerability of a given pharmaceutical product in humans. The general method to gather the needed data is to conduct a randomized, double-blind, placebo-controlled trial with healthy test persons. While such design is not suitable to establish the proof of concept demonstrating the (intended) therapeutic effect, it is necessary for the subsequent application of the pharmaceutical product to (affected) test persons in later phases. As the safety and tolerability in healthy test persons has been established, the process moves on to phase II studies. The main objective of the second phase in clinical development is the proof of concept demonstrating the (intended) therapeutic effect of a pharmaceutical product within the respective indication for which an approval should be attained. In addition, the dosage and final form of application (used formulation e.g. pill) has to be identified. These aims have some implications for the design of phase II studies. First of all, higher ethical standards have to be met in the selection of test persons. Second, the size of the sample needs to be increased compared to phase I trials, normally conducted in smaller groups. Third, the test persons need to be affected by the respective disease in order to prove the therapeutic effect. Upon completion of the phase II study, the collected data has to deliver preliminary evidence on the safety and effectiveness of the pharmaceutical to justify the scale up to phase III studies. The general aim of the third phase is the confirmation of the preliminary results of phase II under more realistic conditions, most importantly the proof of effectiveness. Clinical studies in phase III consist of several multi-centre studies based on several hundred to thousand test persons using different control groups as well as placebo or alternative treatments to establish the therapeutic effectiveness (Schumacher & Schulgen, 2008). Upon completion of phase III, the collected data of all three phases is used for the application for product registration in the third stage of the development process providing enough information to allow for the assessment of quality, efficacy and safety of the given pharmaceutical product. In addition, the application will need to include additional information about the marketed product for example labelling, packaging and prescribing information.

[81] Pharmaceutical development increasingly employs a *Phase 0*, based on few subjects, very limited exposure and no therapeutic intent. The main reason for this new phase can be seen in the need to control development costs, as it can help to specify success rates of the new drug candidate (Hill, 2007; Marchetti & Schellens, 2007).

5.3 Market approval and the regulatory risk-benefit dilemma

The actual risk-benefit assessment is conducted by a (public) regulatory authority. While it formerly evaluates the application, the respective agency relies heavily on the data provided by the pharmaceutical companies.[82] If the pharmaceutical product satisfies the criteria, market approval is granted. However, a positive assessment by the regulatory agency can merely represent a preliminary decision on safety. First, the data underlying the decision do not represent the actual risk that the consumption of a given pharmaceutical might pose. Clinical trials do not represent *real life* conditions and cannot simulate all additional influences affecting the safety and efficacy of a drug, for example drug-drug interactions (Bertz & Granneman, 1997). Moreover, many ADRs occur very rarely, e.g. affecting only one in thousand persons, making them incredibly hard to detect before the drug has been approved (Eichler et al., 2008: 821). Every regulatory assessment has to be interpreted in context of these limitations (Garber, 2008). Second, the standards used to assess the risk of consumption might be specified wrong. Instead of testing new pharmaceuticals against established comparable pharmaceuticals, the general approach is based on standards, against which the new product is tested.[83] Third, the general problem of any (human) decision under imperfect information applies in the case of market approval for pharmaceuticals as well: The expert(s) carrying out the assessment might be wrong (Carpenter & Ting, 2005). These reservations illustrate the limited effectiveness of pre-market assessment as the exclusive regulatory mechanism to ensure the safety of medicines. Regulators thus face a dilemma: either they delay access to a new innovative drug and mandate more testing, or they take the risk of approving a drug to the market, which could potentially cause serious ADRs (Eichler et al., 2009; Eichler et al., 2008; Maynard & Bloor, 2003). Following from this dilemma, the efficacy and safety of pharmaceutical products cannot be assessed upfront by a single evaluation, but rather calls for a procedural long-term perspective and continuous monitoring. Put differently, the safety of a pharmaceutical product remains relative and it has to prove its safety in the long run. The concept of safety therefore has to be expanded: it does not only depend on sound manufacturing and the quality of the pre-market assessment. Beyond the product itself, safety is influenced by activities after market approval: during the distribution

[82] Some authors criticize this *information dependency* as pharmaceutical companies can decide, which data will be submitted (Abraham & Sheppard, 1997). On the other hand, data is collected based on regulatory requirements and there seems to be no (practical) alternative to the current set up.

[83] A second problem of non-comparative assessment is the impact on the development strategy of companies. If pharmaceuticals have to *compete* against previously released products, this would reduce the current risk-averse drug development strategies leading to more and more me-too drugs (Wood, 2006).

of pharmaceuticals, for example by the entering of counterfeit drugs into the distributional chain (ten Ham, 2003), and even more important during consumption. In fact, the biggest risks might result from wrong consumption of pharmaceuticals, either caused by inappropriate prescribing or consumption deviating from the recommendations (Ellickson et al., 1999; McGavock, 2004a; Vermeire et al., 2001).[84] The regulation of safety therefore has to be thought of as a life-cycle: "Life-cycle management of drug safety issues requires vigilant post-market monitoring. Increasingly, however, this concept also includes direct management of how drugs are used, to minimize risks and maximize benefits" (Gottlieb, 2007: 664). Market approval can and should be thought of as a preliminary risk-benefit assessment, which needs to be supplemented by additional regulatory mechanisms ensuring the continuous monitoring of the *risk-benefit ratio*. Even though this cannot prevent ADRs from happening, it will allow for the prevention of additional cases in the broader population. The regulatory measures related to such monitoring activities are subsumed under pharmacovigilance or in more general terms post-authorization regulation.[85] In most cases, producers will be required to gather further information on the pharmaceutical product as used under normal therapeutic conditions, by conducting mandatory *phase IV* studies (Glasser et al., 2007). This might be necessary, if regulators approve a new pharmaceutical because of public health needs, even if the (preliminary) risk-benefit ratio seems to be unfavourable or inconclusive. These post-market approval studies try to identify the long-term effects of new pharmaceuticals, especially regarding the occurrence of adverse drug reactions. The increased importance of *Phase IV* studies reflect a procedural perspective on safety: even though the assessment justifies the marketing of a given drug, this approval is only valid, as long as the safety of the product remains unchallenged. If this is no longer the case, the preliminary market authorization can be withdrawn. Post-marketing will however not only be based on *phase IV* studies. Systems for the reporting of ADR in general will have to be established. These might take the form of regular mandatory reporting by producers and the (spontaneous) reporting by physicians and the wider public (Castel et al., 2003). Regarding the safety and quality issues connected to the production of pharmaceuticals, regulatory agencies will conduct inspections of production sites (Koster & Oetelaar, 2005; WHO, 2002). As this short overview suggests, the development of pharmaceutical products is a highly complex and regulated process. The

[84] According to WHO estimates, 60 percent of ADRs are caused by non-compliance and are therefore *preventable* (WHO, 2010b). Another study estimates the percentage of preventable ADRs between 22-80 % (Madeira et al., 2007: 392).

[85] Pharmacovigilance can be defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems"(WHO, 2002: 7).

need for regulation stems from the peculiar characteristics of the product itself. However, it is not only the complexity of the development process that distinguishes the pharmaceutical sector from others and prompts the need for further regulation.

5.4 The market for pharmaceuticals

Beyond the product characteristics and the specific development process, the pharmaceutical market characterized by a peculiar structure both in terms of supply and demand, as well as specific market imperfections and failures contributes to the *distinctness* of the pharmaceutical sector.

5.4.1 Supply side characteristics of pharmaceutical markets

Starting with the supply side of the pharmaceutical market, a frequently highlighted (and criticized) feature has been the comparatively low level of competition (Backhaus, 1983; Comanor, 1986; DG Competition, 2009; Schweitzer, 2007). At first glance, this objection seems to be lacking empirical support. The pharmaceutical industry ranks upon the most internationalized ones, consisting of several thousand companies. Despite the high number of market participants, however, several big players dominate the industry. The high public exposure of big pharma companies has led to the perception, that the supply side of the pharmaceutical market resembles an oligopoly, resulting in low levels of competition (Greider, 2003). This assertion is supported by a more detailed and specific analysis of the pharmaceutical market, accounting for its specific structure. The (global) pharmaceutical market consists of several thousand products for a comparable number of indications. It seems to be impractical for a pharmaceutical company to cover all these fields. Given financial restrictions to conduct *research and development* (R&D), companies will concentrate on certain therapeutic areas, effectively reducing the overall number of potential competitors. The result is a comparatively low level of competition within therapeutic areas even though the market as a whole may appear much more dynamic (Schweitzer, 2007: 24-27). The low level of competition is sustained by the fact that based on the high R&D costs market entry in the pharmaceutical industry is highly restrictive. In addition, the granting of patents, for new medicines serves as a barrier for new competitors (Foray, 2004). Even though the supply side of the pharmaceutical market might not be as competitive as other industries, it should not be thought of as non-competitive at all. First, promising therapeutic areas will attract competition

and therefore the development of pharmaceuticals with the same therapeutic effect directly competing with established brands. Viagra, for example, was the only pharmaceutical product targeting erectile dysfunction, effectively comprising a monopoly within a single therapeutic area. With the introduction of Cialis and Levitra this situation changed dramatically (Rosenfeld & Faircloth, 2006). While so-called me-too drugs – intended for the same treatment with only minor advantages – might not constitute an innovation, they nevertheless exert pressure on existing products and stimulate competition in the pharmaceutical market.[86] A second driver of increased competition could be seen in so-called generics. Research-based companies will engage in the development (or at least in-licensing) of new pharmaceuticals. As soon as the patent protection of a given pharmaceutical runs out, the second group – producers of generics – is allowed to imitate the former protected original product without engaging into extensive R&D (Schweitzer, 2007; Simoens & De Coster, 2006). As a result, the out of pocket costs for these producers will be significantly lower, allowing for lower price levels. As generic products enter the respective therapeutic area, competition will be almost automatically stimulated.

5.4.2 Distribution in the pharmaceutical market

Under normal market conditions, the interaction between the supply and demand sides, that is manufacturers and consumers, would organize itself. In the case of the pharmaceutical market, an intermediary level exists. Manufacturers in most cases sell their products to wholesalers, which distribute the pharmaceutical products to pharmacists, dispensing doctors (or nurses) and alternative outlets.[87] These services are subject to regulation as well:

> "the activities covered include trading in medicines, their labeling and the maintenance of records, which, in part, serve to facilitate product recalls when necessary.[…] The primary objective of regulating pharmaceutical distribution is conventionally taken to be to protect the public's interests in safety and access to medicines" (Taylor et al., 2004: 198).

From a procedural perspective, the regulation of distribution ought to ensure that only quality products will reach the different outlets. A comparatively new regulatory challenge at least in

[86] Me-too drugs can constitute an alternative treatment, expanding therapeutic options and possibly reducing unwanted side effects in specific patient groups (DiMasi & Paquette, 2004). For a more critical perspective on me-too pharmaceuticals see Angell (2004).

[87] Another related issue regarding the distribution of pharmaceuticals, specifically relevant for the European Union, is the phenomenon of parallel trade and importation. In case of parallel trade, wholesalers use the different pricing levels in countries to buy in low price markets and re-sell in high price markets (Darbá & Rovira, 1998).

industrialized countries in this regard has been the problem of counterfeit drugs entering the distributional chain (Cockburn et al., 2005; deKieffer, 2006; Newton et al., 2002). This development has been amplified by the expansion of e-commerce, creating a hard to control gateway for counterfeit medicine entering the market bypassing traditional (and controlled) distribution channels (Jackson et al., 2010).[88]

5.4.3 Demand side characteristics in the pharmaceutical market

Turning to the actual demand side, a distinct structure can be identified, at least for prescription medicine.[89] Govin Permanand summarizes the characteristics as follows: "The consumer does not usually choose to be sick. Demand comes from the prescribing doctor (so-called proxy demand), and there is a third party – generally the state via some form of medical scheme or insurance – which pays." (2006: 21). This unique constellation reinforces the market imperfection caused by asymmetric distribution of information between producers and consumers. In most instances, end-consumers lack the knowledge and training to decide which pharmaceutical will be suitable for therapeutic intervention. Furthermore there is little awareness of the costs of pharmaceuticals in the first place, as consumers do not pay (directly) for the good in most cases. At the same time, the general expectation of consumer will be to receive the best possible treatment. At first glance, the price-inelastic demand might be considered as conducive to business interests as it facilitates the recovery of R&D costs and the generation of profits through the realisation of higher prices. However, this is not the case. While pharmaceutical demand in general is not affected by prices as much as demand in other industries (Brekke et al., 2007; Tellis, 1988), there are severe restrictions on the pricing strategies of pharmaceutical companies in most industrialized countries, especially within the European Union. While granting general *access* to healthcare is one of the main health policy objectives, its realisation including the access to and availability of pharmaceuticals is restricted. The first restrictions to universal access are pre-market regulatory mechanisms. New pharmaceuticals might not make it to the market, if the respective risk-benefit ratio turns out to be unfavourable. And even if market approval is finally granted, access is delayed. First, the regulatory requirements prolong the development process itself. Companies have to bare high upfront investments, before they could realize profits. Second, the actual risk-

[88] Connected to this problem are the safety issues discussed with regard to official internet pharmacies and their regulation (Montoya & Jano, 2007).

[89] From a demand perspective, two groups of pharmaceuticals can be distinguished. So-called over the counter drugs (OTC) bought without prior prescription by a physician, and prescription medicine (Beitz et al., 2004).

benefit evaluation by regulatory agencies can take months (Keyhani et al., 2006). The second and more severe restriction to general access to pharmaceuticals and the refinancing of pharmaceutical companies must be seen in existing budgetary constraints (Domino & Salkever, 2003). Given an increased pressure to consolidate health budgets, governments in their role as the main (indirect) purchaser of pharmaceuticals will need to balance the policy goals of access and financing. Governments exert considerable pressure on pharmaceutical price levels.[90] In the European Union this is mainly achieved by introducing price controls (Mossialos et al., 2006).[91] While price controls restrict pricing strategies of pharmaceutical companies they might have a temporary or even permanent negative effect on access. Negotiations can postpone access. Moreover, companies might decide to refrain from bringing a new drug to the market, if it fails to realize the required price during reimbursement negotiations. At the same time, the regulation of pricing can have a positive effect on access, as pharmaceuticals (can) become more affordable (OECD, 2008b). A second strategy to reduce expenditure would be the reduction of pharmaceutical consumption. However, governments might use such measures more cautious, because of the political repercussions such (paternalistic) intervention might have. Despite these political considerations, governments use a wide array of more subtle methods to regulate demand for pharmaceuticals for example budgeting for prescription, co-payments and switching pharmaceuticals to *over the counter* status (OTC), effectively shifting costs to the end user, usage of positive and negative lists (determining which drugs are eligible for reimbursement) and generic substitution (Chapman et al., 2004; McGuire et al., 2004; Thomson & Mossialos, 2004). Based on the previous discussion of risks stemming from wrong consumption, such interventions should not only be understood as regulation from a budgetary perspective. Regulating demand can have a positive effect on the consumption, not only from a quantitative but a qualitative point of view, for example the risk stemming from possible over-consumption (Mbongue et al., 2005; Moynihan & Smith, 2002). Another important yet underestimated safety issue in this regard is the increasing trend of switching of pharmaceuticals to OTC status. While it might be tempting from the perspective of increased access and cost reduction to switch pharmaceuticals to OTC status, a stronger trend to self-medication carries a greater risk of unsafe consumption (Bond & Hannaford, 2003; Ferner & Beard, 2008; McGavock, 2004b).

[90] In addition, pressure on both prices and total consumption can result from competition in the insurance market, as insurers try to reduce premiums by reducing costs (Schweitzer, 2007: 177).

[91] For an overview of techniques and methods used by the European member states see (Ess et al., 2003).

5.4.4 Regulation of pharmaceutical marketing

Besides regulating the production, distribution and demand for pharmaceuticals the marketing of drugs is regulated as well. While advertising for OTC is allowed in most industrialized countries, direct to consumer advertising (DTC) of prescribed drugs is only allowed in the United States and New Zealand (Magrini & Font, 2007: 526). The rationale for such limitations relates to the informational asymmetry within the pharmaceutical sector: end users lack the medical knowledge to evaluate the information entailed in such promotional activities. Proponents of deregulation, view DTC as an option to reduce the informational asymmetry and create informed patients, able to participate in health-care decisions and in the long run as a contribution to more efficient allocation of resources within healthcare systems (Finlayson & Mullner, 2005; Kaphingst & DeJong, 2004; Schweitzer, 2007; Shin & Moon, 2005). Supporters of stricter regulation of pharmaceutical marketing argue that the main purpose of DTC is promotion of products instead of information, something that is possible under the given regulatory framework at least in the European case. This sceptical perspective is supported by several studies from the US market: The advertising itself focuses on emotional messages rather than the dissemination of information and (unsurprisingly) does influence the prescription behaviour possibly leading to higher pharmaceutical expenditure with little additional health benefit (Bell et al., 1999; Donohue et al., 2007; Gottlieb, 2005; Mansfield et al., 2005). DTC does only represent one possibility of marketing in the pharmaceutical sector. Even if pharmaceutical companies have limited access to end-users, they successfully try to influence prescription patterns by targeting physicians (Lexchin, 2002). These promotional activities can take the form of detailing of the new products, information sharing, provision of free samples, medical journal advertising and sponsored continuing medical education programs (Schweitzer, 2007: 86-93).

5.4.5 The economy of the pharmaceutical industry

The realization of the outlined health policy goals has to be achieved within certain limits and obviously without jeopardizing the industry: It must be possible for companies to generate profits, while at the same ensuring access to *affordable*, *safe* and *effective* pharmaceuticals. However, companies face very distinct challenges, which have to be taken into consideration in designing such a balanced regulatory approach. Pharmaceutical companies, as all for-profit organisations, need to generate profits. While this goal might primarily be achieved to satisfy

the respective shareholders, they are necessary for the realisation of the highlighted health policy goals. Without profits, companies cannot invest in the development of new and innovative drugs. However, the realisation of profits is complicated by several interrelated factors. First a high level of *uncertainty* characterizes the product development. The chances of success for a pharmaceutical product to pass the different stages of drug development are, at best, minimal. According to an estimation by Jörg Breitenbach, out of 10.000 potential active pharmaceutical ingredients in the first stage of development, only *one* pharmaceutical product will finally pass all four stages and receive market approval (2010: 36). In line with this finding and based on his research of the US pharmaceutical market Joseph DiMasi (2001: 298; 1995) estimates that roughly 21 percent of the pharmaceuticals entering the clinical trials phase will be granted market approval.[92] Even if the product reaches the market, unfavourable *phase IV* study results or ADR incidence might lead to product withdrawal.[93] Secondly, the drug development process is very time consuming. Modern methods of screening might have reduced the time needed for the identification of *DDCs*, but the potential for rationalisation has been much more limited regarding the other stages.[94] Clinical trials represent a major component and the regulated selection of test persons serves as a prolonging factor. At the same time, the aforementioned regulatory expectations have to be met, leaving little opportunity to reduce the time of development. Regarding the development process as a whole, Breitenbach estimates an average time of ten years for a pharmaceutical to complete the four stages (Breitenbach, 2010: 36). For the US market between 1992 and 2002, Kehayni and her colleagues calculate an average of 5.1 years for clinical trials and 1.2 years for the regulatory review phase (Keyhani et al., 2006: 461). Unsurprisingly, the rather time-consuming process leads to exponential R&D costs. While some authors estimate the costs for the development of a new drug to be as high as 1.7 billion US $ based on data from the period between 2000 and 2002 (Gilbert et al., 2003: 1), the majority of recent studies estimate the costs to be around 800 million US dollars (DiMasi et al., 2003; Grabowski, 2002).[95] The costs have risen sharply over time, mainly caused by the exponential growth of clinical trial costs as research by Henry Grabowski shows:

[92] Despite these trends, DiMasi (2001: 304) argues that long-term trends indicate an increase in successfully completed approvals.

[93] No reliable estimates on the extent of withdrawal based on safety concerns in Europe exist. A US study estimates a US withdrawal rate of 2,9 percent for the period of 1975-1999 (Lasser et al., 2002).

[94] While regulation prohibits effective time reduction regarding these stages, this would have a very positive effect on the overall costs/efficiency of drug development (DiMasi, 2002).

[95] Such exact numbers should be interpreted cautiously as the estimates may vary extremely based on the type of therapy and firm. A replication study of the cited DiMasi et al. study (2003) by Christopher Adams and Van Brantner (2006) produced a range of costs between 500 million and 2 billion US dollars.

> "The average R&D costs of a new drug introduction for 1990s approvals is $ US 802 million, compared with $ US 316 million for the 1980s and $ US 138 million for the 1970s [....] the biggest changes have been in terms of clinical expenditures, which experienced a 3-fold increase for 1990s approvals, relative to the 1980s approvals." (2004: 16).

The costs are distributed *unequally* within the pharmaceutical industry compared to other industries "because of the heavy fixed costs that have to be initially incurred for the development and dissemination of knowledge" (Vogel, 2007: 86).

Graph 10: The drug development process

Stage	Development	Clinical Studies			Approval	Post-market
		Phase I	Phase II	Phase III		
Number of Potential Substances/ Products	10.000 in screening 5-6000 in testing	5 in studies	2-3 in studies	1-2 in studies	1 approved	
Time (in yrs.)	4 - 6,5	1 - 1,5	2	3 - 3,5	0,5 - 2,5	Time of marketing
Costs (in mio. €)	200 - 300	200 - 400			20 - 40	30 - 60

Source: adapted from Breitenbach (2010)

Judging on these factors and more specifically the financial risk of such investment, the development of drugs might be perceived as a very unattractive business (2007: 133-134) and this perception is amplified by a highly skewed distribution of returns on investment (Miller, 2005: 4). According to older calculations, the present value net revenue for most marketed drugs is less than the average development costs in the 1990s (Grabowski, 1997). A more recent analysis by Grabowski, Vernon & DiMasi suggests that "only one third of the new drug introductions had present values in excess of average R&D costs" (2002: 27). Realizing profits is not only complicated by the outlined characteristics of product development, resulting (partially) from regulatory requirements, and the regulation of demand, but the wider public perception of the industry as well.

5.4.6 The public perception of the pharmaceutical industry

The public perception of health-related industries can be described as ambivalent. Most consumers would probably agree on the common dictum that health is priceless, yet "many

people believe that profit should not be earned as the consequence of caring for persons who suffer from somewhat random incidence of illness" (Vogel, 2007: 165). While moral reservations cannot keep companies in the healthcare sector from seeking profits, it creates an (possible) unfavourable climate, since "on one hand, we look to new drugs to deliver us from illness and disease. On the other, we view the companies who deliver them with suspicion or disdain" (Delamothe, 2008). The critical stance towards the pharmaceutical industry – despite its undeniable contribution to the safeguarding of public health – has been amplified by general and in instances very specific criticism. The industry has been criticized for investing more money into advertising than new product development (Gagnon & Lexchin, 2008). It has been argued that its research focus is on lifestyle drugs (Harth et al., 2008) and profitable diseases for which treatments are already available instead of developing treatments for serious but financially less promising illnesses, creating an abundance of me-too products (Lexchin, 2001; Wolinsky, 2005). Furthermore, it is suspected to create and exaggerate new ailments, for example female sexual dysfunction (Moynihan, 2003) and contribute the increasing medication of all aspects of life (Mbongue et al., 2005). One of the most persistent accusations has been the alleged excessive profit of pharmaceutical companies compared to other industries (Angell, 2004; Offerhaus, 2005; Pattison et al., 2003). While the general observation that the pharmaceutical industry has been profitable is true, the claim that these profits are excessive is not supported by detailed analysis and ignores the fact that these profits are subject to a high (financial) risk of failure (Grabowski, 2002; Grabowski & Vernon, 1982; Vogel, 2007). Comparatively higher profits can thus be understood as a premium for the higher risk of making no profits at all. [96]

5.4.7 Balancing safety, access and industrial interests

In light of the previous discussion, the conditions under which pharmaceutical companies operate seem to be quite unfavourable. Since pharmaceuticals represent an important product both from the perspective of health and economic policy, governments will have an interest in supporting the well-being of the industry. In trying to create an environment conducive to health and industrial policy interests, governments can adopt different strategies.

[96] In addition, Ronald Vogel (2007: 176) points out that the methods used to calculate profits are ill equipped to account for the capital intensity and reliance on intangible assets characterizing investment in the pharmaceutical industry.

Authorities can try to create more favourable conditions for pharmaceutical companies. This can be done, by fostering strong systems of innovation and collaboration between industry and public (university-based) research (Borrás, 2004; Siegel et al., 2003). An additional lever to foster the industry can be seen in a comparatively low level of interference with the market structures and pricing. Most governments might limit the potential for excessive pricing, but nevertheless allow the pharmaceutical industry to set prices in the first place (OECD, 2008b; Paris & Docteur, 2008). And while the industry as a whole is indeed heavily regulated, comparatively little is done to break the *oligopolistic* structures characterising the supply side, especially within therapeutic areas (DG Competition, 2009; Lacetera & Orsenigo, 2001).

An alternative strategy can be seen in the lowering of regulatory requirements, partially responsible for high R&D costs (Ruffolo, 2006). However, this is commonly perceived as no feasible option. Above all, the safety of medicines has (some) political salience, preventing governments from reducing these requirements. Moreover, there is consensus in the sector that safety is a legitimate reason for regulation and there are strong reasons, why the pharmaceutical industry even tends to embrace such regulation. While these requirements represent costs for the industry in the first place, they represent a general entry barrier to the pharmaceutical market (Schweitzer, 2007: 105). Because of the high costs involved in the development of pharmaceuticals, companies already in the market do not have to fear the entry of potential new competitors. The upfront investment is simply too high, compared to other sectors.[97] Even though there is little evidence that the general level of regulation is decreasing a common trend in the field of (pharmaceutical) regulation has been the regional and global harmonization of differing national regulatory standards (Abraham & Reed, 2002; Juillet, 2007).[98] In the case of the European Union, the Commission itself advocated harmonization in order to complete the single market. On the global level, harmonization has mainly been promoted by a series of meetings of the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH).[99] The ICH is comprised of regulatory and industry representatives from Europe, the United States and Japan. The task of the ICH is subsumed by the organisation as follows:

[97] While these costs are reduced significantly after patent expiry regarding the development process, new producers still have to get market approval. For an inexperienced company this represents a very effective entry barrier.

[98] This trend has been accelerated by continuous lobbying of the pharmaceutical industry on the national and European level (Abraham & Lewis, 1999; Abraham & Reed, 2002; Permanand, 2006; Permanand & Mossialos, 2005).

[99] Another institution active in the harmonization of standards is the *Council for International Organizations of Medical Sciences* (CIOMS). For a description of its activities, see Macrae (2007)

> "The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines." (ICH, 2010).

The main focus of this organisation is the streamlining of requirements and formats used for the application procedure, even though its scope is increasingly expanding towards standards in pharmacovigilance (Bahri & Tsintis, 2005). As it was mentioned previously, European harmonization led to the emergence of European level based procedures resulting in market approval in all member states. While there have been some major harmonization advances in the last decades, there is still considerable room for improvement (Eakin, 1999). The effect of regulatory harmonization from a business perspective is obvious: instead of preparing individual data for several distinct national applications, companies can use the same basic data for these applications. The creation of more favourable conditions and harmonization of regulation per se does not stimulate the development of innovative medicine. As previously mentioned there are two (general) types of manufacturers: originator companies engaging in research and development and generic companies *copying* original medicine. While it will depend on the respective national *industrial* composition, governments can be expected to have a vital interest in ongoing research and development to realize health policy objectives.[100] They must therefore ensure that there are sufficient incentives for these companies to invest in R&D. Governments try to stimulate the innovative process by providing effective protection of *intellectual property* (IP) mostly via patents. As a form of intellectual property rights, patents "are generally speaking national rights that give the proprietor a measure of exclusivity in the subject-matter of protection and in so doing protect the owner of the right from the effects of competition" (Isaac, 2001: 27).

By granting a patent for a product, the respective producer is allowed to act as a monopolist for a limited amount of time in order to recoup the R&D expenses. The regulation of IP therefore does not only serve as recognition of property but can be understood as a reward for the risk taken in developing the product. After patent expiry, other companies and especially producers of generics will enter the market. Even though patents will prevent other producers from curtailing the profits of the original producer, other companies might develop products not covered by the respective patents intended for the same therapeutic area before the patent

[100] Considering the European pharmaceutical market, the relevance of the generic industry from the perspective of industrial policy varies significantly. While the generic industry is strong in some member states, for example, in Germany (Accenture, 2005), it plays a much more limited role in other ones judging from the respective market shares (Perry, 2006).

expires.[101] An additional reservation concerning the use of patents as an incentive for innovative medicine can be formulated at this point. Strictly speaking, patents can only stimulate the development of new drugs, but not necessarily innovative ones. In reality, most patented drugs are me-too pharmaceuticals representing only minor advances (Light & Walley, 2004; Wood, 2006).

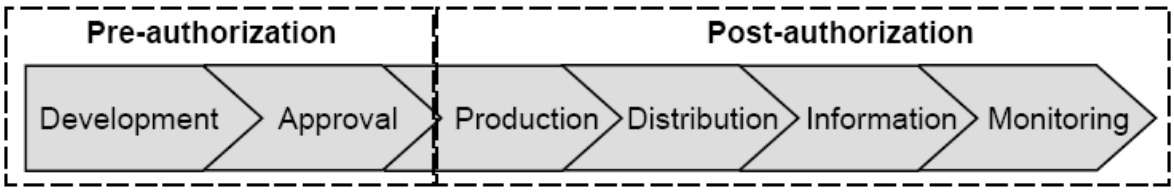
5.5 Conclusion: balancing safety, access and industrial interests

The (risk) regulation of pharmaceutical products has to cover several interrelated aspects while at the same time striking a balance between underlying conflicting policy objectives. Even if the safety of pharmaceuticals is conceptualized as the prime public concern, it has to be balanced against at least two different policy goals. Most importantly, safety considerations might conflict with the provision of access to pharmaceuticals. The possible conflict between these two goals is most obvious in the regulatory decision about market approval. Regulators will have to weigh the risk a new drug might have against the potential benefits based on limited and preliminary information. Depending on their preferences, regulators might emphasize safety by delaying the drug approval and ask for more information establishing the *safety*, *quality* and *efficacy* of the reviewed drug. If the regulator believes that access to an innovative treatment is more important, he will grant approval having to accept the possible negative consequences of this decision. A *precautionary* approach to the approval decision, even though politically recommended, might be the less favourable option. The safety of pharmaceuticals cannot be determined solely *upfront*, but rather calls for a procedural perspective on safety. While a certain level of safety is mandatory for approval, the real risk and benefit of a drug is revealed as soon as it is *tested* in the field. In addition, the safety of pharmaceuticals is not only connected to product characteristics but correct consumption. A precautionary regulatory approach might therefore have only limited benefits. Besides the possible trade-offs between *safety* and *access*, policy conflicts almost certainly arise between *safety* and *access* on the one hand and *industrial policy* on the other hand. The realisation of safety and access can result in severe restrictions of industrial activities, for example, the regulation of the production process, distribution and marketing or the regulation of pricing in favour of health budget consolidation. While these regulatory interventions are justifiable and necessary, they must not become excessive: an innovative and

[101] Even if there seems to be some progress in this matter (Brizmohun, 2009), patents in Europe are still granted on the national level, resulting in continuing variations (DG Competition, 2009).

dynamic pharmaceutical industry is the prerequisite for the effective new medicine. In drawing a conclusion on the discussion of the underlying reasons for and requirements of regulation, the main regulatory challenges in the pharmaceutical sector could be formulated in the following way: Regulation needs to acknowledge the characteristics of regulated risk by adopting a regulatory approach considering the product cycle as a whole while at the same time increasing the understanding of consumers for the underlying risk characteristics. In other words, regulation needs to consider the whole regulatory lifecycle to regulate the underlying public health risk effectively. Starting off with the regulation of the development process and the approval process, regulation will need to cover the post-authorization aspects of production, distribution and information of patients as well as the continuous monitoring of pharmaceutical products in the market. Moreover, legislators (and regulators) must consider the possible policy trade-offs involved in the field. To be effective, regulation has to strike the right balance between access and safety, while at the same time accounting for the possible conflicts between public health, the provision of health care and industrial policy considerations.

Graph 11: The regulatory lifecycle of pharmaceutical risk



Source: author's own

6. The regulatory framework: establishing de jure effectiveness

Drawing on the framework developed in the fourth chapter, the evaluation of regulatory quality commences with the discussion of preconditions. The second section will provide an overview on the development and current state of the legal framework. Considering the large body of European pharmaceutical regulation that has been established since 1965, such description can merely provide an overview of legal developments.[102] Such an overview should suffice to inform the following discussion on the effectiveness of the legal framework. Moreover, units of comparison will be identified, structuring the analysis carried out in the subsequent section. The analysis of the regulatory framework will focus on the regulatory lifecycle, the coverage of the regulatory problem and the realisation of regulatory principles within the framework. In the final section, the transposition of regulatory policy in the pharmaceutical sector is evaluated briefly.

6.1 Preconditions of effective regulation

Regulation as a form of market intervention has to be justified. In the European regulatory context, the need for justification can be conceptualized as a twofold concept: first, an argument for the specific intervention must be developed and second, the case for European level activity has to be established. After establishing the case for intervention, it has to be assessed, if regulation – more specifically state-based as opposed to private regulation – is the appropriate form of intervention. Third it must be asked, in how far a regulatory mandate can be (legally) founded, within the existing European treaties.

6.1.1 Justifying intervention in the pharmaceutical sector

One of the commonly held beliefs in (liberal) market societies is that markets will operate best, if left alone (Biersteker, 1990; Olson, 1996; Shleifer, 1998). External intervention will only be deemed as legitimate, if compelling reasons can be presented. Intervention in the pharmaceutical sector can be legitimized on at least two grounds. First, intervention is necessary in order to reduce negative externalities. While the consumption of pharmaceutical

[102] An elaborate legal analysis is not conducted in this study as the primary focus is on the outcomes of specific regulation rather than the legal acts themselves. A sound examination of all the relevant laws and regulations from a legal perspective would require a separate assessment. For some of the key legal aspects of pharmaceutical regulation see Christopher Hodges (2005).

products clearly contributes to the maintenance of public health it can potentially harm consumers. However, this does not represent a *normal* risk of consumption which can be passed on to the consumer by the pharmaceutical industry. Possible side-effects of drug consumption can have severe and even lethal outcomes. Second, and probably even more decisive with respect to the justification of intervention, the pharmaceutical market is characterized by strong information inadequacies and asymmetries (Cassel et al., 2007; Viscusi et al., 2005). Consumers have limited access to information. Even more important, they cannot be expected to process the information regarding the risk-benefit ratio of pharmaceuticals, since they lack the medical knowledge to do so (Bongard et al., 2002). Even though the specific demand structure in the pharmaceutical market might reduce the severity of the problem, the capacities of physicians and pharmacists to assess the inherent risk of a specific pharmaceutical product are limited as well and will depend on their respective level of experience and information (Hasford et al., 2002). Consequently, intervention can be justified on the grounds of the reduction of negative externalities and the reduction of informational asymmetries.[103] The justification to intervene does not preclude the need for European intervention, which form of intervention is appropriate and who should be responsible.

6.1.1.1 Justifying European intervention

The need to discuss the legitimacy of European intervention goes beyond the assessment of regulatory quality, since " what, how and at what level of government to regulate – is the core of the compromise between the European Community and its member states that made the Internal Market Programme possible" (Majone, 1994b: 77). This core of compromise has been enshrined in the principle of subsidiarity, mandating that the European level should only perform those tasks that could not be performed effectively at the level of member states or were member state activity is insufficient. In establishing an argument, the principle of subsidiarity entailed in article 5.3 (TEC) can serve as a point of departure. The said article states that:

> "Under the principle of subsidiarity, in areas which do not fall within its exclusive competence, the Union shall act only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level."

[103] A third argument for intervention flows from *moral hazard*, as producers might have an insufficient interest in regulating the market (Ochs, 1996).

While the article defines how the principle should be interpreted, further guidance in establishing a case for European intervention is provided by article 5, protocol 30, annexed to the treaty:

> "the issue under consideration has transnational aspects which cannot be satisfactorily regulated by action by Member States; actions by Member States alone or lack of Community action would conflict with the requirements of the Treaty (such as the need to correct distortion of competition or avoid disguised restrictions on trade or strengthen economic and social cohesion) or would otherwise significantly damage Member States' interests; action at Community level would produce clear benefits by reason of its scale or effects compared with action at the level of the Member States."

Applying these requirements to the pharmaceutical sector, the *transnational* dimension of the underlying regulatory problem could be established on several grounds. First, the target of intervention, the pharmaceutical industry represents a globalized and therefore European industry (Busfield, 2003; Gambardella et al., 2000; Schweitzer, 2007). The transnational character is not limited to the regulated industry, but is traceable regarding the product and possible negative effects as well. Pharmaceuticals represent a (tradeable) good and will therefore potentially affect all consumers within the European Union. Given the relatively high genetic similarity of the European peoples (Daar & Singer, 2005; Novembre et al., 2008), unwanted side effects represent a comparable risk for all citizens. It can be argued, that national regulators could take measures to act on the risk of pharmaceuticals and regulate satisfactorily in this matter. Taking the additional guidelines into account, the rationale for a levelling up of intervention can be strengthened further. A strong, yet predominantly economic argument for European intervention can be developed based on the second guideline, since national regulation will most probably conflict with the requirements of the treaty and the creation of the internal market more specifically. Another argument in support of European intervention can be deducted from the third guideline. While in principle, the risk stemming from pharmaceuticals could be sufficiently regulated at the national level, a unified approach will produce benefits. For example, by standardizing and integrating national *post-authorization* controls, the likeliness of detecting unwanted side-effects at an early stage is increasing, providing those responsible with more time to react appropriately. From a business perspective, the *benefit of scale* results from reduced compliance costs, given unified standards. European intervention is therefore justified in achieving the underlying regulatory goal.

6.1.1.2 Determining the right form of intervention

While European intervention is necessary and justified to remedy the shortcomings of the pharmaceutical sector, the appropriate form of intervention remains to be determined. In line with the discussion of regulatory effectiveness in the fourth chapter, the least intrusive mode of intervention can serve as a point of departure. The least intrusive form would be to choose the regulatory option of *doing nothing* (OECD, 2008a). For obvious reasons, this strategy is ill-equipped to cope with the regulatory problem at hand. Subsequently, the viability of soft modes of regulation and private regulation has to be considered.[104] Considering asymmetrical information regarding product risks between the patient (principal) and the manufacturer (agent) as the main regulatory problem, several market-based mechanisms could be employed to reduce this problem. Patients could use screening mechanisms to improve their knowledge, for example, by using other agents (physicians, insurance companies), while producers could employ signalling mechanisms by building a good reputation in the market. By granting the possibility to claim damages via liability law, agents are incentivized to provide quality information (Cassel et al., 2007: 292-293). While such a regulatory approach might be viable and desirable from a theoretical perspective, it is seriously flawed. The problem of pharmaceutical risks is reduced to a mere issue of information inadequacies, overestimating the capacities of patients while at the same time underestimating the underlying risk. While the quality and quantity of information available to patients represents an important aspect, it does not account for the lack of ability to process this information. It remains at least questionable, if the screening mechanisms and the support of agents are sufficient to compensate the lack of knowledge. In addition, the problem of information selection is raised. Another problem of such an approach is the underlying assumption, that producers are well informed about the risks of their own product. In essence, the product risks are severe enough to render the proposed level of regulation as too low. A regulatory approach based on the disclosure of information and naming and shaming mechanisms based on the willingness of producers to gain a certain reputation in the market and the possibility to claim damages is thus insufficient. Since the regulatory problem relates to the product, the introduction of product based regulatory mechanisms represent a promising extension of the regulatory approach. Drawing on different regulatory approaches and strategies identified by Baldwin and Cave (1999), this could take the form of franchising or licensing: a competent authority

[104] In line with the mainstream discussion on regulatory quality, less intrusive forms of intervention can be seen as the *preferred* regulatory solution, justifying a stepwise discussion (OECD, 2008a).

grants market access to the respective product after evaluating product characteristics. By introducing such pre-authorization controls, the emergence of informational asymmetries is effectively reduced. The regulatory authority would serve as an agent providing information to the patient and his respective physician regarding the risk-benefit of the product. As the discussion in the last chapter clarified, pre-authorization controls and the approval of products might be too limited in the pharmaceutical sector. Since the risk-benefit ratio leading to market approval could only be based on limited information and the possibility that some severe side effects might occur very rarely, continuous monitoring mechanism are necessary and justifiable in achieving optimal regulatory results, even though representing a more intrusive regulatory strategy.

6.1.1.3 Identification of the right regulatory set up

After clarifying how to regulate, it must be decided who should carry out this task. Given underlying preferences for less intrusive methods, the task could be carried out by the pharmaceutical sector as a form of self-regulation (Cassel et al., 2007; Sauer & Sauer, 2007). Leaving the evaluation of products regarding their respective risk-benefit ratio to their producers, however, seems not to be supported from a societal perspective. It is true that reputation represents a strong incentive to establish strict standards necessary for effective protection from unsafe products. Nevertheless, a private regulatory regime especially in the pharmaceutical sector will be heavily contested, as the relationship between the pharmaceutical industry and the public is characterized by a prevailing level of distrust (Offerhaus, 2005; Sharma, 2007). Two additional arguments in support of state based regulation can be developed. First, the introduction of private regulatory regimes might imply high (political) costs of introduction. Since the public expects that the regulatory task is carried out by a public agency – which is at least indirectly legitimized – establishing a private regulatory regime can face strong public resistance (Abraham et al., 2002). Second, it could be argued that the industry itself would not prefer such self-regulatory mechanisms. As Daniel Carpenter (2003: 255) notes, “the inherent uncertainty that firms themselves have about the quality and safety of their products”, leads to a higher acceptance of public regulation. In certifying the quality of a given product, the respective public authority reduces the uncertainty of the pharmaceutical producer regarding the quality of its own product.

6.1.1.4 Establishing a legal basis for regulation

The next logical step is the identification of a legal foundation for regulatory intervention. Based on the underlying rationale for intervention, the protection of public health, a respective (constitutional) foundation has to be identified within the European treaties. Such foundation can be found in article 152 TEC stating that "A high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities." As it was discussed in the first chapter, this rather general mandate does not provide the European Union with extensive competencies in health matters (Hervey, 2002). Subsection 5 of the said article restricts the rather general meaning by asking for the respect for national competencies in the field of health policies. Accordingly, article 152 does not qualify as an appropriate legal basis for regulatory intervention. Alternatively, article 153 on consumer protection could be invoked. The first indent states:

> "In order to promote the interests of consumers and to ensure a high level of consumer protection, the Community shall contribute to protecting the health, safety and economic interests of consumers, as well as to promoting their right to information, education and to organise themselves in order to safeguard their interests."

The article is formulated in a very general manner, calling for the contribution of the European level in matters of consumer protection and thus (only) legitimizes complementing measures to national regulatory activities. Therefore, Article 153 does not represent a legal basis for European regulation to ensure consumer protection. The Treaty, as Christopher Hodges rightfully notes, "falls far short of offering a general constitutional mandate to select whatever style of consumer protection policy it regards as appropriate for its aspirations" (2005: 33). Accordingly, an alternative legal foundation has to be found. As it was argued regarding the principle of subsidiarity, European intervention could be justified based on the advancement of the single market. This does however represent a different underlying rationale for regulation: the protection of public health no longer serves as the main aim. In fact, most consumer protection measures introduced by the Community were based on article 95 (Hodges, 2005: 28), stating that:

> "The Council shall,[…] adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market."

Despite implicit (constitutional) tensions that might arise by founding regulation in order to strengthen public health on provisions mandating harmonization of national standards, article

95 does provide a legal basis for regulation. Two preconditions have to be met in order to invoke article 95 as a basis for regulatory activity. Differing *national provisions* must exist (1) and the approximation of these standards must *advance* the creation and functioning of the internal market (2). Both conditions are satisfied in the case of the pharmaceutical sector. Even though comparatively weak, national regulatory provisions existed prior to the emergence of European legislative activity (Collatz, 1996) and the harmonization of these measures contributes significantly to the functioning of the internal market.[105]

6.1.2 Intermediate result: preconditions of effective regulation

The previous section tried to clarify, in how far the identified preconditions of effective regulation could be established regarding the European regulation of pharmaceuticals. Starting off with the justification of intervention, the protection of public health has been identified as a sufficiently legitimized justification and regulatory goal. The need to improve the functioning of the internal market and the expected positive regulatory *scale effects*, resulting from federal level regulation, have been identified as a justification for European involvement in the pharmaceutical sector. As less intrusive modes and reliance on self-regulatory mechanisms were deemed insufficient in order to cope with the underlying regulatory problem, public-based regulation based on market approval and monitoring mechanisms were identified as an appropriate regulatory answer. Finally, a legal basis for regulation protecting *public health* was identified in form of article 95 (TEC). While the said provision represents a legal basis for regulatory intervention, the discussion of possible constitutional foundations revealed that no direct mandate for the protection of public health and consumer protection can be found in the treaties. Accordingly, intervention in order to maintain public health is disguised as a measure to reduce obstacles to internal trade. The justification of risk regulation via the completion of the single market raises additional concerns regarding the European regulatory logic from the citizens' perspective. If risk regulation is merely created to reduce market distortion, disregarding the inherent necessity of regulation as an intervention to protect consumers from harmful products, it seems questionable if the social optimum of regulation is realized.

[105] While these provisions predated the cited legal provisions, they were based on article 100 of the Treaty establishing the European Economic Community now article 95 TEC (Greenwood, 1987).

6.2 The development of European pharmaceutical policy

European pharmaceutical policy can be traced back to the 1960 emerging in the aftermath of the *Thalidomide* disaster (Feick, 2002; Krapohl, 2008; Permanand, 2006). While the Commission had engaged in consultations with various stakeholders on the issue of prospective harmonization prior to this tragic event, the public health threat created an window of opportunity and kick started the process (Permanand, 2006; Vogel, 1998). National regulators reacted to the crisis by strengthening domestic regulatory systems, but the severity of the events helped to create awareness for the transnational dimension and a shared European responsibility.

6.2.1 Initial harmonization after Thalidomide

Consequently, the six initial member states agreed on the harmonization of existing standards. The introduction of directive No. 65/65/EEC marked the beginning of a common European approach to regulation in the pharmaceutical sector.[106] Laying the foundation for the legal framework still governing the sector today, three aspects of the directive must be highlighted. First, the directive established the general and still valid goal of regulatory intervention. The first and second recitals of the said directive state that:

> "the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health; Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community;"

Referring to article 100 (EEC), and therefore the advancement of the internal market, the clear commitment to public health as the main goal of intervention, character, may serve to reduce the potential tensions between the underlying regulatory task and the respective constitutional foundation. Second, the directive introduced a set of clear definitions and standards regarding the control of pharmaceuticals, for example, the types of products covered by the regulation and the concept of a proprietary medicinal product. Article 3 entailed the requirement of mandatory authorisation of these products. While most national systems were based on mandatory registration of pharmaceutical products, this provision marked an important step from a public health perspective (Daemmrich, 2004; Daemmrich & Krücken, 2000).

[106] An overview of the development path of European pharmaceutical regulation is provided in graph 17. A list of key legal acts is provided in the appendix (A.3).

Subsequent articles lined out the approval requirements, procedural and time requirements of market authorisation, the duration of validity, quality controls of manufacturing, labelling requirements for pharmaceutical products and the necessity to engage in continuous post-market controls (pharmacovigilance).

Third, article 5 established the substantial criteria on which market approval as well as refusal and withdrawal of an authorized product ought to be based within the EEC by introducing the concepts of *safety*, *quality* and *efficacy*. While directive No. 65/65/EEC has to be seen as an important step towards safer pharmaceuticals, its focus was rather narrow: it achieved the harmonization of standards and introduced mandatory authorization, but did not contribute to the advancement of the single market. Considering the prevalent reservations on the national level regarding delegation in this sensitive policy field at that time, the directive must be understood as a significant progress. It took the Commission almost a decade to follow up on the first regulatory advancement in the pharmaceutical sector. In 1975, three directives affecting the regulatory framework were released. Directive No. 75/318/EEC established uniform rules regarding the necessary tests and trials informing regulatory decisions.[107] The second directive, No. 75/319/EEC, did not aim at the harmonization of standards, but an approximation of national authorization procedures. It introduced the Committee for Proprietary Medicinal Products (CPMP), comprised of national regulatory experts and representatives of the Commission. The said committee was established to examine questions connected to approval referred to it by the member states. Beyond its function within the emerging regulatory regime, however, the Commission expected it to be a device to harmonize national regulatory approaches through exchange and dialogue (Lorenz, 2006: 48-51). Another procedural change introduced by the directive was the creation of the so-called CPMP procedure. An applicant – after successfully submitting his approval dossier based on the requirements of directive No. 65/65/EEC to one national regulatory authority – who decided to market the approved product in five more member states, could now ask the regulatory authority which granted approval to forward the dossier and the authorization to the CPMP. The CPMP would then distribute the dossiers to the concerned member states. The forwarding of these documents substituted the single application in each of the member states, representing the normal procedure before the introduction of the CPMP procedure. After receiving the application through the CPMP, national regulators could either tacitly accept the

[107] The directive addressed the requirements regarding the testing (analytical, pharmacological, toxicological) and the conduct of clinical trials.

approval documents, or raise objections by forwarding a reasoned objection to the CPMP within a given period. The Committee could then come up with a reasoned opinion reacting on the reservations expressed by the dissenting member state, granting the member states another 30 days to reach a decision on national authorization. However, the reasoned opinion was not binding on the member states. The decision to approve the product remained at the national level. A comparable procedure was established for dissenting opinions of national regulators on the same product, not submitted via the CPMP procedure, regarding the authorization, suspension or withdrawal.[108] In addition, member states were permitted to call on the Committee if interests of the Community were involved. In essence, the introduction of the CPMP procedure reflected the political conviction of the Commission, that integration in the pharmaceutical sector ought to be achieve based on the principle of mutual recognition (Gehring et al., 2005: 85). Beyond procedural innovations, directive No. 75/318/EEC introduced several additional changes. It established rules on the manufacturing and importation of medicine from third countries and introduced the requirement of a qualified person (QP) exclusively responsible for certain aspects regarding the approval process.[109] The fifth chapter introduced requirements regarding the supervision of the manufacturing process and specified the requirements regarding continuous monitoring of pharmaceuticals after approval. The third directive No. 75/320/EEC released in the same year, created the Pharmaeutical Committee acting as an advisory panel to the Commission when preparing proposals for directives regarding the pharmaceutical sector. On first sight, the changes introduced to the regulatory system in 1975 were considerable and marked a shift from the harmonization of standards to the establishment of a mutual recognition procedure. The introduction of the CPMP and the according procedure represented an attempt to introduce a facilitated mutual recognition approach, rationalising market approval within the EEC by making individual assessments by national regulators of the same product obsolete. However, the CPMP procedure did not succeed. Since the opinions of the Committee were non-binding, "the member states could, and generally did ignore them" (Permanand, 2006: 49). The political and public sensitivity regarding pharmaceutical products, the strong national regulatory traditions and the prevailing distrust between the national regulators hampered the success of the newly established procedure (Abraham & Lewis, 2000; Lorenz, 2006). Legislative activity in the pharmaceutical sector decreased in the following years with few

[108] In this case, one of the affected member states could refer to the CPMP for arbitration.

[109] The concept of the qualified person serves as an important mechanism within the European regulatory approach in the pharmaceutical sector effectively shifting responsibilities towards the industry (Brown, 2005; Ladds, 2007).

notable exceptions.[110] The next notable attempt by the Commission to harmonize procedures was included in directive No. 83/570/EEC, introducing the multi-state procedure modifying the existing, yet disappointing CPMP procedure. Under the multi-state procedure, access to the procedure was improved by lowering the number of countries to which the initial authorization should be extended from five to two. In addition, member states were now strongly advised to take former authorizations into due consideration.[111] However, these modifications did not solve the underlying problem of the procedure: Still, the CPMP opinion was non-binding and member states regularly choose to ignore it (Lorenz, 2006).[112] By the mid 1980s, harmonization in the pharmaceutical sector fell short on the Commission's expectations. Sparked by the disappointing performance of the existing regulatory framework, the Commission explicitly highlighted the need for additional efforts in its white paper on the completion of the internal market (European Commission, 1985). This new found enthusiasm has not only been caused by the suboptimal level of harmonization. With the signing of the Single European Act in 1986 and the goal of completing the internal market until 1992 looming in the distance, pressure on the Commission to take action increased.[113] The first result of these efforts – directive No. 87/22/EEC – sought to achieve two goals.[114] First, the underlying policy goal was to create more favourable conditions for research in high-technology pharmaceuticals. Second, the Commission believed that in order to incentivize the industry and strengthen regulatory capacities regarding high-technology products, the introduction of a new procedure was inevitable. The directive introduced the concertation procedure mandatory for products derived from biotechnology. If a pharmaceutical company applied for market authorisation for such a pharmaceutical product the respective regulatory agency had to refer the application to the CPMP, acting as a so-called rapporteur. The CPMP would then issue an opinion regarding the respective pharmaceutical product. However, the CPMP opinion was (still) non-binding and the decision on market approval remained within

[110] Directive No. 78/25/EEC regulated the colouring matters regarding pharmaceutical products and directive No. 78/420/EEC amended the CPMP procedure by asking the reference member state to send the dossier to both the CPMP and the authorities of the concerned member states.

[111] An illustration of the multi-state procedure is provided in the appendix (A.4).

[112] Another important directive, even though not directly connected to pharmaceutical regulation, released during this phase has been directive No. 84/450/EEC, limiting advertising for prescribed medicine. It has been supplemented by the release of directive No. 89/552/EEC, banning TV advertising for prescribed pharmaceuticals.

[113] The need for action in the pharmaceutical sector was highlighted as well by the *Cecchini* report (1988) published in 1988. Chaired by Paolo Cecchini, the report investigated the benefits of market integration covering all industrial sectors including pharmaceuticals.

[114] Another directive released in the previous year, No. 87/19/EEC, must be mentioned. It established the first rules on good laboratory practice and installed the *Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medical Products Sector* supporting the Commission the adaptation of testing requirements.

the discretion of member state authorities.[115] The main benefit of the concertation procedure should therefore be seen in the facilitation of dialogue between national regulators before a national approval decision was taken (Lorenz, 2006: 55). Another measure in this regard has been the creation of so-called notice to applicants (NTA), developed by the Commission in close cooperation with national regulators and published for the first time in 1986, summarizing and harmonizing the requirements regarding the application dossiers. Obviously, neither the issuance of NTAs nor the procedural changes resulting from directive No. 87/22/EEC did suffice to remedy the shortcomings of the regulatory framework at this point of time.

6.2.2 The first revision of the regulatory system (1989/90): a new start

Twenty-five years after the initial directive founded European pharmaceutical policy, policy developments had reached a cul-de-sac: While standards were continuously harmonized, attempts to harmonize the regulatory process and reduce existing duplication of evaluation efforts were undermined by the prevalent level of mutual distrust between national regulators and the reservations of member states to let go responsibilities within a field closely related to healthcare (Collatz, 1996; Currie, 1990; Feick, 2000; Krapohl, 2008). Despite these drawbacks, and with the 1992 single market deadline approaching, the Commission was forced to push things forward. Starting in 1988, the Commission engaged in an extensive two year consultation process with various stakeholders, including the member states, the pharmaceutical industry, consumer groups and professional associations (European Commission, 1990: 5). Several possible new approval systems were discussed in the course of the consultation process, but preferences of the affected stakeholders and the Commission converged around a blended approach (Abraham & Lewis, 2000; Hancher, 1990; Lorenz, 2006). The results of the two year process culminated in the release of a communication by the Commission titled Future system for the free movement of medicinal products in the European Community (European Commission, 1990). While the proposals envisaged several important changes to the existing regulatory framework, three aspects deserve special attention. First, the Commission proposed a structural change by creating a European Agency for the Evaluation of Medicinal Products (EMA). The new European Agency was based on the existing governance structures, namely the CPMP and the Committee for Veterinary

[115] For an illustration of the *concertation procedure* see the appendix (A.5).

Medicinal Products (CVMP) expanded by additional substantial administrative resources. Instead of substituting national regulators, the EMA was intended to take over a coordinating function between national regulatory resources and act as supervisory and organisational body in the so called centralized procedure. Second, a mutual recognition procedure (MRP/DP) based on the former multi-state procedure was proposed.[116] An applicant looking for market approval in several additional member states, could ask the authority granting market authorization for the first time (reference member state) to forward the assessment report and additional data, as lined out by the former directives, to the respective authorities in the target countries (concerned member states)[117]. The concerned member states (CMS) were expected to recognize the first authorization. As under the former procedure, a CMS could refuse approval. However, acceptance could only be denied on risk to public health grounds. Subsequently, the dissenting national authorities were expected to forward their assessment reports to the other member states and engage in a bi- (or multi-)lateral arbitration phase. If no mutual agreement was reached, the matter was referred to the CPMP. As opposed to the former procedure, the CPMP under the decentralized procedure could now take a binding decision, applicable to all concerned member states. The third change envisaged by the Commission, was the introduction of the centralized procedure (CP). The CP resembled the concertation procedure, since it was compulsory for pharmaceutical products derived from bio-technology. If a producer wanted to apply for market authorization, the application now was directed to the agency, which asked the CPMP to start the procedure. The CPMP then selects a rapporteur responsible for the evaluation of the product and a co-rapporteur. The rapporteur was expected to prepare an assessment report and a draft, subsequently asking the CPMP for its scientific opinion. The CPMP then prepares a scientific opinion, if the respective product should be approved. Given the fact, that the agency does not have the power to take a binding decision, the final (political) decision was ought to be taken by the Commission.[118] The proposed changes resulted in a new regulatory system, offering three different routes to market access. If an applicant wanted to market a product only in one country he could do so by applying to the competent national authority, which would evaluate the application based on the European harmonized criteria (national procedure). However, if

[116] The procedure is referred to as both decentralized and mutual recognition procedure and the revision of the regulatory framework in 2004 introduced the formal separation of a mutual recognition procedure and a decentralized procedure. Accordingly, this study will use the abbreviation MRP/DP.

[117] In 1998, the decentralized procedure became mandatory for all medicines not subject to the centralized procedure and introduced in more than one member state.

[118] Still member states have the chance to oppose to the draft decision by the Commission, starting a comitology procedure on the decision (European Commission, 1990; Krapohl, 2008).

he chose to market the product in more than one member state, one of the two envisaged European procedures would apply. If the product satisfied the criteria, the applicant could apply for Community-wide authorization via the CP. If the product did not satisfy the requirements, he could chose the MRP/DP, which – under the normal condition of acceptance by all concerned member states – would result in market authorization in all concerned member states. The Commission – aware of the political sensitivity of the policy field and the circumstances – chose to build on existing structures instead of radically breaking with the former modest achievements. The resulting approach could best be explained by the positions and preferences of the stakeholders involved. As Martin Lorenz (2006: 58-59) notes, a single centralized approach with the EMA taking all regulatory decisions was unacceptable¸ but national regulators and member state governments were at least willing to accept procedural differentiation. And as the proposed CP only covered a relatively small and specific group of pharmaceuticals, "member states agreed to this new procedure for fields where the distributional consequences for existing national procedures was, so far, not very important" (Feick, 2008: 44). In addition, national regulators could not claim a high level of expertise, as the regulatory capacities in this new field were not as advanced.[119] While industry officials probably would have preferred a centralized procedure open for all products (Abraham & Lewis, 2000; Krapohl, 2008), the newly established and differentiated system offered them a certain degree of selection regarding market approval. Furthermore, the abolition of national regulators within the single market would have resulted in the deprivation of established regulatory ties with national regulators as well as regulatory reputation of regulatees. Following up on the proposals of the Commission, two central pieces of legislation were introduced in 1993. Regulation EEC No. 2309/93 introduced the CP and the EMA.[120] Starting of with the provisions concerning the newly established agency, the regulation specified the role of the EMA as a provider of scientific advice and as a coordinator of regulatory resources, as well as defining the agency organisational structures beyond the CPMP and CVMP, operating procedures and agency funding. As envisaged by the Commission, the second change was the introduction of the CP under title two of the regulation. As outlined in the Commission proposal in 1990, the applicant now submits the required documents to the EMA, which then refers the application to the CPMP. The CPMP selects a rapporteur and co-rapporteur, taking into consideration the preference of the applicant, conducting the scientific

[119] This refers back to the recitals of directive No. 87/22/EEC, claiming that the national regulatory experience regarding certain products was insufficient, mandating the pooling of expertise.
[120] The new agency was to take up its responsibilities effectively from January, 1 1995.

assessment. Based on the scientific advice of the CPMP, the Commission subsequently drafts a decision and in case of no further objection from the member states a market authorization valid throughout all member states is granted.[121] In addition to the procedural and institutional changes, the regulation improved the European system of pharmacovigilance by strengthening reporting requirements of applicants and granting the EMA a supervising and coordinating role regarding national pharmacovigilance systems. The second piece of legislation taking up the proposals of the Commission was directive No. 93/39/EEC. Under the new MRP/DP procedure, an applicant planning to market a product in more than one country could send the required documents to the authorities of the concerned member states and the agency.[122] In addition, he would ask the reference member state to draft an assessment report as the basis for the mutual recognition procedure. As outlined in the proposal, the concerned member states were expected to recognize the first authorization, but had the opportunity to refuse market approval if they could provide evidence that the authorization constitutes a serious risk to health.[123] If no settlement could be reached in bilateral discussion, binding arbitration within the CPMP would start, leading to a *binding* decision by the Commission affecting the concerned member states. Besides the responsibilities under the DP, the CPMP had to be involved in case of dissent regarding the suspension or withdrawal of a certain product. However, if no agreement between national regulators was reached, as in the case of market approval, a binding decision by the Commission was issued.[124] While the introduction of the new procedures and the EMA in the early nineties marked a critical juncture in the development of European pharmaceutical regulation, additional legislative acts altering the legal framework governing the sector were released in the aftermath of the first revision. In December 1988, the so-called transparency directive – No. 89/105/EEC – was released, asking member states to provide information on employed price regulation methods (Abraham & Lewis, 2000; Mossialos et al., 2006; Permanand, 2006). In 1989, directive No. 89/341/EEC amended existing rules by introducing the concept of medicinal product substituting the category of proprietary pharmaceutical product and made package inserts mandatory. Three additional directives, No. 89/342/EEC, No. 89/343/EEC and No. 89/381/EEC expanded the applicability of existing rules to additional product groups. Most

[121] An illustrative overview of the centralized procedure is provided in the appendix (A.6).
[122] The procedure could be started either if a product was still under review in one member state or a first market authorization was already granted.
[123] After the revision of the procedure in 2004, discretion of member states has been reduced. Refusing authorities are now asked to provide suggestions how the objections regarding the product could be remedied according to article 10 of the said directive.
[124] For an illustration of the process see the appendix (A.7).

notably, generic pharmaceuticals not covered by the framework before, were brought under the European rules (Lorenz, 2006: 56). In 1991, a first directive No. 91/356/EEC introduced more specific rules on good manufacturing practice and the second directive worth mentioning, No. 91/507/EEC amended existing testing requirements to cover the previously expanded scope of products. In April 1992, four directives were released. Directive No. 92/25/EEC regulated the wholesale distribution of pharmaceuticals, by making authorization of distributors mandatory. Directive No. 92/26/EEC introduced guidelines for the classification of pharmaceuticals, according to their prescription status. Directives No. 92/27/EEC strengthened already existing rules on the design and content of leaflets accompanying pharmaceutical products, with a special focus on the readability of such documents. Finally, directive No. 92/28/EEC specified existing rules regarding the advertising for pharmaceutical products. In addition to the new rules pertaining to proprietary pharmaceutical products, the European framework became more inclusive by releasing directive No. 92/73/EEC governing homeopathic medicinal products.[125] In 1995 three additional regulations were released. Regulation EC No. 540/95 specified the requirements regarding the development of a better pharmacovigilance system while regulation EC No. 541/95 and regulation EC No. 542/95 established rules regarding the examination of variations to an existing approved product.[126] Resulting from the changes developed during the early 1990s, the new European regulatory regime was implemented in 1995 and its fundamental components remained untouched in the following years. However, article 71 of regulation EEC No. 2309/93 envisaged a mandatory evaluation of the regulatory system, leading to the second revision starting in late 1999.

6.2.3 The second revision of European medicines authorization (2000-2004)

In 1999, the Commission awarded a contract to CMS Cameron McKenna and Andersen Consulting asking for the evaluation of the previously introduced authorization system. The consulting companies presented their report in October 2000. Based on the report, the Commission engaged in an extensive consultation exercise before drafting new legislative

[125] Even though, this study does not consider homeopathic products, the directive is noteworthy. It closed a regulatory *gap* from the public health perspective, since homeopathic products are widely used within the European Union and can have unwanted side effects as well (Calapai, 2008; Lewith et al., 2003; Menniti-Ippolito et al., 2008).

[126] Regulating the variation of an existing authorization was necessary to prevent the complete reassessment in case of minor changes. The regulations were amended three years later, by regulation EC No. 1146/98 and regulation EC No. 1069/98 and have been revised subsequently.

proposals. After intense discussions within EP communities and the involvement of the Council of ministers, two new legislative acts were passed in 2004: directive No. 2004/27/EC and regulation EC No. 726/2004.[127] Preceding the two central pieces of legislation, several additional legal acts worth mentioning were introduced. Between 1999 and 2000 two regulations aiming at the improvement of the regulatory regime regarding the development of orphan drugs were passed. Regulation EC No. 2000/141 entailed a definition of an orphan drug and established the Committee for Orphan medicinal products within the EMA, responsible for granting *orphan* status to submitted pharmaceuticals, based on the criteria specified further in regulation EC No. 2000/847 (Watson, 2000). In the following year directive No. 2001/20/EC specified the rules on good clinical practice, strengthening the requirements in the pre-authorization phase. Since the regulatory framework during this stage was based on a large number of single documents and became increasingly complex, it was integrated by the introduction of directive No. 2001/83/EC, representing the new fundamental piece of European pharmaceutical legislation. Based on directive No. 2003/63/EC, the requirements for application dossiers were harmonized further. The directive implemented the Common Technical Document (CTD) developed within the ICH. The second directive No. 2003/94/EC released in that year, specified the rules regarding good manufacturing practice with a special focus on investigational medicinal products. Regulation EC No. 1084/2003 and EC No. 1085/2003 amended existing provisions on the examination of variations regarding authorized products.

6.2.3.1 General modifications based on the revision process

Turning to the changes resulting directly from the revision process, it should be noted that they were rather moderate compared to the first revision of the regulatory framework in the early 1990s. Nevertheless, the revision altered the framework in several ways. Starting off with symbolic changes, several institutional features were renamed. The agency was rebranded *European Medicines Agency* (EMA) and the CPMP was renamed to *Committee for Medicinal Products for Human Use* (CHMP). Mainly due to the Community enlargement in 2004, the composition of the CMHP was changed. Besides one member from each of the (now) 25 national agencies, five additional members could be chosen in order to bring in specific expertise. In addition, the CMHP was empowered to establish standing and temporary working parties. Another change affected the board of the EMA which now

[127] For a detailed analysis of the policy-making process see Andreas Broscheid & Jürgen Feick (2005).

included one representative from each Member State, two representatives of the European Commission, two representatives of the European Parliament, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations.[128] An important harmonization was reached regarding the data exclusivity and protection, leading to the so-called 8+2+1 formula or bolar provision (Roox, 2006). The data needed to submit an application dossier was protected for eight years. After this period, generic producers were allowed to draw on the scientific data and prepare their application even though they were not allowed to market their product until the ten-year mark had passed. In effect, this meant 8 years of data protection and 10 years of market exclusivity. If the respective producer could demonstrate an additional therapeutic benefit of his product, he could even prolong this period by one additional year (Lorenz, 2006: 216). The transparency of the regulatory process was improved by making the publishing of assessment reports mandatory under both procedures.[129] While the previous framework mandated a new assessment of a market authorization every five years, the new provision envisaged one mandatory evaluation of the respective product. After re-examination, however, the market authorization – given a consistent risk/benefit ratio – will be valid without limitation. Another change affecting market authorization was the requirement to market a medicinal product within three years from approval. If an applicant failed to do so, the obtained market authorization will be invalid.

6.2.3.2 Changes affecting the centralized procedure

While the CP had been evaluated positively by most stakeholders (CMS Cameron McKenna & Andersen Consulting, 2000), the Commission proposed several improvements. First, the scope of the procedure was widened, by including medicinal products based on a new active substance or intended for certain therapeutic indications and orphan drugs.[130] Opposed to earlier regulation, it was now possible for a generic medicinal product to receive market approval through the centralized procedure. In principle, the procedure was opened up for other medicinal products offering therapeutic benefit or a special benefit to patients as well. The timelines during the political phase of decision making were tightened and an accelerated assessment procedure was set up, reserved for medicinal products of major therapeutic

[128] During the legislation process, industry representatives tried to lobby for participation in the management board but eventually failed (Broscheid & Feick, 2005: 25).
[129] For the centralized procedure, the European public assessment report (EPAR) was introduced.
[130] As defined in the annex of the said regulation the scope was expanded again in May, 2008.

interest and making specific post-authorization controls necessary. Furthermore, the reduction of fees payable for authorization through the CP for small and medium enterprises was introduced.

6.2.3.3 Changes affecting the decentralized and mutual recognition procedure

Compared to the CP, the MRP/DP was exposed to extensive criticism during the review process (CMS Cameron McKenna & Andersen Consulting, 2000).[131] Accordingly, more far-reaching changes compared to the CP were entailed in directive No. 2004/27/EC. To strengthen the voluntary elements of the process, the previously existing informal mutual recognition facilitation group (MRFG) was transformed into the coordination group (CMD(h)) and was granted administrative support by the EMA. An important change from a procedural perspective was the modification of the binding arbitration procedure. Under the new rules, withdrawal of the product from one of the dissenting concerned member states did no longer prevent binding arbitration. In addition, concerned member states willing to accept the first assessment were now allowed to grant a provisional market approval. Another change to strengthen mutual recognition within the MRP/DP, was the altered sequence. The RMS was expected to share his draft assessment with the CMS's before taking a decision, providing for additional bi-lateral and multilateral discussion.

6.2.4 Recent developments in the regulatory framework

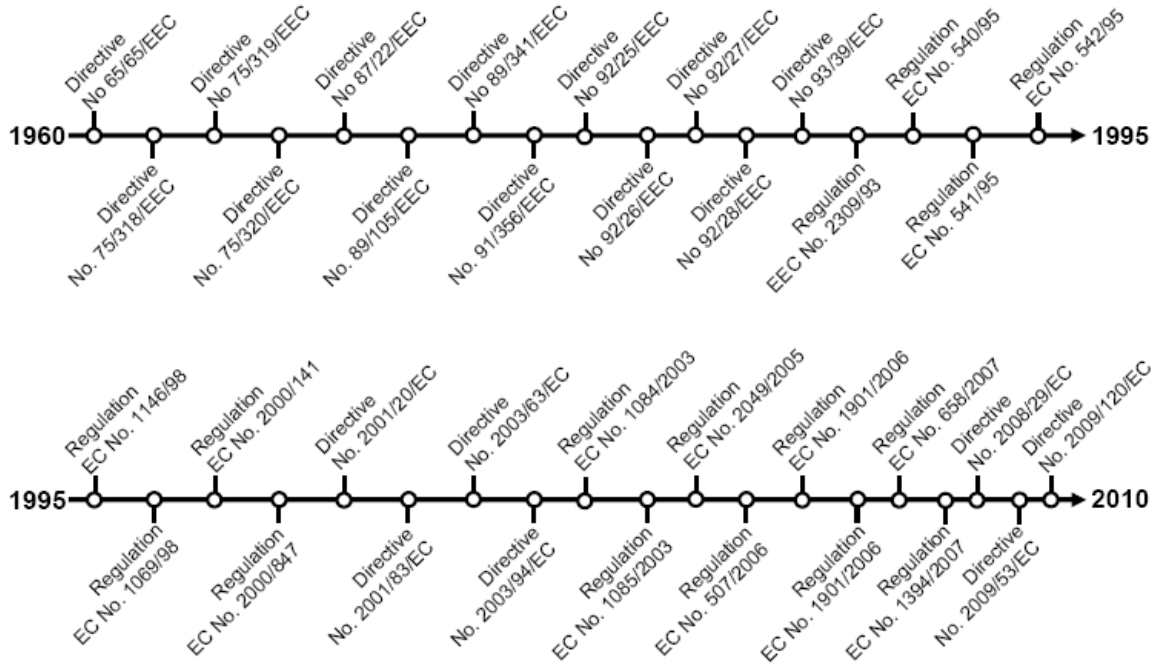
After the second revision, policy developments in the pharmaceutical sector did not lose its dynamic, even though the focus of new legislative acts shifted from the institutionalisation of the regulatory system to its modification. In 2005, directive No. 2005/28/EC integrated former provisions on clinical practice by establishing new guidelines and developing control mechanisms. The same year, regulation EC No. 2049/2005 was introduced, regulating additional support for small and medium enterprises regarding the approval process. 2006 saw the issuance of several legal acts, beginning with Regulation EC No. 507/2006 introducing a conditional market authorization.[132] In December, two additional regulations, EC No. 1901/2006 and No. 1902/2006, concerning medicinal products for paediatric use were

[131] A mutual recognition procedure (MRP) applies, if the product already has received a market authorization in one member state, opposed to the decentralized procedure (DP) where no market authorization has been received prior to the application.

[132] A conditional authorization is granted, even if not all the data necessary for an application can be provided.

released. The most significant changes resulting from the two regulations were the creation of a new paediatric committee (PDCO) within the EMA and the introduction of the so-called paediatric investigation plan (PIP). Since children were not covered in most clinical studies, even though representing a significant subset of the consuming group, the new regulation made the consideration of aspects related to paediatric use in clinical trials mandatory (Auby, 2008).[133] In 2007, two regulations were passed. Regulation EC No. 658/2007 provided the agency with additional powers for sanctioning non-compliance of market authorization holders and levy fines at least indirectly.[134] The second one, regulation EC No. 1394/2007 broadened the scope of the centralized procedure by including advanced therapy medicinal products. Directive No. 2008/29/EC released in March, 2008 clarified the competencies of the Commission regarding changes of the pharmaceutical regulatory framework. Directive No. 2009/53/EC amended directive No. 2001/83/EC regarding the terms of variations to an authorized product and in September 2009, directive No. 2009/120/EC was released, adapting the annex of directive No. 2001/83/EC to account for the increasing importance of advanced therapy medicinal products.

Graph 12: Overview of key European regulatory legal acts (1965-2010)



Source: author's own

[133] A waiver can be granted releasing companies from the obligations. However, the EMA has been restrictive in granting waivers and even engaged in litigation in the case of *Nycomed* (Brizmohun, 2009).

[134] The general possibility to sanction regulatees had already been introduced by regulation EC No. 726/2004, but had to be specified further. Formally, sanctions are implemented by the Commission on request of the agency (Killick, 2007).

At the time of writing, the Commission has engaged in a new review initiative of the regulatory framework to promote its regulatory goals in the pharmaceutical sector. Since these measures are still in the legislative process the potential impact of anticipated changes will be discussed briefly in the ninth chapter.

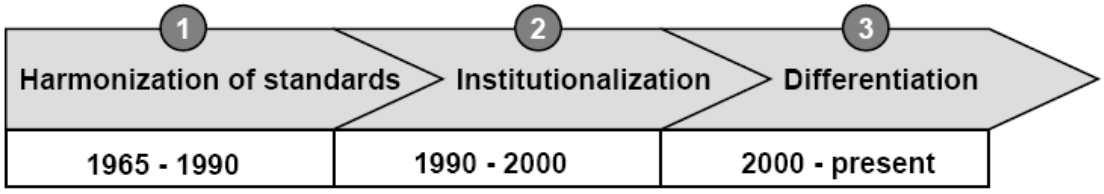
6.2.5 Development paths of European pharmaceutical policy

The main aim of the previous section was to provide a descriptive overview of the policy developments in the pharmaceutical sector. At first sight, the process seemed to be marked by a steady flow of legislation but at same time shaped by coincidences and partial congruence of stakeholders' preferences instead of a clear and distinct strategy.[135] At second glance, however, a development path emerges: summarizing the policy developments it can be argued, that the process started with the harmonization of standards (1), subsequently shifted towards institutionalisation (2) – flanking the still ongoing harmonization of standards – and finally lead to the consolidation and differentiation of the regulatory regime (3). This development path can be projected on the actual timeline. The first policy phase – focusing on the harmonization of standards – started with the release of directive 65/65/EC and ended with the first revision of the pharmaceutical regulatory framework in the 1990s and the instalment of regulatory structures in 1995. As it has been shown, the discussion of the future system started with the consultation process under the hospice of the Commission. Furthermore, the increased legislative activity during the early 1990s could be attributed to the policy dynamics leading to the creation of the new system, rather than being the result of the developments in the first phase. The second phase of institutionalisation, started with the first revision process in 1990, the subsequent instalment of the European agency and the foundation of the still existing (yet adapted) authorization system consisting of a national, a decentralized and a centralized procedure entering into force in 1995. The year clearly marked a critical juncture in the policy process: Besides the creation of an European agency, the successful establishment of European regulatory/authorization structures – mainly through changes in the competencies of existing institution – fundamentally changed the regulatory landscape (Collatz, 1996; Jefferys & Jones, 1995). While the starting point of the second phase can be defined based on previous consideration, at least two endpoints seem to be

[135] This assertion is supported by Govin Permanand claiming that "the history of European pharmaceutical regulation is an inconsistent one" (2006: 53). However, from a theoretical perspective this inconsistency seems to be rather comprehensible as different interests had to be accommodated (Krapohl, 2008).

possible. Using the general perspective applied in the specification of the first phase, no specific cut-off point could be determined and the second phase would be still ongoing. Using such an inclusive definition could be justified, since the basic regulatory system has remained largely untouched despite undergoing several changes. Opposed to this inclusive view, the changes resulting from the second revision and the corresponding legal acts published in 2004 can be used as an alternative cut-off point.[136] While leaving the fundamentals of the regulatory system untouched, the revision nevertheless impacted on the effectiveness of the regulatory system as a whole. An additional practical argument for distinguishing a third phase could be invoked. Since the majority of the changes resulting from the revision process came into force at the time of writing it is too early to discuss their impact on the underlying effectiveness of the system with certainty and in greater detail. In line with the argumentation used to justify the starting point of the second phase, the third phase starting in 2000 until the present day will be used in this study.

Graph 13: Development path of the European regulatory framework



Source: author's own

6.3 Evaluating the effectiveness of the regulatory framework

Using the three policy phases as a structuring device, the effectiveness of the regulatory framework can be assessed. The evaluation is conducted in three consecutive steps. First, it must be assessed in how far a clear regulatory goal has been formulated. In a second step, the coverage of the regulatory lifecycle within the regulatory framework will be considered. In a third step, the framework will be discussed from a good governance perspective using the principles of regulatory quality developed in the fourth chapter.

[136] An additional argument for the distinction of a second and third phase is, that many studies treat the '2001-2004' revision as such a cut-off point (Broscheid & Feick, 2005; Feick, 2008; Lorenz, 2006; Nettesheim, 2008).

6.3.1 Regulatory goals: public health, a single market and a competitive industry

The general aim of European pharmaceutical regulation was established by the first directive No. 65/65/EEC and has remained constant throughout the process. The first two recitals of the said directive state that:

> "the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health; Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community"

Flowing from this definition, the primary policy aim of European pharmaceutical regulation is the safeguarding of *public health*. However, based on the formulation used in the directive, this goal should be achieved in accordance with the policy goal of *industrial development* and the goal of *market creation* (Collatz, 1996; Lorenz, 2006). Instead of providing one clear policy goal, European regulation is thus based on three and potentially conflicting policy goals. While it could be argued that this tension is mediated by granting safety considerations priority over industrial and economic considerations, some doubts from a consumer perspective remain (Collatz, 1996).[137]

6.3.2 The regulatory framework and the regulatory lifecycle

Based on the policy goals lined out in directive No. 65/65/EEC, it must be asked in how far the resulting framework is designed to adequately fulfil them. An effective regulatory framework needs to cover all regulatory aspects with a potential impact on the achievement of the regulatory goal. Based on the discussion of regulatory challenges in the pharmaceutical sector in the previous chapter, this implies that the whole regulatory lifecycle, including pre- and post-authorization aspects, is covered.

6.3.2.1 The first phase: Harmonization of standards (1965-1990)

The release of the first European directive in 1965 did not only mark the start of the first phase but structured the regulatory framework in several important respects, mainly by defining its boundaries. It established the scope of the framework by defining, which products

[137] The ECJ has repeatedly struck down national legal acts aiming to safeguard *public health*, as obstacles to free trade (Kanavos, 2000). On the other side, the Commission increasingly came to understand that the protection of consumer interests has to be considered in the (general) integration process (Pollack, 1997b).

should be covered by regulation. While the focus was on proprietary pharmaceutical products, the directive established an important rule from the perspective of consumer protection. Aware of the problems connected to the delineation of pharmaceuticals and other product groups especially cosmetics, the directive established that *borderline cases* and products belonging to both categories would be treated as a pharmaceutical and therefore subjected to stricter controls (Collatz, 1996: 35). During the following years the definition of products covered by the regulatory regime was updated regularly, leading to a more targeted and differentiated application. In addition, the directive mandated pre-authorization approval of all products falling under the definition of a pharmaceutical product and established approval criteria on which the assessment should be based.

Starting with the regulation of development, the introduction of mandatory approval based on directive No. 65/65/EEC and the criteria of safety, quality and efficacy contributed significantly to the establishment of pre-authorization controls of pharmaceutical product risks. Producers were now obliged to produce data on their products in the course of the development process. These requirements remained rather general until the release of directive No. 318/75/EEC, concretizing the testing requirements underlying the application. In addition to the said measures, directive No. 83/570/EEC specified the testing requirements. While not representing a legal measure in the strict sense, the issuance of NTAs starting in 1986 could be seen as an additional improvement regarding the safety aspects connected to the development process. With the instalment of the Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medicinal Products Sector in late 1986, the Commission created additional supranational expertise to continuously update testing requirements. In this regard the issuance of directive No. 87/19/EEC should be mentioned, as it introduced the concept of good laboratory practice (Collatz, 1996: 40).

Turning to the second aspect of the pre-authorization stage, the actual approval process, the first phase saw the instalment of mandatory market authorization, the definition of underlying decision criteria and the general requirements for the approval process as laid down in directive No. 65/65/EEC. A notable advancement in rationalizing the process was the introduction of Standard Product Characteristics (SPC) as a uniform format for application by directive No. 83/570/EEC. From a public health perspective, the establishing of the CPMP has to be highlighted as well. Supranational expertise drawing on member states' regulatory resources was created in order to support national regulators in decisions on market approval.

While the role of CPMP was of specific relevance in the case of the multi-state and the concertation procedure, its instalment was of general importance for the effectiveness of the system as a whole.

Considering the regulation of the production process, directive 75/319/EEC introduced mandatory authorization for pharmaceutical manufactures and required manufacturers to employ a qualified person responsible for the manufacturing process. These rules were complemented by calling on national competent authorities to carry out inspections of manufacturing sites to continuously monitor, if the requirements of the manufacturing authorization were still met. In addition, manufacturers were obliged to adhere to the guidelines on good manufacturing practice (GMP).[138]

While manufacturing was already subjected to considerable regulatory activity during the first phase, this has not been the case in the field of distribution. Trade was regulated, since importers of pharmaceutical products needed an authorization as well based on the requirements of directive 75/314/EEC.[139] In contrast, the distribution to end consumers in more general terms remained unregulated at the European level at this point in time.

Regarding information requirements, directive No. 65/65/EEC created rules for the appropriate (external) labelling of proprietary pharmaceutical products including specific information, for example, the mode of administration. However, it must be stressed that at this point in time no additional information for customers were mandatory. While the specifications for such additional information in the form of a leaflet were introduced in 1975, they became mandatory in 1989. In addition, the introduction of directive No. 89/552/EEC banning TV advertising for pharmaceuticals strengthened the regulatory framework regarding the availability of right information.

It could be argued, that directive No. 65/65/EEC already envisaged responsibilities of post-authorization monitoring and pharmacovigilance, since withdrawal and suspension of market authorization were ought to be based on the failure to fulfil the approval criteria. However, these responsibilities were obviously rather general and did not mandate the establishment of a systematic pharmacovigilance approach. This situation only changed partially during the first phase. Directive No. 75/319/EEC did entail more specific requirements for supervision of manufacturing and products on the market, but did not specify how data should be gathered in

[138] Adherence to these guidelines was envisaged in directive No. 75/319/EEC and No. 75/318/EEC and the requirement was specified further in directive No. 89/341/EEC.

[139] In 1976, the ECJ established the legality of such economic activity with its ruling in *De Peijer* (Case 104/75) in context of parallel trade, as long as licensing requirements were met (Darbá & Rovira, 1998: 133).

a systematic way. However, the CPMP was now ought to be notified in case of market withdrawal. Finally, directive No. 89/341/EEC introduced reporting requirements for the pharmaceutical producers in case of product withdrawal.

6.3.2.2 The second phase: Institutionalization (1990-2000)

The policy developments between 1990 and 2000 strongly focused on procedural and approval aspects of the regulatory system. However, several changes affected the other aspects of the regulatory lifecycle.

While no new legislative acts were passed affecting the stage of development during the second phase, the density of regulation was increased by employing a soft law approach and the issuance of further guidelines.

Considering the approval process, the establishment of the new approval procedures was an important improvement both from the perspective of European regulatory capacities and the safeguarding of public health. By expanding the competencies of the CPMP in both procedures, cooperation between national regulators was strengthened further. In addition, the introduction of different procedures for market approval incentivized pharmaceutical companies to develop innovative pharmaceuticals, as the market authorization for the whole community implied a reduction of regulatory costs. Moreover, the introduction of new rules regarding the approval of variations to authorized products should be seen as an important step from a point of rationalization. Even though released lately in the second phase, the introduction of the orphan regulation in December 1999 was an important step regarding the improvement of access to medicine at this point as well. It created specific incentives for producers willing to engage in research on ailments for rare diseases. No specific application procedure for these drugs was created, but additional support and specific requirements for the approval process were introduced (Hoppu, 2008; Watson, 2000).

The safety requirements regarding the production process were mainly altered by the introduction of directive No. 91/356/EEC introducing new manufacturing guidelines. As in the case of development standards, the regulation of manufacturing evolved steadily on the basis of soft law instruments, most importantly through the issuance of guidelines (Sarantopoulos et al., 1995). In addition, the creation of the EMA responsible for supervision of manufacturing strengthened the existing regulatory framework.

No fundamental changes to the rules governing (parallel) imports and trade in more general terms were introduced during the second phase. However, in 1992 directive No. 92/25/EEC closed a prevalent regulatory deficit of the first phase – the distribution of pharmaceutical products – by making an authorization for distribution mandatory. Furthermore, the Commission in collaboration with the CPMP was requested to develop guidelines on good distributional practice (GDP). Another change affecting the distribution in a wider sense was introduced by directive No. 92/26/EEC, harmonizing national rules regarding the classification of products.

The most significant changes to the framework from a public health perspective were enacted regarding information requirements. Directive No. 92/27/EEC strengthened existing provisions on the information, accompanying a pharmaceutical product. From now on, producers were obliged to insert package leaflets in accordance with the information entailed in the SPCs.[140] Directive No. 92/28/EEC amended existing regulation on advertising, effectively reducing the potential of possible misleading information on (prescription) pharmaceuticals.[141] With regard to the overall transparency of the decision process, little progress was made in the second phase. Even though assessment reports for products authorized in the decentralized procedure were not intended to be published, transparency was at least improved regarding the centralized procedure through the introduction of European Public Assessment Reports (Abraham & Lewis, 1999).

The previously existing European legal framework provided only insufficient regulation of monitoring and pharmacovigilance. This changed with the instalment of the EMA and the pharmacovigilance requirements laid down in directive No. 93/39/EEC and regulation EC No. 2309/93. Most notably, producers were now mandated to have a qualified person for pharmacovigilance at their service responsible for regularly updating safety information on marketed products and sharing of this information with the competent authorities (Brown, 2005). National authorities were requested to install pharmacovigilance systems and asked to exchange these information with the agency and within the network of national regulatory agencies.[142]

[140] Another important requirement in this regard was that pharmaceutical leaflets must be written in a comprehensible manner (Anon, 1995a; Kenny et al., 1998).

[141] However, the directive did not only cover promotion to the public, but entailed regulations regarding the provision of information to the dispensing doctors.

[142] It should be noted, that the pharmacovigilance requirements at this point were formulated in a rather general way, prompting the need of further guidance.

6.3.2.3 The third phase: Differentiation (2000-present)

The third development phase in pharmaceutical regulation led to the consolidation and differentiation of the existing regulatory framework. This is demonstrated for example, by the introduction of directive 2001/83/EEC integrating most of the existing rules developed in the course of nearly four decades. In addition, the framework was consolidated further by the continuous revision of EudraLex, including all rules and regulations comprising the legal regulatory framework. As in the previous phases some specific changes regarding the distinct regulatory aspects must be mentioned to illustrate the dynamic of developments in this phase.

Despite releasing several guidelines on the conduct of clinical requirements, the most important change in the regulation of the development process must be seen in the release of the clinical directive, No. 2001/20/EC, and the additional rules laid down in directive No. 2005/28/EC, streamlining clinical trials throughout Europe.[143] Additional changes were introduced by the new paediatric regulation in 2007 improving safety especially for the patient group of children (Jong et al., 2002; Kölch et al., 2007; Seyberth et al., 2005).

While the approval process regarding the centralized and decentralized procedure was altered during the second revision, these modifications had only minor impacts on the overall effectiveness of the legal framework. Tthe scope of products to be assessed under the centralized procedure was widened, but no changes were introduced regarding the assessment itself. A change with a possible impact on public health protection was the restriction of reasons for refusal of an initial assessment within the MRP/DP. In contrast it can be argued that instead of taking the possibility from member states to react to health risks, the possibility to block market access based on unqualified reasons was reduced. Four additional important aspects from the perspective of public health must be mentioned in this regard. First, the creation of an accelerated approval procedure and the general tightening of timelines under the CP improved the access to new and innovative drugs by speeding the regulatory decision. Second, in 2004, compassionate use was increasingly legalized improving access to medicine (Suñé-Arbussá, 2009). Third, the new approval regime foresaw the possibility of conditional approval contingent upon additional requirements (Carroll et al., 2008). Fourth, an increased pre-application discussion between the applicant and the respective agency was

[143] Comments from academia and industry suggest that the directive did neither improve patients' (and test subjects') safety nor strengthened the competitiveness of the European pharmaceutical industry (Houlton, 2004; Woods, 2004).

encouraged.[144] Some authors believe that these changes negatively affect public health, as they represent a relaxation of approval requirements (Abraham & Davis, 2007). However, this view could be challenged, as approval still is based on the same criteria, mandates essentially the same pre-authorization assessments and in those cases were a conditional approval is granted, the producers is obliged to fulfil strict reporting requirements.[145]

Regulations concerning production were included in directive No. 2001/83/EC as well and the release of directive No. 2003/94/EC amended previous rules on manufacturing which were subsequently advanced by the release of additional guidelines in Volume 4 of EudraLex. However, the level of regulation concerning this aspect remained constant.

The same assertion holds true regarding the distribution of pharmaceuticals. Existing rules were included in the newly established directive No. 2001/83/EC, without changing the underlying rules and therefore the regulatory impact.

While no changes were made regarding the labelling and leaflet requirements, the revision process affected the regulation of information as public availability of data was increased. New regulation mandated the publication of assessment reports – after clearing commercially sensitive information – under the DP and greater openness regarding the previously introduced European Public Assessment Reports (EPAR) under the CP (Pimpinella & Bertini Malgarini, 2007). Furthermore, the EMA was mandated to make publicly available pharmacovigilance information.[146]

Turning to the regulation of monitoring and pharmacovigilance, new legislation strengthened the role of the EMA regarding the coordination of pharmacovigilance activities, most notably the creation of an electronic system, and the introduction of measures for increased collaboration between national regulators. In addition, the signalling of ADRs by patients channelled through the respective physician was encouraged. Extensive obligations of pharmaceutical producers were introduced and the mandate of the responsible person was widened (Lorenz, 2006).[147]

[144] Pre-application consultation has been a task of the EMA since its foundation (Dejas-Eckertz & Schäffner, 2005).

[145] Discussions before the application procedure can be understood as a rationalization of the process and therefore can be expected to have a positive effect on approval success and public health (Regnstrom et al., 2009; Toivonen, 2005).

[146] This provision led to the creation of the electronic pharmacovigilance network which can be accessed under www.eudravigilance.org. Public access to the side is still restricted.

[147] Another important change has been the introduction of the so-called *EU risk management plan* (EU-RMP) for products based on new chemical entities, mandating detailed additional post-market studies on possible ADRs (Giezen et al., 2009).

And as in other fields, the increased use of guidelines could be seen as measure to strengthen the self-regulatory aspect of the regulatory framework.[148]

6.3.3 Regulatory principles within the regulatory framework

Assessing the realisation of policy principles, the regulatory framework in its current is considered, referencing to previous periods and evolutionary steps throughout time.

Beginning with openness, the framework did only partially cover the principle during the first two policy phases. The European framework largely adapted the national regulatory approach based on regulatory secrecy, which has been criticized repetitively in the national and European context (Abraham & Lewis, 1998; Boissel & Chiquette, 1999; Kopp, 2000). The informational requirements were rather limited and the framework provided regulators with the opportunity to invoke confidentiality as a reason to withhold information to the wider public (Kesselheim & Mello, 2007). Even though room for improvement remains, the changes enacted in the third phase support the assertion that the legal framework moved towards greater respect for the principle: The introduction of transparency measures and the publication of assessment reports as a result of the second revision may serve as a proof in this regard.

At first glance, the realisation of participation in the European framework is skewed: While consumers are only mentioned in an indirect manner, the framework largely focuses on the participation of the pharmaceutical industry (Collier et al., 1997). However, based on the previous analysis of the regulatory acts – and in opposition to the findings of former studies (Abraham, 2002a) – the current framework does not seem to reflect an overwhelming industry bias, which would indicate a lack of participation or acknowledgement of other interests. While the policy process itself surely has been driven by the pharmaceutical industry (Permanand, 2006) this does not preclude, that the resulting policies automatically reflect a business position. In fact, it did not prevent the European Commission from recommending increasingly stricter regulation, for example the clinical trials directive and the paediatric regulation primarily serving consumer safety interest, while at the same time leading to

[148] While an increase in guidelines might represent a positive aspect, concretizing the at times rather general requirements laid down in the legal acts, they might cause an overburdening of regulatees signifying the emergence of overregulation (Tor & Brian, 2008).

increased regulatory compliance costs (Ladds, 2004; Watson, 2003).[149] Again, the third policy phase had been decisive in the advancement of public interest, probably leading to a more balanced consideration of interests at least at the level of regulation. Even though consumers are still excluded from regulatory assessment, the most recent changes to the EMA structure providing permanent representation for consumer groups point into the same direction.[150]

Turning to the principle of accountability, the policy framework did clearly address the responsibilities of the actors within the regulatory field – except for those fields where no regulation was put in place at that time – from the beginning. An example for the assignment of responsibilities and an increase of accountability could be seen in the gradual introduction of responsible persons in the different subfields, for example production and monitoring. However, while these examples support the notion, that the framework realises accountability, it should be noted that the legal framework has been perceived as providing only relatively general requirements leading to subsequent problems in compliance (Tor & Brian, 2008).

The principle of coherence, both in its internal and external meaning, is traceable throughout the regulatory framework. While coherence in the first policy phase was lacking because the regulatory lifecycle was only covered partially, this changed during the second and third phase. The external coherence became visible for example in the case of advertising regulation, incorporating and specifying existing rules entailed in other directives.

As the discussion of preconditions at the beginning of this chapter revealed, the current regulatory approach based on market approval and additional regulatory mechanisms in the post approval stage represents a justifiable intervention in the market. Accordingly, the requirement of proportionality is fulfilled within the regulatory system. Since less intrusive regulatory approaches were deemed insufficient, the current approach can be considered a proportional regulatory answer.

Closely connected to the principle of proportionality, the adequate targeting of the regulatory problem within the framework has been achieved. While directive No. 65/65/EEC clearly defined the scope of the regulatory framework, problems of delineation between pharmaceuticals and other product groups, for example cosmetics, can be seen as a derogation

[149] This argument can be generalized in the context of European pharmaceutical regulation. Stricter rules resulting in considerable compliance costs have been introduced in many areas, explaining increased discussions on the need to streamline pharmaceutical regulation on the European level (European Commission, 2007).

[150] However, recent studies on the funding of consumer and patient groups may raise concerns on the positive effect on balanced representation. Most groups working with the EMA are funded by the pharmaceutical industry (Lambert, 2009; Mintzes, 2007)

from the principle of targeting. However, based on the rulings of the ECJ and the resulting non-cumulation rule (Gagliardi & Dorato, 2007: 6) it seems that the still existing ambiguity in this field is tolerable.[151]

The sharing of regulatory burden within the regulatory framework seems to represent an imbalanced situation, as the regulatory costs are borne almost exclusively by the pharmaceutical industry. However, two arguments can be made to correct this perspective. First, the framework does not only burden the pharmaceutical companies but national regulators as well. National regulators had to adapt to the rules implying compliance costs for these agencies. Second, pharmaceutical companies do not only carry the burden of regulation but realize profits from approved products, legitimizing the prior imposition or regulatory burdens.

Finally, the current framework influenced by prevailing considerations of political necessity puts a strong emphasis on the respect for the principle of subsidiarity (Gehring et al., 2005). Member states' competencies are clearly delineated within the policy framework and while supranational competencies were increasingly expanded throughout the policy phases, the general design principle underlying the regulatory framework was not abandoned. The framework still builds on national activities, expertise and regulatory resources, increasingly coordinated throughout the policy phases (Dehousse, 1997). Judging from the regulatory framework and considering the distribution of regulatory work, the network approach to regulation is dominated by the national regulators, rather than by the European level. While the EMA has increased European level steering capacities, it largely depends on the resources of the national agencies.

6.3.4 The transposition of European rules

While the (de jure) effectiveness of European regulation depends on the regulatory framework, the peculiar characteristics of the European regulatory system represent a potentially intervening variable since "effective regulation not only depends on legislative decisions, but also on the extent to which these decisions are actually implemented and complied with."(Knill & Lenschow, 2003: 7).

[151] Non-cumulation means that a product can either be a pharmaceutical or a different product but not both.

As the analysis of the legal framework has shown, regulation of pharmaceuticals is mainly based on directives raising possible issues of right transposition. Transposition problems can be of mere temporal nature, if member states chose to ignore the deadlines for transposition.[152] Qualitative compliance issues however turn out to be more critical. Member States could for example choose to engage in gold plating, raising national standards beyond the intentions of the European regulator, or choose the opposite and implement national measures not adequately transposing the content of the European directive.[153] Given the potential existence – and distorting effects on regulatory effectiveness – of such transposition problems, compliance issues regarding European pharmaceutical regulation must be assessed.

There are two possible approaches in measuring (correct) transposition. Either, transposition is measured directly by focusing on the national, or the lack of transposition from a European level perspective is measured. Studies based on the first approach, measure transposition based on national data and notification obligations regarding the implementation of European directives (Kaeding, 2006; König et al., 2005; Mastenbroek, 2003). The alternative approach applies a proxy-measure in assessing compliance by measuring the degree of non-compliance from the European perspective. Usually, this is done by relying on the monitoring activities of the Commission and infringement procedures more specifically (Börzel, 2001; Perkins & Neumayer, 2007). In deciding which approach should be employed, the complementary character of the two perspectives must be emphasized. Transposition is either achieved or not achieved. Considering the higher complexity of data generation and the possible differences in the conceptualization of compliance, assessing non-compliance from the European perspective has the principle advantage that data availability and data gathering constitutes at least a smaller problem. The Commission has been publishing annual reports on the application (and transposition) of Community law at least since 1984.[154] Furthermore the Eur-Lex database enables – even though limited – research on the infringement procedures considering the last two steps. Moreover, the focus on non-compliance reduces the underlying ambiguity regarding the correctness of transposition: The Commission will most likely start an infringement procedure if it has a reason to believe that member states failed to comply.

[152] For a discussion of the national differences in *timeliness* and problems of measurement see (Falkner et al., 2005; Hartlapp & Falkner, 2009; R. Thomson, 2009)

[153] Compliance research differentiates between problems of *timeliness* and problems of *correctness* in transposition (Falkner et al., 2005; Kaeding, 2006; König et al., 2005).

[154] The reports are available on the internet. Unfortunately, it was not possible to retrieve the reports for the phases from 1984-1989 and 1991-1992.

Despite these advantages, the analysis of transposition using infringement data is flawed as well. Infringement data represents an incomplete picture of the real extent of transposition, as they merely represented a subset of the transposition process or put differently the "'tip of the iceberg' of non-compliance [original emphasis]" (2009: 292).[155] Monitoring activities and the general approach to monitoring can be described as inconsistent over time and influenced by strategic considerations of the Commission, leading to differing levels of scrutiny (Hartlapp, 2008; Hartlapp & Falkner, 2009; Mbaye, 2001). The Commission and more precisely the responsible units will thus have to make a choice in which areas they will make an effort to investigate cases of non-compliance and were to pursue infringement proceedings.[156] Another limitation for analysis based on infringement data could be seen in data availability: transposition was not monitored in a comprehensible form before 1984, limiting the usability of infringement data for the assessment of transposition in the specific case of pharmaceutical regulation.[157] Weighing benefits and drawbacks of the two possibilities, the advantages of a non-compliance approach seem to justify its usage at least as a rough estimate of transposition.[158]

Looking at previous studies of pharmaceutical regulation, it is rather surprising that transposition into national law has not been assessed in a systematic way, neither on the aggregated nor on the single case level. One notable exception is the analysis by Matthias Wismar and his colleagues (Wismar et al., 2002) discussing transposition patterns regarding health related directives focusing on Germany compared to the UK, Spain and Sweden.[159] In addition, several studies partially consider the transposition of European measures within the reform process of legislation on the national level (Hohgräwe, 1992; Murswieck, 1983; Smith, 1991; Winter, 2004). However, these studies focus on the qualitative impact of European law as a contextual variable, rather than tracking the general national transposition records over a longer period of time.

[155] While it is necessary to highlight the relativity of results based on European data, Kaeding (2008) is right in noting that despite issues of data quality, the results confirm the existent of a general implementation deficit.

[156] This will depend on a variety of factors, for example the position and capacities of the respective units (Hartlapp & Falkner, 2009).

[157] While Eur-Lex covers the whole period, serious data problems especially regarding the completeness of data prevail (Börzel, 2001).

[158] An optimal approach would combine European *non-compliance* and national *compliance* data and has been employed in few studies, focusing on a small number of countries (Haverland & Romeijn, 2007; Mastenbroek, 2003). Since the main focus of this study is not on transposition and the gathering of national data for the pharmaceutical sector for all 27 member states is not possible from a pragmatic perspective, the following discussion will be limited to the *European* data.

[159] However, Matthias Wismar and his colleagues (2002) do not discuss pharmaceuticals in greater detail.

The next two sections will assess in how far key directives in the pharmaceutical sector have been transposed, based on the notifications by the member states entailed in Eur-Lex and the annual reports. Unfortunately, the data availability in the first policy phase (1965-1990) is seriously limited. While the annual reports have been published since 1984, it was not possible to retrieve the documents for the period of 1984-1989. Eur-Lex covers the entire phase allowing at least for the tracking of National Execution Measures (NME). Acknowledging the fact, that the assessment of NMEs can only provide an overview of general transposition dynamics rather than a measure of correct transposition, it will be assessed, if infringement procedures are commonly used in the pharmaceutical sector based on the data in the annual reports. To assess the transposition dynamics in the pharmaceutical sector, data on NMEs from all member states were gathered for five key directives in each of the three policy phases.[160] In addition, the year of the most recent measure and the timespan between the official transposition deadline set up by the EU and the most recent measure, calculated in years, were included to estimate the respective transposition time lag.[161] While the reliability and explanatory value of these two variables should not be overstated, it provides at least rough measures on the general transposition dynamic of member states.[162]

An interesting observation drawn from the data in the first policy phase but not included in the tables should be highlighted. The data show a strong variation regarding the number of measures to transpose single European measures, with the strongest variance for directive No. 89/105/EEC. Some member states (Greece, Hungary) transposed the directive with one single national measure, others needed as much as 57 (Netherlands) and 58 (Poland) measures for the same directive. While these differences could be partially explained by national contextual factors, for example, differences in legislative instruments, they point to the existence of different transposition strategies highlighted in previous studies.

[160] Key directives were identified drawing on the previously conducted analysis of the regulatory framework. They were selected either because they represent central pieces of legislation, amended by other directives in the subsequent process, or there importance has been proven by the frequent mentioning in previous research on pharmaceutical policy.

[161] While it would be more precise to calculate the months between deadline and NME, this strategy is complicated by the fact that Eur-Lex provides only insufficient data for this task. Accordingly, if a deadline was set, for example, on November, 31 1994, 1995 is used as the year of deadline.

[162] The NMEs do not tell anything about the correctness of transposition, but represent the perspective of the member states. However it could be argued, that an increased phase between the deadline and the last measure points to a certain lack of sufficient transposition beforehand. For those countries that joined the EU after the deadline of a directive, the accession year was used as the transposition deadline.

Turning to member states performance based on the data gathered for the first policy phase, member states showed a high level of transposition. Out of the five directives, four were transposed by all member states.

Table 6: Transposition of key directives during first phase (1965-1990)

	Directive No. 65/65/EEC		Directive No. 75/318/EEC		Directive No. 75/319/EEC		Directive No. 87/22/EEC		Directive No. 89/105/EEC	
Country	**Last NME**	**Time span**	**Last NME**	**Time Span**	**Last NME**	**Time span**	**Last NME**	**Time span**	**Last NME**	**Time span**
Austria	1994	-1	1994	-1	1994	-1	1994	-1	2004	9
Belgium	1983	17	1983	17	1983	17	1987	-1	1990	0
Denmark	1995	22	1995	18	1997*	20	1982	-6	1990	0
Finland	1995	0	1995	0	1995	0	NRA	n.a	2006	11
France	1972	6	1975	-2	1998	21	1988	1	2007	17
Germany	1976	10	1994	17	1976	-1	1993	5	2002	12
Greece	1992	11	1992	11	1992	11	1987	-1	1990	0
Ireland	1976	3	1976	-1	1975	-2	NRA	n.a	1984	-5
Italy	1977	10	1977	0	1977	0	1988	0	2007	17
Luxembourg	1983	17	1976	-1	1983	6	1987	-1	1989	1
Netherlands	1977	10	1977	0	1977	0	1988	0	2009	19
Portugal	1993	8	1990	4	1993	7	1993	5	1993	3
Spain	1995	9	1995	9	1997	11	1993	5	2006	16
Sweden	1994	-1	1992	-3	1993	-2	1992	-3	2002	12
UK	1977	4	1977	0	1977	0	1968	-20	n.a.	n.a.
Bulgaria									n.a.	n.a.
Czech republic									2008	4
Cyprus									2001	-3
Estonia									n.a.	n.a.
Hungary									2004	0
Latvia									1998	-6
Lithuania									2002	-2
Malta									2009	5
Poland									2008	4
Romania									2008	1
Slovenia									2005	3
Slovakia									2009	5

Source: Eur-Lex; Note: NRA: no reported actvities; n.a.: not applicable

Two member states (Finland and Ireland) did not reference transposition measures for directive 87/22/EEC. This does not imply that the directive was not transposed, but could simply mean that the NME was not communicated. Turning to the timing of transposition, the first phase shows the strongest variance regarding the time distance between the official deadline and the last recorded NMEs. While in several cases member states were able to *transpose* the directive even before the deadline – because existing national measures already covered the requirements entailed in the directive – others needed as much as 22 years to transpose a directive. Again, this does not mean that member states did not take action before, but that existing measures were subsequently supplemented by new measures.[163]

[163] In the specific case, Denmark released three NMEs before the last one published in Eur-Lex.

In trying to explain the rather long transposition times, three possible reasons can be singled out: previous measures were not sufficient (1), changes were necessary to account for amendments of directives (2) or the Commission demanded additional measures (3). The first two reasons can be expected to explain the largest part of additional NMEs and longer transposition phases.

The second policy phase – based on the NMEs – saw a slight decrease in transposition compliance. Out of the five selected directives, only two were transposed by all member states.[164]

Table 7: Transposition of key directives during the second phase (1990-2000)

	Directive No. 92/25/EEC		Directive No. 92/26/EEC		Directive No. 92/27/EEC		Directive No. 92/28/EEC		Directive No. 93/39/EEC	
Country	**Last NME**	**Time span**	**last NME**	**Time Span**	**Last NME**	**Time span**	**last NME**	**Time span**	**last NME**	**Time Span**
Austria	1994	1	1994	1	1995	2	1994	1	1996	-2
Belgium	1993	0	1993	0	1993	0	1995	2	NRA	n.a
Denmark	1997	4	1993	0	1993	0	1993	0	1995	-3
Finland	1993	0	1995	2	1993	0	1993	0	1996	-2
France	1998	5	1994	1	1994	1	1996	3	1995	-3
Germany	NRA	n.a	1994	1	1995	2	NRA	n.a	NRA	n.a
Greece	1995	2	1993	0	1993	0	1993	0	1995	-3
Ireland	1993	0	1993	0	1993	0	1993	0	1996	-2
Italy	1992	-1	1992	-1	1992	-1	1992	-1	1997	-1
Luxembourg	1995	2	1992	-1	1992	-1	1992	-1	1996	-2
Netherlands	NRA	n.a	1996	3	1996	3	1997	4	1995	-3
Portugal	1995	2	1994	1	1994	1	1994	1	1995	-3
Spain	1994	1	1993	1	1993	0	1994	1	1995	-3
Sweden	1997	4	1992	-1	1995	2	1995	2	1996	-2
UK	1993	0	1992	-1	1992	-1	1994	1	NRA	n.a

Source: Eur-Lex; Note: NRA: no reported activities; n.a.: not applicable

Germany did not communicate national measures for directive 92/25/EEC, directive 92/28/EEC – along with Italy – and directive 93/39/EEC. These developments could be seen as an indication of Germany's reluctance towards the integration of European law which has been highlighted by previous studies (Collatz, 1996; Winter, 2004). In addition, the Netherlands did fail to communicate transposition for 92/25/EEC as well, while the UK and Belgium did not communicate measures regarding directive 93/39/EEC. Despite this negative development, transposition time lags decreased dramatically during this period with a maximum transposition phase of five years.[165]

[164] The new 12 member states were excluded from the computation, since the respective directives were repelled before 2004 and 2007 respectively.

[165] Unsurprisingly, the number of NMEs did decrease as well during the second phase.

During the third policy phase, transposition compliance increased, with communicated measures for four out of five directives. Seven member states claimed that no measures for implementation were necessary regarding directive 2001/83/EC.[166] Transposition times remained on a rather low level, while the number of transposition measures grew.

Table 8: Transposition of key directives during third phase (2000-2008)

	Directive No. 2001/20/EC		Directive No. 2001/83/EC		Directive No. 2001/83/EC		Directive No. 2003/94/EC		Directive No. 2004/27/EC	
	Last NME	Time span	Last NME	Time Span	Last NME	Time Span	Last NME	Time span	Last NME	Time Span
Austria	2006	2	2006	4	2003	-1	2005	0	2006	0
Belgium	2004	0	MPN	n.a	2004	0	1960	-45	2006	0
Denmark	2003	-1	2005	3	2003	-1	1997	-8	2008	2
Finland	2002	-2	MPN	n.a	2003	-1	2005	0	2006	0
France	2006	2	MPN	n.a	2004	0	2006	1	2008	2
Germany	2004	0	2004	2	2004	0	2004	-1	2005	-1
Greece	2003	-1	MPN	n.a	2003	-1	2003	-2	2004	-2
Hungary	2002	-2	2004	2	2004	0	2000	-5	2009	3
Ireland	2007	5	2007	5	2007	3	2004	-1	2007	2
Italy	2003	-1	2006	4	2003	-1	2003	-2	2003	-3
Luxembourg	2005	1	MPN	n.a	2003	-1	2004	-1	2006	0
Netherlands	2006	-2	MPN	n.a	2003	-1	2006	1	2007	1
Portugal	2004	0	2006	4	2006	2	2003	-2	2006	0
Spain	2004	0	MPN	n.a	2003	-1	2004	-1	2007	1
Sweden	2003	-1	2006	4	2003	-1	2004	-1	2009	3
UK	2004	0	2006	4	2003	-1	n.a.	n.a	2005	-1
Bulgaria	2000	-7	2008	1	2007	3	2009	2	2007	0
Czech republic	2008	4	2008	4	2008	4	2008	3	2008	2
Cyprus	2004	0	2007	3	2004	0	2004	-1	2007	1
Estonia	n.a.	n.a.	n.a.	n.a	2005	1	n.a	n.a	2005	-1
Latvia	n.a.	n.a.	2003	-1	2001	-3	2001	-4	2006	0
Lithuania	2007	3	2002	0	2001	-3	2002	-3	2004	-2
Malta	2004	0	2006	2	2003	-1	2004	-1	2008	2
Poland	2008	4	2008	4	2009	5	2009	4	2009	3
Romania	2006	-1	2006	-1	2003	-1	2003	-2	2006	-1
Slovenia	n.a.	n.a.	n.a.	n.a	n.a.	n.a	2003	-2	n.a.	n.a
Slovakia	2006	2	2009	5	2004	0	2004	-1	2008	2

Source: Eur-Lex; Note: MPN: no measure necessary; NRA: no reported actvities; n.a.: not applicable

However, this could be seen as a possible *catch up* effect of the new member states, necessitating more measures to fully comply with the directives. Drawing on the transposition data, a decreasing transposition gap is traceable in the pharmaceutical sector. While in the majority of reviewed directives transposition was achieved, not all member states did comply. However, these results have to be interpreted cautiously. A lack of notification should not be equated with incorrect transposition. At the same time, notification of measures does not

[166] Belgium, Finland, France, Greece, Luxembourg, the Netherlands and Spain claimed that no NME were necessary ("MNE pas necessaire"). This is especially problematic since directive 2001/83 represents such a crucial directive. However, since it integrated former directives the claim of member states is possibly supported by previous transposition activities.

necessarily imply full transposition of a directive. Accordingly, reports on infringement have to be consulted in order to specify the transposition problem in the pharmaceutical sector.

The investigation of infringement proceedings is complicated by the lack of continuous monitoring of member states' transposition compliance before 1984. While the Eur-Lex database provides information on infringement judgements affecting a specific directive, only one case has been registered during the first phase. An infringement procedure was successfully launched against Italy for the failure to comply with directive 65/65, directive 75/318 and directive 75/319.[167] In light of data restrictions it must be assumed, that no additional severe transposition violations justifying referral to the Court were recorded before 1984 and during the first phase respectively. This perception is supported by the eighth annual report on the application of Community law stating that: "The situation regarding pharmaceuticals is positively encouraging." (European Commission, 1991a: 15). This does not imply that the compliance record during the first phase was flawless. Even though there was only one reasoned opinion concerning the labelling of pharmaceutical products issued in 1989 affecting Germany, several member states received letters from the Commission in the early nineties for a lack of transposition of directives No. 89/341/EEC, No. 89/342/EEC, No. 89/343/EEC and No. 89/381/EEC. In addition, directive No. 89/105/EEC – despite being transposed in all member states according to the NMEs – was mentioned in nearly all following annual reports and lead to a considerable number of infringements by the Commission.[168]

During the second policy phase, transposition problems in the pharmaceutical – due to more vigorous monitoring – became more visible.[169] The introduction of the new mutual recognition system and the respect of national authorities for procedural timelines were perceived as the most pressing general compliance issues by the Commission (European Commission, 1997: 34-35). Focusing on the transposition efforts and besides starting proceedings for the already cited measures the Commission saw the need regarding several additional measures. Obviously, the positive transposition record in the pharmaceutical sector was supported by the vigorous monitoring activities of the Commission. However, it must be noted that most of the proceedings were terminated the following year, after member states

[167] This points to the limited reliability of transposition data, as Italy *officially* transposed all three directives.

[168] Unfortunately, the available reports do not list all infringements but simply highlight the relevance of certain transposition problems. Data on infringement is only available on an aggregated level listing the total number of infringements for each member state.

[169] While the area of homeopathic products is not covered in this study, the Commission specifically highlighted compliance problems in this sector (European Commission, 1995: 28).

took additional measures to transpose directives. This suggests that member states during this phase did not oppose transposition in general, but had to be *reminded* of their duties. Accordingly, national transposition efforts in the pharmaceutical sector were encouraging, showing a high rate of transposition during the 1990s, with France having transposed "only " 81,3 % of all directives as the laggard within the EU 15 (European Commission, 1997: 35). In 1998, the Commission – despite highlighting the positive developments in the sector – identified the management of the *re-authorisation* of old medicinal products, initially brought to the market before the European framework applied, as a key concern of compliance for the years to come.[170] In its seventeenth report released in 2000, the Commission stated that except France all member states transposed the pharmaceutical directives (European Commission, 2000: 15).

While the second phase saw an increase in infringement procedures in the sector, this trend continued in the third policy phase. In 2002, several proceedings regarding the transposition of directive No. 2000/38/EC were issued, resulting in two reasoned opinions (Italy) and a referral to the ECJ (Germany). The introduction of the clinical trials directive No. 2001/20/EC led to an increase of infringement proceedings in 2003 (European Commission, 2003: 12). The same year, the European Court of Justice decided that Germany failed to transpose directive No. 2000/37/EC and No. 2000/38/EC (European Commission, 2003: 12). Reacting to the judgment, Germany proposed specific measures to be introduced in 2005. In 2005, the Commission sent 18 letters of formal notice for failure to notify measures to transpose Directive No. 2004/27/EC amending Directive No. 2001/83/EC (European Commission, 2005b: 37). Additional (notable) transposition problems were encountered regarding No. 2004/24/EEC covering herbal products and directive No. 2005/28/EC. While information on the termination of these proceedings could not be retrieved, it seems rather likely, that the *infringement dynamics* between the Commission and the member states traceable in the second policy phase prevailed during the third phase and is most likely to prevail in the future: While the Commission regularly notifies member states to transpose measures, escalation of infringement remains the exception and is mainly confined to a small group of member states.[171]

[170] The problem of *re-authorisation* (Nachzulassung) has been and still is an issue in many member states especially Germany (Kurth, 2008; Murswieck, 1983).

[171] An exception from this general dynamic seems to be the transparency directive No. 89/105/EEC, resulting in several escalations over the years. However, this deviation is less surprising given that the said directive is the only way for the Commission to exert (limited) influence on national pharmaceutical pricing strategies.

In light of the fundamental transposition problems encountered in other fields, for example environment (Jordan, 1999) and based on the limited evidence available, transposition in the pharmaceutical field proves to be less problematic. While the Commission increasingly employed measures to stimulate transposition throughout time, the comparatively low levels of escalation indicate, that most member states were willing to comply rather than actively opposing further harmonization. As the analysis suggests, the *willingness* seems to vary between member states – with Germany and France as the most deviant cases – in the pharmaceutical sector, falling in line with previous research on different cultures of compliance (Falkner et al., 2005; Treib et al., 2007). While it is suggested that the reservations of France to transpose certain directives could be attributed to a "posture of arrogance" (Falkner & Treib, 2007: 4) the lack of transposition in Germany can be attributed to the comparatively complex national bargaining environment and the different stakeholders and interests (Collatz, 1996; Lorenz, 2006).

6.4 Conclusion: the *de jure* effectiveness of the European regulatory framework

Based on the framework developed in the fourth chapter, the quality and de jure effectiveness of regulatory policy has been conceptualized as the result of three interrelated aspects: the satisfaction of specific preconditions, the coverage of the regulatory lifecycle as well as the realisation of regulatory principles and finally the effective transposition of European rules into national law.

Starting off with the *preconditions* of regulatory quality, it has been found that the requirements are met in the case of European pharmaceutical policy. Specific market failures necessitate public intervention and justify regulatory activity. Since less intrusive forms of intervention were deemed insufficient, market regulation based on licensing mechanisms and post-authorization controls were identified as the appropriate form of intervention. Considering scale effects as well as the transnational character of pharmaceutical risks, European involvement is justified in the sector. Turning to the legal mandate and constitutional foundations of European pharmaceutical regulation, it was shown that no clear consumer protection and public health mandate could be established within the European treaties. However, based on the characteristics of pharmaceuticals as marketable goods, the establishment of a single market and the reduction of obstacles to free trade were identified as constitutional basis for regulatory intervention. Considering the coverage of the regulatory lifecycle and the realisation of regulatory principles, the conducted analysis revealed a mixed

result. While the current regulatory framework seems to cover all regulatory principles in a sufficient way, supporting the notion of effective regulation and regulatory quality, the regulatory framework revealed some flaws. On the positive side, the effectiveness of the regulatory framework clearly increased throughout time. Three different policy phases were identified. While the regulatory framework during the first phase mainly focused on the *harmonization* of pre-authorization aspects, the second phase – starting in 1990 – saw an expansion of the framework to post-authorization aspects and a strengthening of European regulatory structures leading to a more inclusive and dense regulatory framework. While this positive development path is can be considered as a natural result of policy learning mechanisms (Feick, 2008), it does not represent an automatism. Furthermore, the comparatively long phases of inactivity might serve as an indication that regulatory changes emerged after complex negotiation rather than representing a *self-sustaining* process.

Table 9: Coverage of the regulatory lifecycle (illustration)

	Phase I (1965-1990)	Phase II (1990-2000)	Phase III (2000-present)
Development	++	+++	+++
Approval	++	+++	+++
Production	+	++	+++
Distribution	0	+	+
Information	+	++	++
Pharmacovigilance	+	++	+++

Source: author's own; Note: (0) no regulation; (+) general requirements; (++) specific requirements; (+++) detailed requirements

In contrast to these positive developments and even though the current regulatory framework manages to cover all aspects of the regulatory lifecycle, a certain imbalance considering different degrees of regulation in the pre- and post-authorization stages has been identified. While pre-authorization aspects are regulated rather extensively and some authors consider that the system moves towards a state of over-regulation (Baeyens, 2002; Ruffolo, 2006; Schofield, 2008; Tor & Brian, 2008), regulation in the area of distribution and information can be considered under-regulated. This finding is especially striking given the predominately economic and *market-based* justification of European pharmaceutical risk regulation. The creation of the single market serves as the constitutional basis, yet trade aspects and most importantly the stage of distribution and information remain comparatively unregulated.

Beyond the realisation of regulatory principles and the coverage of the different regulatory aspects, the discussion of the framework and its development provided some general insight characterising the European regulatory approach and its alternation. First, the regulatory approach in the first policy phase was clearly built on the paradigm, that product safety could be achieved solely based on regulation of development and market approval. Starting in the second policy phase and the first revision, the regulatory approach shifted subsequently to a more reflected approach increasingly incorporating post-authorization regulatory aspects. Second, the increased acknowledgement of the regulatory lifecycle led to a more inclusive but at the same time more complex regulatory framework. Instead of substituting existing pre-authorization mechanisms by introducing stricter post-authorization measures, requirements were raised in both segments. This development might be interpreted as an evidence for the explanatory value of the *uncertainty avoidance* argument in the sector and a manifestation of the precautionary principle underlying the general European risk regulatory approach (Callréus, 2005). While such an approach could be seen as preferable from the public health perspective, there might be reason to believe, that legal framework increasingly drifts towards *over-regulation* as regulation is becoming more complex, but not necessarily more effective. This remark is closely connected to another notion of the shift in the regulatory approach. Especially during the last policy phase, the regulatory approach seems to increasingly incorporate soft regulatory tools and emphasizes cooperation and guidance. An indicator for this *cooperative turn* could be seen in the increase of guidelines, guidance documents and the encouragement of interaction between regulators and regulatees, for example the pre-authorization consultation (Dejas-Eckertz & Schäffner, 2005). On first sight, this could be interpreted as a shift towards private regulation and a stronger reliance on discussion, instead of sanctioning mechanisms in regulation. At the same time, this shift could be interpreted as an indication, that the current regulatory framework has reached a stage of complexity and hyper-fragmentation (Tor & Brian, 2008). More specifically, regulation might suffer from complexity and vagueness at the same time. While the situation might have improved throughout the policy phases, the regulatory requirements regarding most aspects of the regulatory lifecycle remain relatively *general*.[172] The current framework seems to foster a certain level of uncertainty regarding requirements leading to an increased need of guidance

[172] In addition, regulation is mainly based on directives, leaving member states with a certain level of discretion in transposing them.

on the side of the regulatees.[173] Finally, the analysis of transposition in the pharmaceutical sector showed that member states in general managed to integrate the European regulation into the national body of legislation. As in the case of the European regulatory framework, a positive development is traceable throughout the different policy phases. Despite relatively long transposition periods during the first stage, member states started to adopt measures more quickly in the subsequent phases. While increased compliance of member states can be partially ascribed to increased monitoring and sanctioning activities by the Commission, a learning effect might have influenced the improvement of compliance as well.

Drawing a conclusion on the evaluation of the European regulatory framework, the evidence suggests that despite some remaining flaws, effectiveness *de jure* of pharmaceutical regulation is achieved. Unfortunately, de jure effectiveness and the transposition into national legislation do not necessarily translate into effective governance. Moreover, the identified characteristics of the European regulatory approach serve as additional source of unsettlement in this regard. If the framework potentially amplifies uncertainty instead of reducing it, *de facto* effectiveness will most certainly be challenged. Therefore the following chapter will assess the governance in the pharmaceutical sector.

[173] This can be considered as a structural deficit of the current regulatory framework and is probably not limited to the risk regulation of pharmaceuticals.

7. Regulatory governance in the pharmaceutical sector

While the regulatory framework serves as the basis for effective regulation, the implementation stage must be viewed as critical in achieving regulatory goals, since: "policies are not just applied mechanically but they have to be made applicable in the implementation process which makes that polices are somehow completed by operationalisation and implementation" (Feick, 2004: 4). Based on the neo-institutional claim that institutions do matter (Bulmer, 1993, 1998; Mayntz, 2009; Peters, 2000) for the realisation of regulatory outcomes, an assessment of the regulatory regime is necessary to develop a more inclusive understanding of regulatory quality and de facto effectiveness.

Drawing on the discussion in the fourth chapter, the following section will assess regulatory interests of the involved stakeholders.[174] In contrast, possible conflict between regulatory interests can result in a distortion of the regulatory regime and its performance. Considering the large number of actors in the pharmaceutical sector, the discussion will start with the identification of relevant actors. Subsequently, their underlying regulatory interests will be identified. Based on the assumption that (general) regulatory interests do not vary over time, it is argued that they can be distinguished from (case-specific) regulatory policy preferences. While the policy preferences of actors will depend on the specific content of the policy, an underlying set of perceptions and interests exists, how the risks stemming from pharmaceuticals should be regulated (Feick, 2005a: 30). In a second step, the effectiveness of the governance system and its development through time will be assessed. The regulatory lifecycle concept as well as the policy phases deducted in the previous chapter will be used to structure the assessment. In assessing the European regulatory regime in the pharmaceutical sector, several aspects need to be considered in greater detail.

First, the discussion should consider the complete regulatory lifecycle. Due to the central importance for the protection of public health, the analysis will have to consider the European approval regime and the changes that have been introduced in greater detail. Second, the institutional changes affecting the approval regime as well as the regulatory network, consisting of national authorities and the EMA, necessitate a more detailed discussion. The EMA represents a specific type of institution, an international regulatory agency (IRA). Therefore, the impact of institutional choice on the overall effectiveness of the regulatory

[174] Aligned interests serve as a precondition for effective sectoral governance, strengthening compliance and overall stability of the regulatory regime (Chayes & Chayes, 1993; Langbein & Kerwin, 1985; Oliver, 2000; Parker, 2000)

system and more specifically its legitimacy must be determined.[175] Third, the realization of openness, participation and accountability within the regulatory network and the EMA in particular must be discussed. Fourth, the governance structure will be evaluated briefly from the perspective of effective risk governance.

7.1 Regulatory interests in the pharmaceutical sector

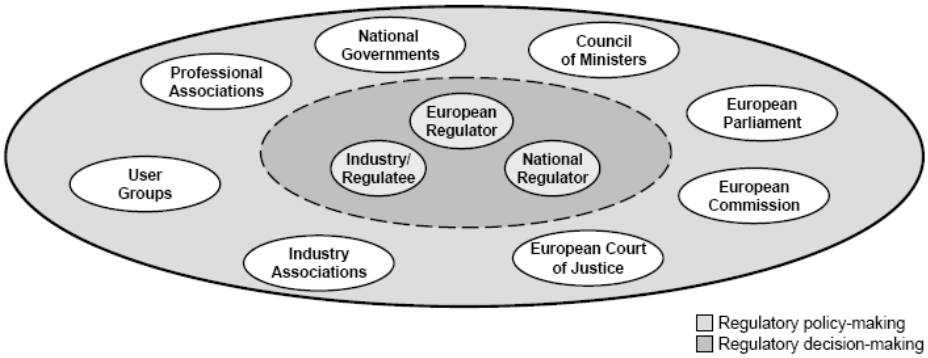
Conceptualizing the policy field from the perspective of regulatory governance, the regulatory arena (Lowi, 1964a) in the pharmaceutical sector consists of a wide variety of actors and stakeholders. Based on the different notions of regulation, different subsets can be identified. If regulatory policy-making is considered, the number of relevant actors increases. If the discussion focuses on regulatory decision-making and the implementation phase, the number of relevant actors is effectively reduced.[176] Recurring to the metaphor of the regulatory arena, the implementation phase represents the inner circle within the wider arena of regulatory policy-making. While many stakeholders and interest groups try to influence regulatory policy, these groups do not participate directly in the actual implementation of regulatory policy and governance of the sector. However, these interests can be expected to cast a shadow (Héritier & Lehmkuhl, 2008) on regulatory decision-making and interaction between the main stakeholders, in this case regulators and regulatees. Clearly, this conceptualization simplifies matters: the distinction between regulatory policy-making and regulatory decision-making is not as clear-cut as suggested. Several actors, most notably the Commission, are involved in the decision-making process as well.[177] Nevertheless, these interests impact on the regulatory decision-making process indirectly and intermediated.

[175] While European IRAs have been the subject of several studies, the issue of legitimacy has only begun to stimulate scientific discussion (Majone et al., 1999; Thatcher, 2002b; Vibert, 2007).

[176] It is important to note, that this classification focuses on the actors actively involved in the respective domain rather than including stakeholders affected by it.

[177] The Commission is involved in several committees accounting for the soft mode of governance and is involved in the political decision in the centralized procedure and, in case of arbitration, in the MRP/DCP as well. In addition, the ECJ influences regulatory decision-making by limiting the zone of discretion of the regulators (Krapohl, 2004a; Krapohl & Gehring, 2007).

Graph 14: Main actors in the pharmaceutical regulatory arena



Source: author's own

While the public interest is excluded from the model up to this point, it is accounted for at least indirectly. The public interest is represented by three of the relevant actors: national governments, user groups and professional associations. Even though these intermediaries will pursue their own interests, the public interest will influence their position. Based on this conceptualization, the discussion of interests can be narrowed down to the public interest, the interests of regulatees and the regulators.

7.1.1 Regulatory interests of the public

While the public does not participate directly in the respective regulatory decision-making process, their interests potentially influence the regulatory process. It is assumed that a public interest in effective regulation translates into a general and predominant interest in safe drugs. While this claim has a high face validity, it omits the fact that people do not only want save drugs but access to quality treatment as well, giving rise to the classic regulators' dilemma of safety versus access (Eichler et al., 2008: 818). Obviously, *the* public interest can not be pinpointed exactly on this continuum. While no systematic research on public interests in pharmaceutical regulation exist, recent contributions on the impact of private groups on US pharmaceutical regulation and the FDA highlight the fact that different patient groups do show different regulatory interests (Daemmrich, 2004). Patients suffering from a severe illness, for example, can be expected to be more willing to accept a greater risk in light of potential benefits (Johnson et al., 2007: 776-778). Numerous additional factors – both on the individual and the group level – can be expected to alter individual regulatory interests and the respective valuation of safety and access, for example the personal awareness of

pharmaceutical risks.[178] To add an additional layer of complexity, interests might vary regarding different product groups and between specific products as well (Aronson, 2006: 136). Based on previous research on risk perception, individual perceptions will be influenced by the respective group of references, the social background, personal encounter of risks and gender (Chauvin et al., 2007; Greenberg & Schneider, 1995; Sjöberg, 2000; Sjöberg et al., 2004). Considering the complex interaction of factors on the individual level, it seems to be more promising to move beyond the individual level to derive a public regulatory interest. Recent studies of risk perception point to the impact of (national) cultural differences influence the personal acceptance of risks and their regulation, specifically in the European context (O'Riordan et al. 1998; Sjöberg, 2000; Ferrari, 2008).[179] Accordingly, different risk cultures should be identifiable within Europe, impacting on the *acceptance* of risk and their governance. Regulators depend on the public support and will therefore try to regulate in the public interest at least to some degree (Levine & Forrence, 1990; Thompson et al., 1982). National regulatory preferences, conceptualized as a function of the national public interest, can clash and undermine the effectiveness of joint regulatory decision-making. It can be argued that the existence of different risk cultures will have an impact on the (input) legitimacy of the respective regulatory regime, since:

> "ignoring public anxieties, or dismissing them without due attention is a violation of the basic tenet of consumer sovereignty. It also ignores that certain areas of safety are perceived by the public as the sole domain and responsibility of government (as opposed to other domains where individual safety behaviour is perceived to be indicated)" (Vertinsky & Wehrung, 1990: 14).

To specify the issue in the European context, social legitimacy can be expected to diminish if the general precautionary regulatory approach is not supported by according national risk cultures. The cultural theory of risk has its main roots in the works of anthropologist Mary Douglas and political scientist Aaron Wildavsky (Douglas, 1992; Douglas & Wildavsky, 1982, 1983). While the claim that culture matters has been accepted lately by the mainstream psychometric approach on risk perception (Peters & Slovic, 1996), cultural theory in general has been exposed to substantial criticism. First, several conceptual and methodological problems have been identified (Boholm, 1996, 2003; Oltedal et al., 2004). Second, the suggested link between culture and risk perception is only supported by "a not very

[178] Even though no systematic research exists on this topic, public awareness for pharmaceutical risks and side effects is best described as low. Lay people expect medicines to work and reflect to a lesser degree about the possible problems associated with consumption (Bissell et al., 2001).

[179] These effects have been discussed for risk perception in broader terms and specific risks. It can be assumed that perceptions of pharmaceutical risks are subject to the same general influences. For a general argument, why risk perceptions should play a role in drug assessment see Vertinsky and Wehrung (1990).

impressive set of correlations" (Sjöberg et al., 2004: 22). Yet even critics acknowledged that "the basics of the theory is easily comprehendible and might seem intuitively reasonable, which of course will make it easier to gain acceptance." (Oltedal et al., 2004: 33). Even though the initial concept of cultural biases on risk perception is not fully supported it thus seems to be a valid assumption that cultural aspects do influence the way risks are perceived (Boholm, 2003: 174). A cultural concept, partially drawing on the previous work of Mary Douglas, has been developed by the Dutch social psychologist Geert Hofstede. Hofstede defines culture as "the collective programming of the mind which distinguishes the members of one group or category of people from another" (Hofstede, 1998: 17) traceable in differing values, attitudes and beliefs. This definition allows for the inclusion of the national level as a *unit of comparison* since for some of these values "the nationality component is relatively strong" (Hofstede, 1998: 20).[180] Based on individual survey data collected at the multinational corporation IBM, Hofstede constructed four cultural (value) dimensions: *Power Distance*, *Individualism*, *Masculinity* and *Uncertainty Avoidance*.[181] The original dataset has been used and replicated in numerous studies, supporting the validity of the underlying cultural dimensions (see, for example Litvin et al., 2004; Merritt, 2000). Despite the overwhelmingly positive reception of the concept in many social science disciplines, it has been criticized on conceptual and methodological grounds (Baskerville, 2003; McSweeney, 2002a, 2002b; Williamson, 2002).[182] While this calls for a cautious interpretation of Hofstede's dimensions, it does not justify to abandon the concept altogether, since that would mean "to throw away valuable insight." (Williamson, 2002: 1391).

Drawing on Hofstede's concept, the next section will try to verify the claim that different risk cultures exist within the European Union. In developing a concept of risk cultures, two of Hofstede's dimensions are relevant. First, the dimension of *uncertainty avoidance* (UA) can be related to the concept of risk perception and risk assessment. Hofstede defines uncertainty avoidance as "the extent to which the members of a culture feel threatened by uncertain or

[180] It is important to note, that values – opposed to attitudes and beliefs – proved to be very stable over time, since such cultural programming is *acquired* early in life. Following from this, it can be expected that values will impact on behaviour and perceptions of group members.

[181] A fifth dimension *long-term orientation* was added later to the concept (Hofstede & Hofstede, 2005).

[182] Three main arguments can be highlighted in this regard. First, Hofstede's sample does not seem to fulfil the criteria of representativeness, as it is solely based on data from a multinational corporation. Critics argue that the survey measured differences in corporate rather than national culture. Second, Hofstede treats national cultures as homogenous ignoring the fact that cultures can show differing patterns on the regional and individual level. Accordingly, the uniform impact of culture on behaviour and perceptions is challenged. Third, the assumption of *time-invariance* of national cultures and the possibility that national culture can be measured by using questionnaires is challenged. For a response see Hofstede (1998).

unknown situations. The basic dilemma in this case is dealing with the unknown" (1998: 26). It is assumed that the tolerance for uncertainty will have an impact on risk acceptance. Lower UA scores will most probably be associated with higher risk acceptance. The second dimension that proves valuable in assessing risk culture is *power-distance* (PD) defined as "the extent to which the less powerful members of institutions and organizations within a country expect and accept that power is distributed unequally; from relatively equal (that is, small power distance) to extremely unequal [original emphasis]" (Hofstede, 1998: 25). The level of PD is expected to impact on risk management preferences. Nations with higher power distance will, according to the underlying construct, accept the delegation of risk regulation and more closed forms of risk governance. Based on the two dimensions, national profiles for the risk perception and preferred governance approach for the EU 15 member states and the EU 27 can be constructed using the most recent dimension scores (Hofstede et al., 2010).[183] Based on Hofstede's data, differences in perceptions of risk and risk governance are traceable within the EU 15 and EU 27 group. Starting with the interests regarding the management of risk, it can be deducted that the public in the majority of the EU 15 Member states does not generally prefer delegation of risk regulation, since most states show lower power distance. Even though the (data) range between member states increased with the enlargement of the Union, delegation of risk regulation as a general mode of governance does not necessarily enjoy the public support to the same extent that the current European regulatory approach based on delegation does.

Table 10: Risk perception and risk governance preferences (EU 15 & EU 27*)

	Dimension	Mean	Median	St. Deviation	Spread	Min. Value	Max. Value
EU 15	UA	66,4	70	27,64	89	23	112
	PD	42,12	38	17,55	57	11	68
EU 27	UA	70,35	70	23,51	89	23	112
	PD	50,77	48	21,17	93	11	104

Source: Based on data from Hofstede *, 2010 #3703'; Note: * no data for Cyprus was available

Turning to the general risk acceptance, the EU 15 shows a weak tendency towards lower risk aversion. When the enlarged European Union is considered, risk aversion seems to increase gradually. This finding could be interpreted as an indirect legitimization for the precautionary approach in European risk regulation: if the European demos is less willing to accept risks, being more cautious represents a responsive form of risk governance. The identified national

[183] The scores are available at Hofstede's homepage (http://www.geerthofstede.nl/research--vsm.aspx). Unfortunately, Hofstede remains unclear about the scales used to calculate the scores. Results are not rescaled on a comprehensive scale. Instead, single scores are added.

differences in risk perceptions and risk governance can be expected to affect individual perceptions of pharmaceutical risks, forming distinct national pharmaceutical risk cultures. However, considering the specific character of pharmaceuticals and their consumption, it is necessary to establish a relationship between general and specific risk cultures. In a first step, the theoretical relationship between underlying risk dimensions and field-specific indicators must be established. Starting with the UA dimension, it most likely will impact on the perception of risks associated with pharmaceutical consumption and on actual consumption. It is assumed, that people with a higher tolerance for uncertainty will accept pharmaceutical risks more willingly compared to persons with higher uncertainty scores and thus a lower risk tolerance. The impact on consumption represents the inverse relationship: People with higher UA scores will consume more pharmaceuticals, while people with lower scores will wait before they consume pharmaceuticals. While the PD dimension can impact on the acceptance of risk as well, for example, as a tendency to delegate the responsibility for the right treatment to the respective physician, it will mainly impact on the interest regarding the risk governance of the sector. A higher PD score can be expected to result in a higher acceptance of delegation and depoliticisation of the regulatory sector. In trying to identify proxy measures, Eurobarometer surveys, covering aspects of health and risks, were evaluated.[184] The last two indicators were selected based on the increasing role of biotechnology regarding pharmaceutical products. In addition, data on pharmaceutical consumption has been collected. However, rather than using existing measures based on per capita expenditure, consumption measured in packs is used.[185] While per capita expenditure serves only as a crude measure of consumption, depending on the respective national pricing level, the number of packs consumed can be linked more directly to the notion of risk acceptance.

Given that individuals show a higher level of uncertainty, they can be expected to consume more pharmaceuticals as they want to reduce the uncertainty stemming from illness. In turn it could be argued, that the state of illness is perceived more negatively than the possible risks of pharmaceutical consumption (Deschepper, 2008: 87). What should be noted is the fact, that the number of consumed packages – due to the respective price inelasticity in demand – is

[184] For a general discussion of the *Eurobarometer* survey and their use in research see (Karmasin & Pitters, 2008; Schmitt, 2003).

[185] Standardized data on national consumption – measured in standardized packaging sizes – has been retrieved from a study conducted by Evelyn Walter and her colleagues (2008).

only partially influenced by the price: the correlation between the pricing level in the EU 15 in 2005 and consumption in 2008 was -0.49, however, the result was not significant.[186]

Table 11: Indicators of pharmaceutical risk cultures

Variable	Question	Source	Used category
Likeliness of serious medical error	All in all, how worried are you to suffer a serious medical error?	Q 7 SEB 241: "medical errors" (2006)	Worried (%)
Likeliness of Medication error	Thinking of the following types of adverse events in your view, how likely, if at all, is it that each of them might happen to you if you were to receive healthcare in (our country): *Medication related errors* (wrong prescription, wrong dose, dispensing error in pharmacy, wrong administration route)	Q 5.4 SEB 327: "Patient Safety" (2009)	Very unlikely (%)
Effect of medicine	I am going to read out a list of areas in which new technologies are currently developing. For each of these, do you think it will have a positive, a negative or no effect on our way of life in the next 20 years? Medicines and new medical technologies	Q 13.13 SEB 225: "Social values, Science and Technology" (2005)	Positive effect (%)
Confidence in regulation	Public confidence in the 'biotechnology system'	Report on EB 64.3 Figure 22: "Public confidence in the 'biotechnology system'" (2006)	Level of confidence (%)
Principles of Governance	Segmentation of the European public on principles of governance	Report on EB 64.3 Figure21:"Principles of Governance across Europe" (2006)	scientific delegation (%)
Consumption	Consumption in packs (2008)	Walter et al. 2008	Consumption in packs

Note: EB = Eurobarometer SEB = Special Eurobarometer Q = Question

Accordingly, the number of consumed packs relates to other factors than pricing. To validate the connection between general risk perceptions and specific pharmaceutical risk cultures correlations between the six selected indicators and risk culture dimensions were calculated. Even though most of the results are not statistically significant, the assumed relation between national risk cultures and individual perceptions of pharmaceutical risks is supported by the results. The existence of distinct national pharmaceutical risk cultures has several implications for the governance of the pharmaceutical sector. First, the divergence of pharmaceutical risk perceptions can clash with a standardized European regulatory approach. If national risk cultures are rather diverse, and likely to persist over time, a common European regulatory approach is harder to achieve.

[186] Pearson coefficient was used to calculate the correlation and a two-tailed test was employed (Wagschal, 1999-203).

Table 12: Correlations for general and pharmaceutical risk cultures (EU 15)

Variable	Uncertainty Avoidance	Power Distance
Likeliness of serious medical error	,682**	,627*
Likeliness of Medication error	- ,086	-,523*
Effect of medicine	-,359	-,176
Confidence in regulation	-,350	-,090
Principles of Governance	,151	,586*
Consumption	564*	,632*

Note: (Pearsons, two-tailed test), ** significant on 0,05, * significant on 0,1.

Second, the input legitimacy of a regulatory regime based on such an approach will necessarily be reduced. Third, such cultural differences are most likely to translate into regulatory differences as the discussion of regulatory interests will show. The general public interest in safe medicines remains a viable assumption, yet the notion of safety and acceptable risks may vary throughout the European Union.

7.1.2 Regulatory interests of the pharmaceutical industry

The European pharmaceutical industry consists of a wider variety of companies, which based on structural differences can be expected to have differing regulatory interests. Moreover, these differences are complemented by variance on the national level (Ruane, 2007; DG Competition, 2009). Two main categories can be used to classify the industry: company size and product type. Starting with the first category, located on the one end of the continuum are the big multinational pharmaceutical companies acting on a pan-European and even global scale. On the other end of the continuum are the smaller regionally-focused and generally less innovative companies. The second dimension differentiates companies based on their product. While less innovative and less research intensive products, with the notable exception of highly innovative therapeutics and biotechnological products, are mainly produced by smaller companies, bigger multinational companies engage in the development and marketing of innovative and research intensive products. Generic producers form a middle-category.[187] While their product is by definition not innovative, some of these companies have a considerable size and engage in multi-national activities. Turning to the regulatory interests of

[187] While there are some companies focusing exclusively on generic manufacturing, for example *Ratiopharm*, many originator companies, most prominently *Novartis*, engage in generic activities (Sohal, 2008). Despite their significance, the distinct position of *generic* producers and their interests has not been sufficiently recognized by most previous studies, except for the contributions by Feick (2005a).

these groups, divergent and convergent aspects are traceable.[188] Divergence can be mainly attributed to the regulatory processes. Small and medium-sized companies (SMEs), given their limited capacities to penetrate the whole European market, can be expected to have a stronger interest in a national regulatory approach. Bigger companies, given the international character of their operations, will prefer a more rationalized and Europeanized approach, possibly serving as an additional entry barrier for competitors. Considering the consolidation in the sector, starting in the early nineties (Chaudhry et al., 1994; Karrer-Rueedi, 1997) and continuing unitl today (Sheridan, 2006), it can be argued that the interests of the big pharmaceutical companies – despite their internal heterogeneity – tend to overshadow the interests of smaller and less innovative producers. Moreover, they possess greater leverage and political influence on the European level (Greer et al., 2008: 428). Turning to the mutual interests of pharmaceutical companies, the most basic one can be seen in the reduction of regulatory costs (Abraham, 2002a; Rawson, 2000). A second and closely connected interest can be seen in fast regulatory decisions. The development of pharmaceuticals is a time-consuming process and pharmaceutical companies will therefore have a vital interest in speedy approval (Pieterson, 1992; Thomas et al., 1998).[189] Generally speaking, the main regulatory interest of pharmaceutical companies will thus be on quick and cost-efficient *market access*.[190] Based on this general interest, previous studies on European pharmaceutical regulation are quick to conclude that safety – as opposed to access – must play a subordinate or minor role from the industrial perspective (Abraham, 2002a; Abraham & Lewis, 1999, 2002). While access and safety can be treated as different ends of a continuum, the valuation of one aspect does not preclude that the other aspect is automatically irrelevant (Lexchin, 2007: 36). The pharmaceutical industry needs to generate profits, which is contingent on fast approvals, but this does not imply that safety is not considered sufficiently. Pharmaceutical companies and the respective developers are aware of pharmaceutical risks. In addition, the possible negative impact a defective medicinal product represents a strong economic

[188] The divergence is apparent in the policy-making arena with the different groups represented by different associations. The *European Federation of Pharmaceutical Industries and Associations* **(**EFPIA) represents the big and innovative companies, the *European Generic Medicines Association* (EGA) represents the producers of generics and the *European Confederation of Pharmaceutical Entrepreneurs* (EUCOPE) represents small and medium-sized companies. In addition, there are several other interest associations on the European level most notably the *Association of the European Self-Medication Industry* (AESGP) for the OTC and self-medication industry and the *European Association of Euro-Pharmaceutical Companies* (EAEPC) representing the interests of the parallel traders.

[189] More specifically, generic producers will be interested in fast approval of their own products and in fast approval of those products they want to imitate as soon as their patent protection expires.

[190] While *access* in this study mainly relates to the market authorization process, the pharmaceutical industry perceives the reimbursement phase as a second major component (McGuire et al., 2004; Miller, 2005).

argument against the negligence of safety considerations on behalf of the industry. If a product has to be withdrawn after market authorization because of unwanted side effects, this will obviously negatively affect the products turnover. In case of blockbuster pharmaceuticals generating billions in turnover each year, the negative impact can be considerable. Additional indirect effects of such an event will serve as a strong incentive for the pharmaceutical industry to value safety accordingly. Victims may claim damages and sue the pharmaceutical producers. While law suits will be settled eventually and most likely represent manageable costs, the loss of *reputation* in the stock market can have a detrimental effect on pharmaceutical companies. The most recent and well publicized example for such a development has been the market withdrawal of *Vioxx*, produced by the US company Merck & Co Inc., after several severe side effects. The withdrawal and the following litigations resulted in a

> "a litigation bill […] put at between US$10 and $15 billion. The company has seen its revenues and market capitalisation slashed. It has been financially disabled and its reputation lies in ruins. It is not at all clear that Merck will survive this growing scandal." (Horton, 2004: 1995)

Another example involving a European-based company has been the withdrawal of *Lipobay*. In 2001, Bayer recalled the product from the European and US market and shortly afterwards from the Japanese market, after reports on serious side effects. After a series of public accusations and numerous litigations, Bayer's pharmaceutical division was on the verge of collapse (Angelmar, 2007). The two examples illustrate the possible and severe consequences of unsafe products for the respective manufacturer.[191] The potential financial and reputational losses connected to drug failure serve as an incentive for a more balanced regulatory interest of the pharmaceutical industry. It can be argued, that more intense pre-authorization testing might not prevent such events from happening. On the contrary, this could lead to more frequent denial of market authorization. However, drug companies accept the underlying risk of non-approval and most likely believe that a stricter test of their product at least helps to reduce the uncertainty about the risk benefit ratio and therefore the likelihood of known side effects (Carpenter, 2003: 254). Given that market approval serves as mechanism to reduce uncertainty, the industry will have an interest in the predictability of the regulatory process and outcome.[192] Moreover, reputation-building and the establishment of regulatory ties with

[191] Incidents like the Halcion controversy (Abraham & Sheppard, 1998; Berger, 1999) or the more recent incidents in relation to Avandia (rosiglitazone) (Bloomgarden, 2007; Cohen, 2010) support the assumption.

[192] Regulatory uncertainty has been discussed in relation to reimbursement decisions (Claxton, 1999; Sculpher & Claxton, 2005). However, the importance of limited predictability from the regulatees' perspective is evident in the case of market approval.

regulators is in the interest of regulatees. While approval mainly depends on *convincing* data it would be naïve to assume, that such a decision is not influenced by interaction between the two parties. The European regulatory approach increasingly emphasizes the need for dialogue in regulation and producers will have an interest in establishing a sound working basis and predictable regulatory decisions (Coen, 2005b; Parker, 2000). While small and medium sized companies focusing on one market will need to establish such basis with the respective national regulator, European companies will need to establish these ties with the EMA and – due to the regulatory structure – with the national regulators as well. Summarizing the previous arguments, it is assumed that the interests of the industry will be on fast access (1), but without completely sacrificing the safety of pharmaceuticals and the building of sustainable regulatory relations (2).

7.1.3 Regulatory interests of regulators

Regulators have self-interests, but their interests will be partially determined by external factors as well. Regulators have a (social) coordinating and mediating function and will therefore engage in interaction with their two main stakeholders: the regulated industry and the public. A possible third influence on their interest results from the specific institutional set up chosen for the regulation of pharmaceutical risks. Nearly all European member states chose to delegate the regulatory field to a (independent) national regulatory authority, resulting in a principal-agent relationship between national governments and national regulators.[193] Principals can be expected to shape the agents interests to a certain degree. Yet this influence should be mainly traceable in the policy-making process, establishing the regulatory playing field. If the theoretical claim of uncertainty avoidance as a motivation for delegation holds true, national governments consciously delegate in the field of risk regulation to avoid participation in the regulatory decision-making arena. The same could be said regarding the possible impact of the European Commission and the ECJ. The European Commission can effectively influence policy-making by structuring the behaviour of the regulatory agencies, but it can be expected to have little interest in intervening in regulatory operations. While the ECJ can cast a shadow on regulatory behaviour (Alemanno, 2008b) it does not shape the regulators interests. Regulatory interests can thus be conceptualized as a

[193] Even before the agencification on the national level, member states used relatively isolated institutions for the national regulation of pharmaceutical risks (Hart & Reich, 1990: 51-61). This finding supports the idea of uncertainty and depoliticisation as driving factors in national risk regulation and the public acceptance of secrecy as a mode of governance.

function of self, public and industrial interests, shaping the regulators "bureaucratic agenda" (Carpenter & Ting, 2007: 835). Drawing on the research of bureaucratic behaviour and P-A theory, the most general interest of a regulatory agency is organisational stability and organisational survival (Faure-Grimaud & Martimort, 2003: 414; Spiller, 1990).[194] Based on the assumption, that governments delegate the regulatory task in order to *get out of the firing line*, the drug regulatory agency will still need to adhere to the will of its political principal and accommodate interests in the regulatory arena. More specifically, the agency will need to build an institutional and regulatory reputation towards the public and the industry in order to survive and this is where public and private interests come into play (Carpenter & Ting, 2005: 1; Maor, 2009: 1).

In building a reputation towards the public, regulators will need to satisfy the general public expectation by only granting approval to safe products. While the perception of safe enough products will vary according to the national pharmaceutical risk cultures identified above, the general assumption of the public – given the public unawareness for the perpetual character of pharmaceutical risks – will be that if a product is approved it is safe.[195] The emergence of controversy surrounding a harmful product and potential market withdrawal will necessarily impact negatively on the public reputation of the regulator (Carpenter & Ting, 2007).[196] This general assumption holds true, even if the reason for the withdrawal must not necessarily be based on initial regulatory error. As Carpenter and Ting note regarding the FDA:

> "The logic of reputation protection suggests that regulators will see the decision to approve a new product as irreversible.[…] Yet if the FDA secures the withdrawal of a product it previously approved,

[194] For the sake of clarity it should be noted that most theories focus on the individual behaviour of bureaucrats and regulators, which can be motivated by a variety of interests, ranging from personal career development and the maximization of regulatory budget to the advancement of a specific public good (Levine & Forrence, 1990).

[195] This assumption is supported by studies providing evidence that lay people tend to adopt a perspective focusing on the benefits rather than risks of drugs as long as no regulatory crisis involving the specific product emerges (Bissell et al., 2001; Moldrup et al., 2002). For a more critical account of lay perceptions on pharmaceutical risks see (Abraham & Sheppard, 1997; Britten et al., 2004).

[196] According to Moshe Maor (2009: 6-14) a withdrawal can have a positive or a negative effect on the reputation of a regulator, depending on the *basis* of reputation. If regulatory reputation is based on expertise, withdrawal will have a negative effect since the agency must revoke its own decision. If reputation is based on guaranteeing public safety in the media, withdrawal will have a positive effect. The concept is based on the idea that non-expert agencies could blame expert agencies, as they based their decision on the previous decision of the expert agency. This conceptualization seems to be flawed. It is true that the level of expertise between national agencies varies and obviously many agencies are influenced by the decisions of the US agency (FDA), representing the gold standard (Coombes, 2007) of global drug regulation. Yet, a withdrawal will always have a negative effect on reputation and it is hard to believe that an agency would admit that the decision of market approval was completely based on a previous assessment – with the DP/MRP procedure as a notable exception. In addition, Maor seems to assume that the regulatory agency can simply determine how it is perceived by the public – an assumption that can be challenged as well.

> or attaches important new information to the product which was not detected at earlier review stages, it will only publicize its own 'error'.[original emphasis]" (2005: 1)

The safeguarding of reputation towards the public will push regulators towards a more risk-averse regulatory approach. Moreover, it will impact on the interests during the post-authorization phase and the general mode of governance. In contrast to Moshe Maor (2009: 6), arguing that some regulators will have an interest in public exposure, encouraging media-effective drug withdrawals to generate reputation as a public guardian, previous studies on regulatory behaviour indicate that most European (national) regulators pursue a low public profile (Abraham & Davis, 2007; Wiktorowicz, 2003). While the viability of such a strategy will depend on the public exposure of the regulator as well as the public interest in the subject of drug safety and the media, this study assumes that regulatory agencies will try to omit public exposure and media attention to maintain a positive public reputation.[197]

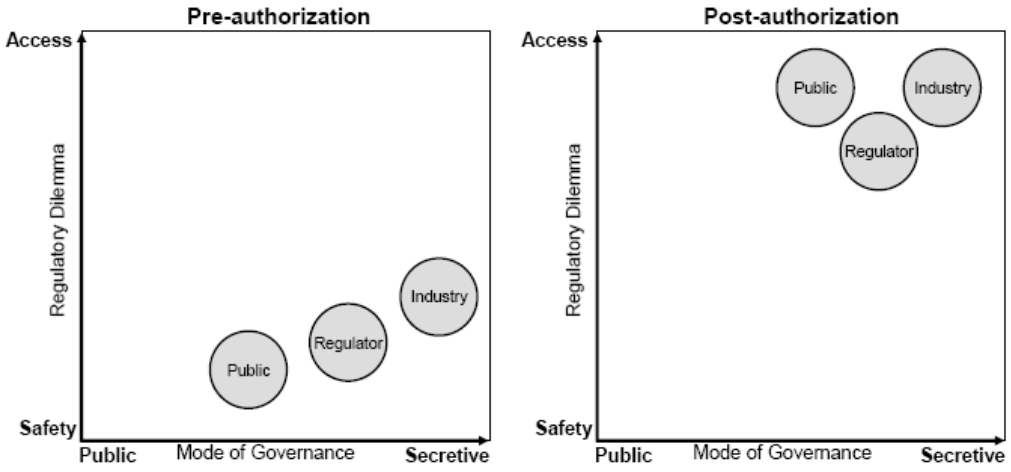
While the need to build a public reputation is obvious, the need to build a reputation towards the industry flows from the specific mode of funding of (public) pharmaceutical regulators. In light of financial dependence on regulatory fees and the depoliticized character of pharmaceutical regulation, regulators might even lean towards regulatees, overemphasizing their interest in the formation of their own regulatory interest. The main influence on the interests of the regulators can be seen in the previously discussed interest in low public exposure of the regulatory process. The regulator's preferred secretive mode of governance advances the reputation towards the industry as well. The industry has no specific interest in a highly transparent and participative regulatory process, mainly because of confidentiality reasons (Abraham, 2005; Garattini & Bertele, 2001). Given that the industry prefers an efficient and predictable regulatory process, regulators can be expected to develop stringent regulatory processes and guidelines to facilitate the regulatory process for the regulatees and reduce procedural uncertainties. Turning to the valuation of safety and access regulators and regulatees, as well as the public, share a common position. In order to advance the reputation towards the industry, the regulatory assessment should be conducted in a timely fashion, but without compromising the safety of the product.

[197] Compared to the high public exposure of the FDA, most European national regulators and the EMA are arguably left alone by the public, even though the EMA – intentionally or unintentionally – becomes increasingly exposed.

7.1.4 Intermediate result: Interests and conflicts in the regulatory arena

The functioning of a regulatory system and the realization of regulatory goals, presupposes the alignment of the key stakeholder interests. In the case of the pharmaceutical sector an overlap of interests can be identified. Considering the regulatory dilemma of safety versus access a consensus between the three considered stakeholders exists. The provision of safety is a shared goal, even though individual reasons for this consensus vary. While interests diverge regarding the valuation of access, the differences can be described as gradual rather than fundamental. The second dimension of alignment considers the organisation of the regulatory decision-making process. Since the public interest does not necessarily prefer a specific regulatory set-up but focuses on regulatory outcomes, alignment of interests concerns regulators and regulatees. Again, no conflict of interest is traceable. Both regulators and regulatees can be expected to prefer a science-based and secretive mode of regulation. While an equilibrium of interests exists within the regulatory arena, there are several factors potentially preventing it from translating into a functioning regulatory regime in the European pharmaceutical sector. First, the assumption of time inconsistency regarding regulatory interests can not be upheld, if the whole regulatory lifecycle is considered. While all three parties consider safety as an important issue in the pre-authorization stage, the constellation of interests moves towards access considerations in the post-authorization stage. The industry wants to keep the product on the market for commercial reasons. The public considers the drug as safe enough – at least as long as no regulatory crisis emerges – and will not accept that a drug is withdrawn from the market. The regulator, in light of reputational considerations, has little interest to withdraw a drug that he had previously considered as safe enough. Paradoxically, this situation still represents an equilibrium of interest, but has certain negative implications for regulatory effectiveness. In general terms, compliance of regulators and regulatees can be expected to be lower in the post-authorization stage. Regulators reputation is mainly based on the pre-authorization process. While pre-authorization regulatory science has evolved throughout time and the accumulation of regulatory experience provides at least partial certainty, the right decision in the post-authorization stage is marked by an even higher level of uncertainty (Anon, 1995b; Hughes et al., 2007).

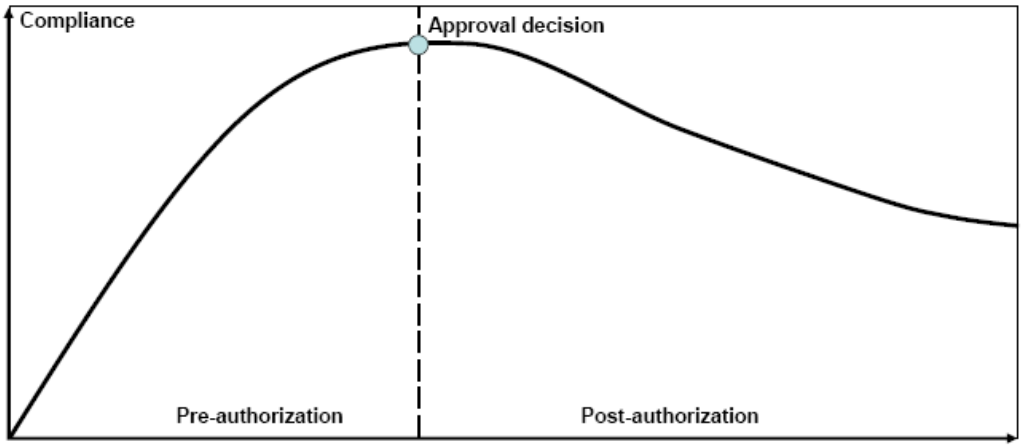
Graph 15: Regulatory interests pre- and post-authorization (illustration)



Source: author's own

More importantly, the decision to withdraw the drug will negatively impact on the public perception, at least if the withdrawal causes public and media attention, and on the reputation towards industry. Beyond the regulator's lack of interest in vigorous post-market control the effectiveness of post-market controls is hampered by the possible lack of regulatee's compliance.

Graph 16: Compliance in the pre- and post-authorization stage (illustration)



Source: author's own

In the pre- authorization stage, the will to comply is high and increases as the review process moves closer to the regulatory decision. As soon as the product has passed the regulatory hurdle, it can be assumed, that the willingness of industry to comply with additional regulatory burdens decreases. Furthermore, the interest to detect safety signals and follow up on them is arguably low, since the more safety signals are detected, the higher the risk of label warnings, additional studies and eventual withdrawal. Companies do not want to risk a regulatory crisis, but driven by commercial consideration they might tend to increasingly

ignore the signals. Beyond theoretical arguments, evidence from the US market supports the idea of time-inconsistency in compliance. Based on analysis of FDA data, a study by Jerry Avorn shows that 71 percent of requested post-marketing studies were not started, even though producers were obliged to deliver additional safety data (2007: 1698). Second, the equilibrium of interest does not prevent conflicts resulting from national regulatory differences. As pharmaceutical regulation is conducted in a European regulatory network, national authorities are pitted against each other in the European level regulatory procedures, driven by the collection of industrial fees. This competition may lead to more cooperative regulatory interaction, but it remains unlikely given the identified interests that regulators will dramatically reduce testing requirements. The more decisive element of conflict results from the reputation considerations of national regulators. Drawing on the previously introduced concept of national pharmaceutical risk cultures, differences will affect regulators in their behaviour because of two reasons. First, the need to build a reputation towards the public will make regulators consider public risk perceptions. Second, regulators themselves are affected directly by the underlying national pharmaceutical risk cultures. National regulators can be expected to oppose assessments of other national regulators representing a possible thread to their own reputation. While learning and repetitive interaction between national regulators can help to increase trust in the regulatory capacities of other regulators, the underlying reason for these conflicts are rooted in different risk cultures and therefore will be eradicated only gradually. Two main conclusions can be drawn at this point. First, the regulatory system will work more effectively during the pre- authorization phase, while the post- authorization phase might suffer from a general lower level of compliance based on the time-inconsistency of regulatory interests. Second, national pharmaceutical risk cultures will translate into differing regulatory cultures, resulting in different risk perceptions in drug assessment and a lower level of acceptance of external assessments serving as the basis of authorization in the mutual recognition system characterising the European regulatory approach.

7.2 Evaluation of the regulatory regime

The development of the European regulatory regime is closely connected to the general policy developments in the sector. Regarding the evolution of the regulatory regime the critical juncture must be seen in the establishment of the EMA and the according European level

procedures. The next section will focus on the sectoral governance considering the regulatory lifecycle before 1995.[198] In the following section, the phase after 1995 will be considered.

7.2.1 The effectiveness of regulatory regime until 1995

The regulatory regime initially consisted of the six competent national authorities connected by the introduced harmonized authorization criteria entailed in directive No. 65/65/EEC. Adherence to these standards was however not fostered by the creation of supranational structures. Despite this lack of institutionalization, the harmonization of assessment criteria must be understood as improving the effectiveness of national approval procedures and the regulation of development process.

7.2.1.1 Governance of development

With the introduction of the testing directive in 1975 and the increasing density of the regulatory framework, discretion of applicants regarding the development process was reduced. However, the governance of the development process remained largely within the responsibility of the respective applicants. The lack of regulatory involvement is exemplified in the diverse practice regarding the supervision of clinical trials. While some states demanded notification of trials, some made authorisation of clinical trials mandatory but a common approach especially considering the requirements of trial design was clearly missing (Jefferys & Jones, 1995; Lemmens, 2004). This did not only result in concerns regarding the quality of results, but led to possible problems for the mutual recognition of trial data. Above all, it compromised the idea of a high level of patient protection throughout the European Community (Hart, 1989). Furthermore, the lack of a central register of clinical trials in Europe made the suppression of unfavourable results more likely (Lauritsen et al., 1987).

7.2.1.2 Governance of approval

As the *thalidomide* scandal proved, no adequate approval controls existed in most member states. From the perspective of European sectoral governance, the CPMP represented a first step towards establishing a “hub in a network of national experts” (Burkard & Abraham,

[198] The following assessment deviates from the previously identified policy phases, using 1995 as the cut-off point. However, this is justified by the fact, that the EMA as well as the new approval regime were introduced at that time.

2008: 28). This intention was reflected as well in the *CPMP procedure* aiming at the rationalisation of decision-making by reducing duplication efforts inherent in the purely national regulatory approach. However, the procedure did fail to realize this goal, given the refusal of national authorities to accept the CPMP assessments.[199] During the eight years of its existence (1976 to 1985), 41 applications were made of which 28 received a favourable opinion (Cartwright, 1991: 222).

On first sight, the *multi-state procedure* improved the situation considering the higher number of applications. In the first four years of its existence applications nearly quadrupled from 41 to 142.[200] Despite this arguable success, the procedure did not lead to a reduction of assessment efforts. Instead it resulted in additional work, as every single application led to a CPMP opinion. With the exception of Luxembourg, all member states raised reasoned opinions with Italy using this option in 93 percent of all applications (European Commission, 1991b: 17-18). While national authorities were expected to communicate regulatory measures after CPMP decision within 60 days, several national authorities still failed to comply with this task after 46 months. In 1990, out of the 142 applications only 45 were completed (European Commission, 1991b: 13-19). In 1993, more than 300 products had entered the Multi-State Procedure, with only one product authorized without reasoned objections, and the request of an opinion by the CPMP remained the *standard* procedure (Jefferys & Jones, 1995: 473).

The *Concertation procedure* established in 1987 – limited to innovative products derived from biotechnology – saw a comparative decline in the total number of applications. Between 1987 and 1994, 51 products used this authorization route (Earl-Slater, 1996). The procedure foresaw specific timelines to which national agencies were expected to adhere to. Unsurprisingly, compliance remained low: national regulators needed as long as 27 months to comply with notification requirements (European Commission, 1991b: 28). As it was argued previously, none of the three procedures did manage to life up to the expectations (Earl-Slater, 1996; Lorenz, 2006). The reasons for the malfunction of the system can not solely be ascribed to the procedures itself.

[199] This assertion is based on two facts. First the number of applications was relatively low compared to the number of national procedures. Second, the products that were licensed through the procedure were mostly old products (second applications and generics) (Cartwright, 1991-26).

[200] To put this trend into perspective, it must be noted that the applications using this procedure represented less than 4 per cent of the products licensed by national authorities in the EU (Earl-Slater, 1996: 18).

Table 13: Performance of European application procedures (1965-1995)

	CPMP procedure (1976-85)	Multi-State procedure (1986-1993)	Concertation procedure (1987-1994)
Number of applications	41	> 300	51
Positive	28	n.r.	n.r.

Source: adapted from (Earl-Slater, 1996; European Commission, 1991b); n.r.= no information was recorded

In light of the previous discussion of regulatory interests and the inherent uncertainty in risk regulation, the explanation for the weak compliance can be seen in the interplay of two factors. First, national regulatory authorities – despite differences in the range of competencies, administrative traditions and structures – enjoyed considerable discretion from the outset of Europeanization of the pharmaceutical sector. Formally, in all member states – except the Netherlands – the final decision on approval "was granted in the name of Ministers who form the final authority and hence are answerable to the national parliaments and through them to the people" (Jefferys & Jones, 1995: 472). Yet these decisions were predetermined by the national regulators. On first sight, it would have been highly probable that the regulatory crisis surrounding the *Thalidomide* incident led to a stronger political supervision and more rigid political control. Instead, national governments raised the level of regulation, but did not increase political control over regulatory bodies (Hart & Reich, 1990; Jefferys & Jones, 1995). Applying the uncertainty avoidance argument, this counter-inductive development in the sector can be explained: regulators were isolated, because of governmental political benefit/risk assessments, providing them with comparatively high regulatory *discretion*. Political isolation hence amplified the impact of regulatory cultures on risk perceptions and assessments underlying regulatory decision-making. National regulators had little interest to trust other national regulators since the building of reputation was limited to the contacts within the CPMP, representing an immature institution at this point in time. The second factor allowing for the impact of national differences was a lack of control within the regulatory regime. Essentially, all procedures enacted before 1995 were non-binding and required the national willingness for mutual recognition. By granting the CPMP only a coordinating function, the constellation of national interests was not *outbalanced* by the regime. While the established procedures clearly failed to fulfil their purpose, this did not necessarily impact negatively on the regulatory effectiveness concerning the pre-authorization stage: based on the directives enacted during the 1960s and 1970s, all pharmaceuticals were subjected to approval based on the same criteria. While harmonized standards could not ensure a uniform

understanding and interpretation, their application represented a clear improvement to the previous situation from a public health perspective.

Even though the CPMP did not contribute to the effectiveness of the initial European procedures as expected, its creation must still be understood as an important step for development of the regulatory regime. Beyond the regulatory arena, the CPMP and the PC served as scientific advisory panels for the Commission in the development of new policy proposals and the starting international harmonization within the ICH which was established in 1990.[201] Within the regulatory arena, the CPMP facilitated dialogue creating the preconditions for stronger collaboration in the following years. More specifically, the CPMP and its numerous working parties developed most of the *soft law* instruments that helped to govern the pharmaceutical sector until this very day most notably the *Notice to Applicants* document advancing the harmonization of dossiers and the Eudralex database (European Commission, 1991b: 6-11). These instruments are of crucial importance for the effectiveness of governance, since the legal framework was and is inherently characterized by rather general and imprecise requirements (Glaeske et al., 1988: 34).

7.2.1.3 Governance of production

The regulation of pharmaceutical production was a shared responsibility of the industry and national authorities. However, activity on behalf of the regulators was rather limited and must be seen in context of under-regulation identified in the previous chapter. While the WHO already published guidelines on *good manufacturing practice* (GMP) in 1967, European rules were introduced in 1975. The role of the *qualified person*, responsible for the assurance of quality in the production process and the requirements for good manufacturing, remained fairly general. While inspections were envisaged within the document, no systematic and coordinated assessment of production sites based on uniform European rules and an exchange of information was mandatory.[202] The creation of the CPMP did not contribute significantly to the reduction of the *governance gap*, even though a working party on quality was established. While after the adoption of directive No. 91/356/EEC, the control of manufacturing was improved, the sector was still lacking a clear governance structure (Jefferys & Jones, 1995).

[201] The ICH played an important role for the development of the European pharmaceutical policy and the harmonization of global pharmaceutical regulation (Abraham & Reed, 2002; Eakin, 1999; Vogel, 1998).

[202] Even though no European coordination took place, it must be acknowledged that several member states joined the *Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme* (PIC/S) aiming at the mutual recognition of national inspections (Brunner, 2004).

7.2.1.4 Governance of distribution

The regulation of distribution remained the *blind spot* of the regulatory regime until the wholesale directive No. 92/25/EEC was released. Even after the introduction of the directive, control of distribution channels remained on the national level and was mainly based on licensing and the adherence to certain standards. Moreover, wholesalers were expected to check whether their customers were licensed (Andersson, 1994: 275). Beyond the control of distribution, the dispensation of pharmaceuticals remained unregulated on the European level, since it constituted an integral part of national health systems remaining within the domain of exclusive national competencies (Erbsland & Mehnert, 1992).

7.2.1.5 Governance of information

While informational requirements regarding the pharmaceutical product were subjected to uniform rules after the introduction of several directives in 1992, no distinct governance structures safeguarding the distribution of information on pharmaceutical risks were established. Direct information to patients was limited to package leaflets and differences in transposition as well as dispensation practices lead to different levels of patient information in the member states, even after the introduction of European rules. In the UK for example, the repackaging of pharmaceuticals resulted in the separation of the product and the accompanying leaflet (Anon, 1995a: 86).[203] Central and publicly available national databases did neither exist in most member states nor on the European level.

7.2.1.6 Governance of monitoring

The monitoring of pharmaceutical risks during the first policy phase was highly fragmented. National pharmacovigilance systems developed in parallel and due to a lack of European rules reflected no systematic approach, as the adoption of pharmacovigilance measures was voluntary.[204] Most monitoring systems were based both on input from the medical profession and the pharmaceutical manufacturers subsequently gathered by regulatory authorities

[203] While the practice in the UK surely represented a distinct case, repackaging still affects the provision of information to the consumer, even if European rules were ought to be transposed until 1999 (Raynor & Knapp, 2000).

[204] The German system of pharmacovigilance for example, was based on the collaboration of the national regulator (BGA), authorities of the German federal states, a special commission of the physicians association (Arzneimittelkommission der deutschen Ärzteschaft), the pharmacists association (Arzneimittelkommission der Apotheker) and the reports collected by the pharmaceutical association through their medical representatives (Glaeske et al., 1993: 42-44).

(Griffin, 1986: 84-85).[205] Based on administrative traditions and political structures, member states chose very different regulatory systems to gather information and assess risk/benefit ratios of marketed medicinal products, resulting in differing levels of compliance and signal detection across the countries (Glaeske et al., 1988: 20-26). These differences were amplified by a lack of sanctioning power of regulatory agencies in case of *non-compliance* with reporting requirements (Hart & Reich, 1990: 102). In contrast to pre-authorization regulation, the governance of post-authorization aspects obviously diminished the regulatory effectiveness of the regime. National pharmacovigilance systems based on different definitions and methods did not produce comparable results, representing the basis for effective cross-national pharmacovigilance and more rapid signal detection (Lindquist, 2007). The low institutionalisation of post-authorization controls mainly resulted from the prevalent regulatory philosophy at the beginning of modern European pharmaceutical regulation, emphasizing pre-authorization controls. Despite the differences and isolation of national pharmacovigilance structures, some collaborative efforts on the supranational level were traceable. The CPMP established a rapid alert system for the exchange of information on ADRs and installed a working party on pharmacovigilance in 1989 (European Commission, 1991b: 32-33; Wood, 1992). Moreover, the committee regularly conducted pharmacovigilance meetings and discussed specific actions regarding the management of safety signals. However, as in the case of authorization, these discussions had a non-binding character. Alongside the CPMP, the international drug monitoring programme by the WHO established in 1978 and the corresponding *Uppsala Monitoring Center* (UMC) completed the respective regulatory structures.[206] Even though the decision to take regulatory measures as a reaction to safety signals in all national systems was based on the same criteria, concrete actions were negotiated with the industry rather than obstructed by regulators (Hart & Reich, 1990: 114). This regulatory approach might have contributed to the general compliance of the industry, but its effectiveness must be questioned. Given that the industry was in favour of less intrusive instruments, regulators might have refrained from stronger forms of intervention based on previously negotiated consensus. This speculation has been supported to some

[205] For an overview of the different systems, see Griffin (1986), Inman (1980) and Wille & Schönhöffer (2002)

[206] The UMC (http://www.who-umc.org/) collects data from WHO countries on ADRs to facilitate the detection of safety signals. The European regulatory framework mandates regular communication of safety signals to the centre.

degree by the actual practice of national regulators, often favouring weaker forms of intervention (Hart & Reich, 1990: 115).[207]

7.2.1.7 Regulatory principles within the regulatory regime before 1995

Considering the realisation of regulatory principles – *participation*, *transparency* and *accountability* – the criteria were only partially met. Participation of other stakeholders and the public both in the pre- and post-authorization stage, in comparison to the strong involvement of the industry, was practically non-existent during the first phase. The public was largely excluded from the pre-authorization stage in national procedures and in the emerging European procedures as well. Regarding the post-authorization stage and the conduct of post-authorization controls the public participated only indirectly – with the notable exception of Ireland allowing direct patient reporting – while the industry assumed an active role. This practice can only be justified from a practical and necessarily science-based perspective. Letting *uneducated* patients report on ADRs can lead to false and more crude signals and runs the risk of over-reporting in more general terms (Egberts et al., 1996; van Grootheest et al., 2003).[208]

The *transparency* of the regulatory process on the national and European level was very limited. Publication requirements only affected the internal communication between national regulators. The creation of a regulatory *black box* covering the interaction between national regulators, the CPMP and the applicants, was possible because of the political isolation of the regulatory field and the previously identified confluent interests of regulators and regulatees.

In considering the overall *accountability* of the regulatory regime, no uniform assessment is possible. First, *legal* accountability of regulatory decision-making was comparatively weak as all decisions both in national and European procedures were made by member states. Therefore, the ECJ had no competence in scrutinizing regulatory decisions (Krapohl, 2008). Despite Germany, where regulatory decisions could be and were regularly challenged by the applicant, most national regulators were subjected to limited forms of judicial review (Hart & Reich, 1990: 58-60). Accountability was skewed as regulatory decisions could only be

[207] Since these results are based on analysis of the initial six member states, one should abstain from generalization. In addition, the tendency towards softer forms of intervention can be seen as an approach based on *proportional responses* and does not necessarily reflect a state of capture.

[208] Considering the prevalence of under-reporting in pharmacovigilance (Lopez-Gonzalez et al., 2009; Wysowski & Swartz, 2005), it could be argued to the contrary that increased patient reporting and education seems to be necessary to improve post-market regulation.

challenged by applicants, while the public, based on the claim that it was not directly affected, had virtually no possibility to challenge decisions. Considering the *financial* accountability of the regulators control was mainly exercised through budgetary games between regulators and their respective political principal, in most cases the national ministry of health. Financial accountability vis-à-vis the applicants arguably played a minor role: since the regulatory competition for conducting assessments was rather limited, as the comparatively low levels of applications for the European procedures indicates, applicants had no means to assert pressure on regulators. Evaluating the *procedural* accountability of the regulatory regime is complicated by the lack of openness of the national procedures. Considering the fact that national regulatory procedures were revamped and codified in distinct national pharmaceutical law after the *thalidomide* scandal, procedural accountability was reflected in the design of regulatory structures. Especially in those countries with a high degree of legalization of regulatory procedures, most notably Germany, national regulators had a strong interest in clear procedural rules and adherence to avoid possible infringements of applicants (Hohgräwe, 1992: 219). In case of the European procedures, the detailed procedural requirements and timelines warranted the procedural accountability at least in principle. *Substantial* accountability of the regulatory regime both regarding purely national and European procedures was mainly based on directive No. 65/65/EEC. Given the (unavoidable) vagueness of the three criteria quality, safety and efficacy, room for regulatory discretion remained (Hart & Reich, 1990: 24). While the CPMP was created with the intention to limit such regulatory discretion, as decisions could be referred to the Committee in case of differing interpretations of the directive, this internal accountability mechanism was ineffective since CPMP opinions were non binding.

7.2.1.8 Intermediate result: governance as patchwork

Drawing on the brief discussion of the regulatory lifecycle, the regulatory regime in the pharmaceutical sector before 1995 is best described as a *regulatory patchwork* (Héritier, 1996). While the regulatory framework after almost 30 years reached a considerable level of density, the establishment of governance structures was lagging behind. Implementation was largely shifted towards private actors, most notably pharmaceutical manufacturers and wholesalers. The CPMP was lacking the necessary competencies to effectively tie in national authorities. Accordingly, the effectiveness of the regulatory regime before 1995 must be considered as constrained. While public health was safeguarded in principle, as market

authorization became mandatory and based on specific criteria, a single market in the sense of functioning mutual recognition was clearly not established. From the perspective of industrial policy and innovation, the regulatory regime did not rationalize the regulatory process as intended. The lack of collaboration and appropriate structures was even more problematic regarding the post-authorization stage. While national pharmacovigilance systems existed, little was done to streamline and rationalize the exchange of information. Instead, the situation clearly represented a state of under-regulation and under-institutionalization (Hart, 1989: 350-351). The overall dissatisfying situation was aggravated by a lack of openness, participation and accountability of the regulatory regime. These results are in line with the expectations drawn from the interests of actors in the regulatory arena and the uncertainty avoidance argument. Even though national regulators were not totally independent, most of them enjoyed considerable regulatory discretion. Based on a logic of reputation and the lack of power of the European institution, national regulators opposed to stronger collaboration regarding regulatory decisions both in the pre- and post- authorization phase.

7.2.2 Institutional transformation of the regulatory regime after 1995

The two new European regulatory procedures and more importantly the EMA, created in 1995, marked a turning point and heralded a new governance approach. In contrast to its predecessor, the CPMP, the EMA did not simply represent another expert committee, but an independent regulatory agency (IRA). Since the instalment of an agency was not limited to the regulatory field under review but a European trend, the reasons for the creation of the EMA must be understood beyond the sectoral *necessity*, but within the context of a shift in the general European approach to sectoral governance.

7.2.2.1 The European regulatory state and the rise of regulatory agencies

While independent regulatory agencies were a common and longstanding feature of regulatory regimes in North America (Shapiro, 1997), the trend of *agencification* (Christensen & Laegreid, 2005) in Europe has been a comparatively recent phenomenon starting with the increased deregulation of industrial sectors, the diffusion of *New Public Management* (NPM) and the subsequent instalment of new independent regulatory institutions in the 1980s (Eberlein & Grande, 2005; Scott, 2000; Thatcher & Coen, 2008). These institutions emerged in several waves on the national level. While some agencies date back to the 1950s and 1980s,

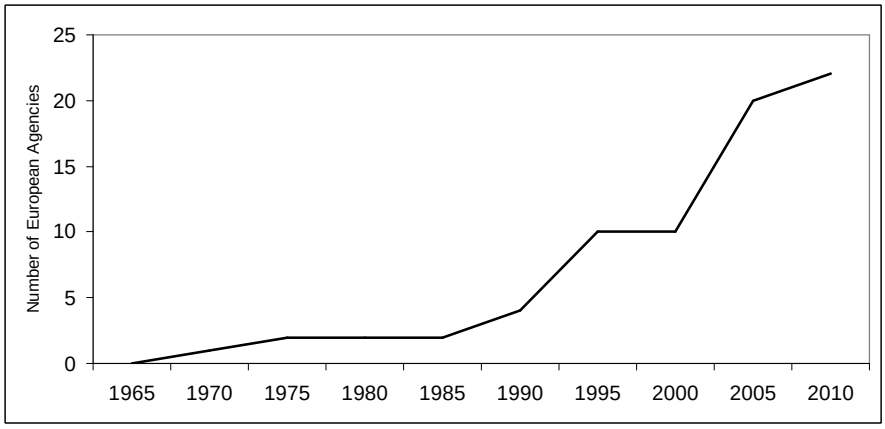
most organisations were created in the nineties and at the start of this millennium (van Thiel, 2009: 12). The term agency subsumes a wide array of different institutional forms since "what an agency is and what it does varies considerably across national and organizational cultures, legal systems and political systems" (Christensen & Laegreid, 2005: 5).[209] Research of agencification in European member states has developed into a vivid research field mainly based on comparative qualitative studies (Christensen & Laegreid, 2007; Gilardi, 2005; Jann, 2007; Thatcher, 2007; Thatcher & Coen, 2008). While agencification at the European level through the creation of European agencies (EA) is "no new phenomenon" (J. Pollak & Riekmann, 2008: 775) and some authors contributed to the field (Chiti, 2000; Everson, 1995; Fleischer, 2005; Kreher, 1997; Majone, 1997; Shapiro, 1997), in-depth research on the functions and consequences of these organisations from a comparative perspective is still in an early stage (Barbieri & Ongaro, 2008; Geradin & Petit, 2004; Krapohl, 2004, 2008; Vos, 2000, 2005). While two agencies were already founded in the 1970s, two main *waves* are traceable in the emergence of EAs. The first one happened in the mid 1990s including the creation of the EMA and the second one in the 2000s.

European agencies represent a heterogeneous group of organisations given their distinct tasks and competencies and several classifications have been proposed (Chiti, 2000; European Commission, 2002; Geradin & Petit, 2004). As a common feature agencies share "that they have their own legal personality and a certain financial autonomy" (Pollak & Riekmann, 2008: 777). In addition, all agencies – at least those created from the 1990s onwards – have the basic task of *information gathering*. Turning to the reasons for the establishment of European agencies, variations of general delegation arguments are invoked as theoretical reasons: the improvement of efficiency (1), the improvement of the capacity of the central government (the Commission) to focus on strategic aspects rather than administrative tasks (2), Creating specialist agencies concentrating policy expertise to facilitate objective, unbiased and better regulation (3), Enhancing policy credibility through depoliticization (4) and improving the overall legitimacy of a regulatory regime based on better output (5) (Geradin & Petit, 2004; Majone, 2002; Pollak & Riekmann, 2008). Beyond the theoretical claims, it is important to highlight the politics involved in their creation. While the first wave of agencification at the European level was a concerted approach of the political actors, their foundation was mainly driven by the European Commission and can be linked to the previously discussed *better regulation* debate (Chiti, 2004). While the Commission saw a

[209] For a widely recognized definition see Pollitt et al. (2001: 274-75).

window of opportunity to expand its activities in the wake of the single market initiative, independent agencies seemed to be the only feasible option from a political perspective.[210]

Graph 17: Agencification on the European level (1965-2010)



Source: based on EU data (http://europa.eu/agencies/community_agencies/index_en.htm) (last accessed January 2, 2010))

Agencies at least partially controlled by the Commission allowed for an indirect expansion of governance capacities, providing the Commission with the opportunity to focus on its strategic task by delegating sensitive and work intense activities to expert institutions.[211] Beyond the advancement of regulatory capacities, the Commission envisaged the creation of agencies as a means to improve the quality of European regulation (European Commission, 2001: 23-24).

7.2.2.2 European agencies: a challenge to social legitimacy

The positive notion of European agencies advocated most prominently by Giandomenico Majone (1997, 2006, 1999) and several other authors (Fleischer, 2005; Tarrant & Kelemen, 2007), is based on the claim that agencies can play a vital role in achieving effective European regulation. What is largely downplayed by the proponents of European agencies, are the possible problems that may arise from their creation. First, it is questionable in how far the creation of agencies really meets public expectations. The Commission's logic seems to be based on the notion that "because Europeans don't like the technocrats in Brussels and fear

[210] In fact, some Commission officials viewed the creation of agencies as a *second best* option, since expanding resources within the Commission would have been in their interest (Kelemen, 2002).

[211] Member states demanded a strong position in the control of the agencies. Moreover, their cautious position of delegating competencies to these expert bodies resulted in a rather limited mandate for some of the agencies (Kelemen, 2002: 102-103). However, the official mandate does not necessarily imply that agencies do possess a low degree of *de facto* independence (Gilardi & Maggetti, 2009). In the case of the EMA, the creation was surrounded by less controversy, as interests between member states did converge around its creation (Kelemen, 2002: 103-104).

concentrating even more governance there, if we want more EU technocrats, we split them up and scatter them about Europe" (Shapiro, 1997: 281). Second, the creation of European agencies raises questions of legitimacy. European agencies are created through acts of delegated bodies criticized for a lack of social legitimacy and it is at least questionable if the chain of delegation is strong enough to legitimize these bodies (Bauschke, 2009; Vibert, 2007). If the delegation of certain tasks to an agent is contested, delegation activities by the agent should be contested as well. Closely connected to the issue of social legitimacy is the legal discussion surrounding the creation of European agencies in light of the *Meroni* doctrine, preventing the Commission from delegating regulatory powers to bodies not foreseen in the treaty (Geradin & Petit, 2004; Majone et al., 1999). Consequently, none of the regulatory agencies involved in decision-making processes takes the final decision. Instead this is done by the Commission and the other institutions involved based on the respective decision procedure. Even though most of the agencies only carry out information gathering tasks and provide expertise, they can have considerable influence on the resulting policy decisions. As Martin Shapiro notes, "What research we do, determines what policies we make. What policies we wish to make, determines what research we do. In this way information agencies are always policy agencies." (1997: 285). Even if agencies do not determine the respective decision they pre-structure decisions especially in high expertise regulatory fields (Barbieri & Ongaro, 2008). Majone, for once acknowledging the existence of the criticism raised regarding European agencies, concludes that:

> "The growing importance of nonmajoritarian institutions in all democratic countries, in spite of persistent doubts about their constitutional status and democratic legitimacy, shows that for many purposes reliance upon qualities such as expertise, professional discretion, policy consistency, fairness, or independence of judgment is considered to be more important than reliance upon direct democratic accountability." (2005: 37)

From this perspective, neither the claims of lacking social legitimacy of the European Union as a whole, nor the concerns regarding regulatory agencies are valid, since output legitimacy is the main interest of all parties concerned, and the mode of governance is generally accepted.[212] While the importance of output legitimacy for the legitimacy of European regulation is undeniable, Majone's perspective is based on assumptions lacking a sound empirical foundation. Majone simply assumes that the European people only care for

[212] Interestingly enough Majone explicitly refers to the acceptance of national regulatory agencies as a reason for the same acceptance on the European level. At the same time, he rejects the validity of applying legitimacy concepts developed in the context of the nation state to the European Union.

outcomes, while there is public indifference how these outcomes should be achieved.[213] He seems to believe that delegation to agencies will be tacitly accepted if the right outcomes are produced. While another question would be, what is considered as right outcomes, a decisive precondition for the assumption of *tacit acceptance* is the public awareness of European agencies (Pollak & Riekmann, 2008: 783-784). No systematic research on public awareness for regulatory agencies exists, but it can be expected on theoretical grounds, that the awareness for agencies, especially in risk regulatory areas, is low. The creation of agencies thus is not necessarily based on permissive consensus, but represents integration activities largely unnoticed by the public. Following from this, the creation of an agency in the field of pharmaceutical regulation necessitates a thorough discussion of its legitimacy and control. The question of control goes beyond the external control of the agency. Even more decisive from the perspective of legitimacy is the internal control of experts who are responsible for the actual regulatory decisions as these experts inhabit a privileged position enjoying delegated authority without being backed by a sufficient public mandate (Jasanoff, 2003: 158). Accordingly, the creation of a regulatory agency might represent a bigger challenge to legitimacy of the European regulatory state, as proponents of IRAs are willing to admit.

7.2.2.3 The EMA: role and structure

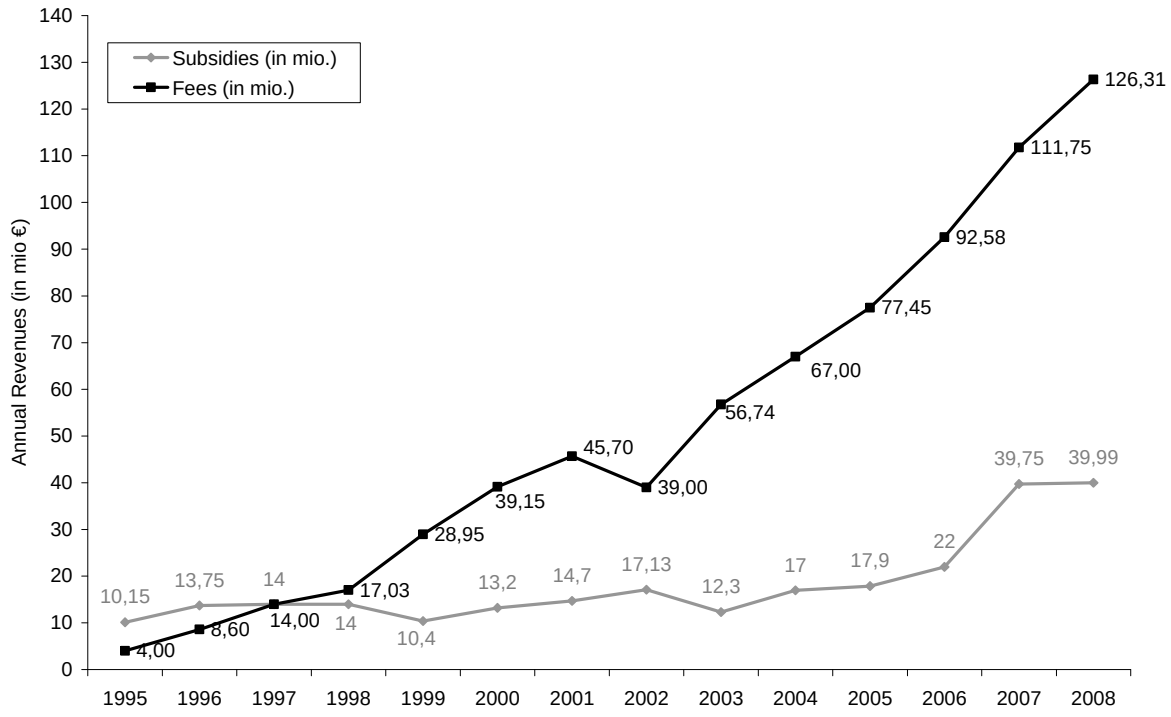
The creation of the EMA has been the result of a lengthy process and came at a time when the regulatory regime had more or less reached a *dead end*. Discussions did not only concern its powers and tasks but location as well. Several member states bid to site the newly created agency, but London was finally selected. Commentators argued that besides the strong position as one of the leading European industries and markets, the improved efficiency of the recently established UK regulator, the *Medicines Control Agency* (MCA) founded in 1989, played a decisive role (Horton, 1993: 1275). A condensed role description can be drawn from the mission statement at the agencies' website. Essentially, the role of the EMA is twofold: coordination of the European regulatory network consisting of the EMA and the national agencies (1) and the provision of scientific advice (2), especially regarding the authorization procedures on the European level (EMA, 2010). The EMA thus represent the supranational hub inside the regulatory network. Based on the heavy reliance on national resources, the

[213] This assumption resembles the efficiency perspective traceable within the broader *better regulation* debate and does not necessarily reflect the public perception. While in the case of pharmaceutical regulation the European public might actually support a *secretive* mode of governance, this assumption cannot be generalized for all regulatory fields.

EMA has been labelled a *virtual* agency. This assertion stems from the fact, that the structure of the agency evolved around the existing CHMP recruited from national experts in most cases located within national competent authorities, supplemented by administrative structures. Initially, the EMA consisted of an Executive director, a (financial) controller, a management board, the two scientific committees CHMP and CVMP and a Secretariat supporting their work.[214]

The EMA was initially financed exclusively through Community subsidies, but fees played an increasing role in agency funding. These were nevertheless not able to prevent the agency from experiencing budgetary deficits especially during the first years (Rogers, 1998). However, this situation changed with the significant increases in revenues from 1999 onwards. With an increase in regulatory activities and workload, staffing of the EMA has been expanded considerably as well from 68 in 1995 to 624 in 2008.

Graph 18: European Medicines Agency: development of funding (1995-2008)



Source: EMA annual reports; Note: Values for 1995-98 are measured in ECU.

To carry out its steering capacity more proactively, the *European Union Drug Regulating Authorities Network* (Eudranet) was established in 1998 and its function has been expanded in the following years (Rinaudo, 2001). The system is managed by the EMA but operates under

[214] During revisions of the regulatory system the structure of the EMA was differentiated further in 2004. In 2007, two additional committees were established: the *Paediatric Committee* (PDCO) and the *Committee for Advanced Therapies* (CAT).

the overall responsibility of the *Pharmaceuticals and Cosmetics Unit* within the European Commission's DG Enterprise and Industry.[215] It covers all aspects of the regulatory lifecycle, except *distribution*.[216] On May, 1 2004 *EudraCT*, the European clinical trials register, has been introduced. The *EudraTrack* system is used to manage the approval phase and has been operational since the establishment of the EMA. *EudraGMP*, launched in 2007, contains information on manufacturing authorisations and certificates. Already in 2006, *EudraPharm* was launched containing all products authorized under the centralised procedure. *EudraWatch* covering the pharmacovigilance activities has been operational since 1998 and was replaced by *EudraVigilance*, launched in 2001. Initially, the closed network was installed to facilitate communication between national agencies and the EMA regarding the approval process. During the following years, new modules were introduced that allow for the surveillance of nearly all phases of the regulatory lifecycle. It is important to note, that most parts of the Eudranet are not open to the public. As of 2010, only the databases covering authorized products are publicly available.[217] While the data base will be expanded it recently does not contain products authorized under national procedures and in the decentralized procedure. A separate database, the *European Product Index* (EPI), administered by the *Heads of Medicines Agencies* (HMA) exists for those products introduced after 2005 under this procedure.

Table 14: European governance tools and databases

Phase	Development	Approval	Production	Distribution	Information	Monitoring
Tool	EudraCT	EudraTrack	EudraGMP	n.a	1) EudraPharm 2) EPI	1) EudraWatch 2) EudraVigilance
Founded (year)	2004	1995	2007	n.a.	1) 2006 2) 2005	1) 1998 2) 2001

Source: EMA website; n.a.= no tool available

Considering the scientific advice function of the EMA, this task is carried out by the CHMP. Even though its main task is the scientific assessment within the centralized procedure and arbitration within the decentralized procedure, the body has a monitoring function in the post-approval stage as well (European Commission, 1991b). In addition, the committee engages in the development of guidelines and documents in order to increase the understanding of and

[215] At the end of 2009, the unit has been shifted to the DG for Consumers and Health.
[216] For an overview see Meencke (2002).
[217] The public databases contain restricted data, since products authorized before the database has been launched are not included. At the time of writing plans to open up the GMP database were discussed by the Commission.

compliance with European pharmaceutical regulation. The CHMP has therefore been granted the power to form working parties (ad hoc and permanent). Most existing working parties were formed before 1995 for example *Efficacy and Safety* was created in 1977, *Quality* in 1985 and *Pharmacovigilance and Operations* in 1989 (European Commission, 1991b: 8).

7.2.3 Regulatory governance after 1995

The changes in the pharmaceutical sector and the creation of the EMA did not only alter the regulatory network, but affected all aspects of the regulatory lifecycle. As the following analysis will show, the impact has been most pronounced in the governance of approval, but helped to rationalize the regulatory approach as a whole.

7.2.3.1 Governance of development

The EMA has been granted a supervisory role regarding clinical trials (Binns & Driscoll, 2000). The current governance approach – based on the combination of licensing and monitoring mechanisms – has mainly been the result of the clinical trials directive in 2001. Clinical trials conducted within Europe now must follow a comparable procedure and start with an authorization of a *research ethics committee* (REC) (Hedgecoe et al., 2006). The EMA remains involved in the governance of the development stage through the EudraCT database. In order to assess, if clinical trials are conducted according to the standards of *good clinical practice* (GCP IWG), the EMA can mandate inspections.[218] It is important to note that as a general rule the EMA does not conduct the inspection but asks competent national authority to do so. While using such *policing* mechanism can have an important effect on compliance, it seems questionable if the current regulatory practice does support this need. First of all, the tool – based on the limited evidence available – has been rarely used. In 2008, the EMA mandated 50 inspections (GCP IWG, 2009).[219] Furthermore, national regulatory capacities in the field of clinical inspections are underdeveloped and despite involvement of the EMA inspections (still) remain uncoordinated (Ward, 2006: 40). The European cooperative regulatory approach does expand to the conduct of clinical inspections as well, as

[218] Beside the requirements entailed in the respective guidelines the requirements which have to be met are defined in volume 10 of the pharmaceutical code (EudraLex).

[219] This number does only consider inspections mandated by the EMA/CHMP. National regulators still have the authority to conduct inspections.

the majority of inspections are previously announced routine inspections.[220] It thus seems that the introduced structural measures improved the control of development, even though coordination problems and the potential for a more effective inspections approach must be acknowledged.

7.2.3.2 Governance of approval

Judging the new approval regime based on its performance, both procedures show a high level of activity compared to the situation before 1995.[221] Within the centralized procedure, despite an incline in applications during 2001 and 2005, a constantly rising level of new applications is traceable. This increase is less surprising since the centralized procedure was gradually opened up to a wider range of products. At the same time the number of withdrawals under the CP increased. While no recent analysis on the current development is available, it can be argued that the reasons explaining higher withdrawal levels in the period between 1995 and 1999 are still valid.[222] Considering the number of applications, the decentralized procedure shows an impressive performance compared to the previous procedures based on mutual recognition.[223] While the number of referrals (arbitration) still points to room for improvement regarding the willingness to accept prior assessments, the introduction of the CMD(h), based on the limited evidence available, can be expected to have a positive effect on the overall compliance. The changes in sequence and the discussions prior to the market authorization of an RMS under the DCP can be expected to improve the situation further.[224]

7.2.3.2.1 Remaining challenges of the approval regime

Going beyond the assessment of application levels, the (external) evaluation of the approval system conducted by CMS in 2000 sheds some more light on the qualities and perceptions of the new system. Drawing on the position of regulators and regulatees, the report highlighted

[220] This implies that the regulatee can prepare himself, potentially diminishing the continuous compliance effect of policing mechanisms.

[221] The reliability of the approval data is at least restricted, especially considering the data on the decentralized procedure. Numbers provided on the HMA website differ from those published in the EMA annual reports. However, these differences may be explained by the annual data revisions.

[222] In its analysis, the EMA concluded, that the reason for this could be seen in *premature* submissions and concerns regarding efficacy (EMEA, 2000: 1)

[223] It is important to note that a significant part of rejections of the first assessment can be attributed to the product characteristics. The decentralized procedure is mainly used for the licensing of generics. Since the *Summary of Product Characteristics* (SPC) of these generics imitate the original SPCs and a lot of them have not been created based on harmonized rules, member states find it difficult to accept them (Janse-de Hoog, 2007).

[224] In light of an increasing number of CMD(h) referrals such developments seems to be likely.

an overall satisfaction with the CP by regulators and regulatees and to a lesser degree with the MRP/DP (CMS Cameron McKenna & Andersen Consulting, 2000: 71-76). While criticism regarding the CP mainly affected the political stage – the decision by the Commission and the Standing Committee – of the process, criticism regarding the MRP/DP was more fundamental and directly linked to the work of regulatory bodies. In effect, applicants regularly chose to withdraw their applications from the dissenting CMS in order to avoid binding arbitration. In 1998, for example, withdrawal from at least one member state happened in 47 percent of all procedures finalized in that year. However, this trend decreased in the following years to 30.5 percent in 2000 (Feick, 2002: 24). Considering the procedural changes after the second revision and the number of successful procedures, it can be argued that despite remaining drawbacks the current MRP/DP represents an improvement compared to the previous approval regimes based on mutual recognition. Accordingly the new approval regime can be deemed as clear improvement compared to the system in place before 1995, as cooperation in the sector increased. However, the reasons for these improvements cannot be attributed solely to the design of approval procedures, but are the result of several interrelated factors.

Table 15: Overview centralized procedure (1995-2008)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
Applications*	30	25	60	55	51	54	58	31	39	51	41	78	90	103	766
Decisions **	8	28	24	37	30	42	33	39	26	34	25	55	65	73	401
Positive by consensus***	8	28	23	21	24	31	31	34	20	34	24	51	58	66	453
Positive by vote***	0	0	1	13	2	11	1	5	4	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.
Negative	0	0	0	3	4	0	1	0	2	0	1	4	7	7	29
Withdrawn	1	3	7	20	8	11	11	13	4	7	15	8	9	23	140

Source: EMA annual reports (1995-2008); Note: *applications are considered product based; ** calculated based on positive and negative decisions; *** type of decision (consensus/vote) not recorded after 2003

Table 16: Overview mutual recognition/decentralized procedure (1995-2008)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
Procedures started	30	171 (since 1995)	190	183	275	373	484	587	620	935	857*	1046 *	1429*	1899*	9049
Completed during year	10	84	147	179	210	309	443	420	529	760	954	592	827	1174	6638
Arbitration	n.r.	2	1	1	2	2	1	2	5	9	10	127 (22)	44(25) CMD(h) 15(7) CHMP	39(43) CMD(h) 12(7) CHMP	n.a.

Source: EMA annual reports (1995-2008); Note: * including MRP and DCP; arbitration: number in brackets signifies DCP; n.a.: not applicable

7.2.3.2.2 Explaining the performance of the new approval regime

The first important factor leading to improved performance of the approval regime must be seen in the institutional convergence, affecting national pharmaceutical regulators. As it has been argued previously, agencification has been a common phenomenon both on the national and European level. Considering the dynamics of agencification and interaction between the two levels, institutional change mainly is a horizontal phenomenon: waves of agencification either happened on the national or the European level. In the pharmaceutical sector, agencification was traceable as well and it is argued here that it was mainly triggered by the emergence of the EMA.[225]

Agencification in the European pharmaceutical sector

Until 1990, only four member states had *agency-like* national regulators: *The College ter Beoordeling van Geneesmiddelen* in the Netherlands established in 1963, the *National Organisation for Medicines* established in 1983 in Greece, the *Medicines Control Agency* in the UK established in 1989 and the Swedish *Medical Products Agency* founded in 1990.[226] Starting with the first revision of the framework, following up on the Commission proposal, the number of agencies doubled until 1995 and tripled until 2000.[227] Today, Luxembourg is the only EU 15 member without an agency, explained by the lack of national pharmaceutical market and pharmaceutical industry. Of course, Europeanization and the instalment of the EMA, can not solely explain the agencification, but given the rapid increase of national agencies surrounding the creation of the EMA they should be understood as a catalyst in the process (Hauray, 2009: 439; Permanand, 2004: 49). While the national regulatory agencies in the pharmaceutical sector represent similar organisational types and their internal management structure resembles the EMA, the tasks and structures of the respective agencies differ widely.[228]

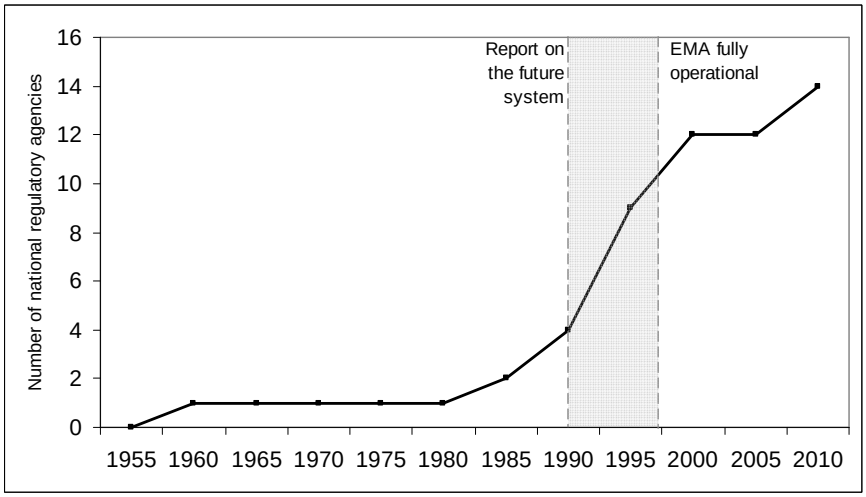
[225] In fact, the institutional blueprint of the EMA was mainly based on the previously created national regulator in the UK, the MCA (Abraham & Lewis, 2000).

[226] Since Sweden was no member state until 1995, it would be more precise to count only three agencies in EU countries before 1990.

[227] The accessing east and central European member states established agencies as well. However, the reasons for agencification presumably differ compared to the situation within the EU 15. A list of the national regulatory bodies is provided in the appendix (A.8).

[228] Data collection was complicated by the differing level of information provided by national agencies. If data could not be retrieved, agencies were contacted. In most cases, no additional information could be retrieved.

Graph 19: Agencification in the pharmaceutical sector EU 15 (1955-2010)



Source: websites of national regulatory agencies, Note: Luxembourg was excluded, since pharmaceutical regulation is carried out by a division of the health ministry

All national agencies operate under the supervision of the national ministry of health.[229] Looking at the responsibilities of the national agencies, their role in Denmark and Italy as well as in Portugal differs from other national counterparts, since they are not only involved in the process of safety evaluation but in the reimbursement decision as well.[230] At first glance, the agencification of national authorities clearly raised the level of independence, since national regulators now enjoyed even greater *regulatory discretion*.[231] Accordingly, previously encountered problems of coordination were most likely to increase. At the same time, agencification did not only increase regulatory *independence* but external *accountability* as well. Looking at the financing of the national agencies, the new regulators became increasingly dependent on the fees of applicants, especially from the European procedures.[232] This financing model increases the pressure on regulators to play by the rules, while at the same time raising questions about the objectivity of assessment, triggering a discussion on the immanent competition that characterizes the new approval system (Abraham, 2000; Garattini, 2001).

[229] This is one of the key differences to the EMA operating under the supervision of DG *Competition and Industry* raising criticism of several authors. The EMA was *relocated* at the end of 2009 and is now under the supervision of *DG Health and Consumers* (DG Sanco).

[230] While in Denmark and Italy agencies have the power to decide on reimbursement, the Portuguese agency (INFARMED) decides on reimbursement status in cooperation with the health ministry and the ministry of economy (Gouveia Pinto & Teixeira, 2002).

[231] Looking at the *de facto* independence of national pharmaceutical regulators compared to other regulatory fields, the higher level of autonomy is striking (Gilardi & Maggetti, 2009).

[232] The dependence on fees proved to be a problem during the economic downturn and resulting decrease in applications and public subsidies both for the EMA and the national regulators (Anon, 2006a).

Table 17: National regulatory agencies in the pharmaceutical sector (EU 15)

Country	Abbreviation	Authority Name	Funding	Staff*	Responsibilities
Austria	AGES PharmMed	Austrian Agency for Health and Food Safety	Fees Subsidies (20%)	250	Pharmaceuticals (H+V) Medical devices
Belgium	FAMHP	Agence Fédérale des Médicaments et des Produits de Santé	Fees Subsidies (30%)	350	Pharmaceuticals (H+V), Medical devices
Denmark	n.a.	Lægemiddelstyrelsen	Fees Subsidies	500	Pharmaceuticals (H+V) Reimbursement Pharmacies Medical devices
Finland	n.a.	Lääkelaitos Läkemedelsverket**	Fees Subsidies (20%)	190	Pharmaceuticals (H+V) Medical devices
France	AFSSAPS	Agence française de sécurité sanitaire des produits de santé	Fees Subsidies (10%)	990	Pharmaceuticals (H) Medical devices Cosmetics
Germany	BFARM	Bundesinstituts für Arzneimittel und Medizinprodukte	Fees Subsidies (30%)	800	Pharmaceuticals (H) Medical devices
Greece	EOF	National Organization for Medicines	Fees Subsidies	238	Pharmaceuticals (H+V) Medical devices Cosmetics
Ireland	IMB	Irish medicines Board	Fees Subsidies (20%)	280	Pharmaceuticals (H+V) Medical devices
Italy	AIFA	Agenzia Italiana del Farmaco	Fees Subsidies	250(2008) 459(2009)	Pharmaceuticals (H) Reimbursement
Luxembourg	n.a.	Direction de la Santé Villa Louvigny Division de la Pharmacie et des Medicaments	Fees Subsidies	n.r.	Pharmaceuticals (H+V) Pharmacies Cosmetics
Netherlands	CBGMED	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board	Fees Subsidies (30 %)	194	Pharmaceuticals (H+V) Novel foods
Portugal	INFARMED	Instituto Nacional da Farmácia e do Medicamento Parque da Saúde de Lisboa	Fees Subsidies	251	Pharmaceuticals (H+V) Medical devices Cosmetics Reimbursement studies
Spain	AEMPS	Agencia Española de Medicamentos y Productos Sanitarios	Fees Subsidies	470	Pharmaceuticals (H+V) Medical devices Cosmetics
Sweden	MPA	Medical Products Agency	Fees Subsidies (10%)	496	Pharmaceuticals (H+V) Cosmetics Medical devices
UK	MHRA	Medicines and Healthcare products Regulatory Agency	Fees Subsidies (15%)	875	Pharmaceuticals (H+V) Medical devices

Source: Websites of national agencies, annual reports; * 2007 was used as year of reference regarding the staffing levels; the level of subsidies has been included if data was available; n.r.: not reported; n.a.: not applicable; ** since 2009, the Finnish agency is called *Finnish medicines agency* (FIMEA)

Competition, beyond the lowering of standards is possible on several levels. First, there is an indirect conflict between the EMA and the national agencies manifested in the two available approval routes (inter-procedural). Given the financial dependence of agencies competition can arise regarding those products eligible for both procedures. Second, competition may arise within procedures (inter-agency). National authorities will have an interest to serve as rapporteur or RMS in the respective procedure. As a consequence, it is believed that the need to generate fees will drive regulators towards a more industry friendly position and, as it is feared by some commentators, to a general lowering of assessments standards to attract regulatory business (Abraham & Lewis, 1999).[233]

Competition within the regulatory system

Starting with the *inter-procedural* competition and drawing on the numbers of new applications of the two procedures, competition seems to be very limited. Growth trends in both procedures have been fairly stable. Furthermore, many applicants chose the mutual recognition procedure because of the flexibility, which is not as high in the centralized procedure.[234] While it might be likely that competition will rise in the future given a further expansion of products eligible for both procedures, the current trends do not point towards such a development. Considering *inter-agency* competition, data from the centralized procedure indicates some competition between national regulators regarding rapporteur status, but rather points to a stable *regulatory market* with few agencies responsible for the majority of the conducted assessments.

UK, Sweden, France, Germany together with the Netherlands and Denmark represented the lead agencies between 1995 and 2000 within the centralized procedure and the dominance of this group largely remained stable (MHRA, 2009: 14).[235] In addition, the selection process of the rapporteur within the EMA renders tough competition as rather improbable since "usually the manufacturer and the CPMP chairman suggest one rapporteur each."(Garratini & Bertele,

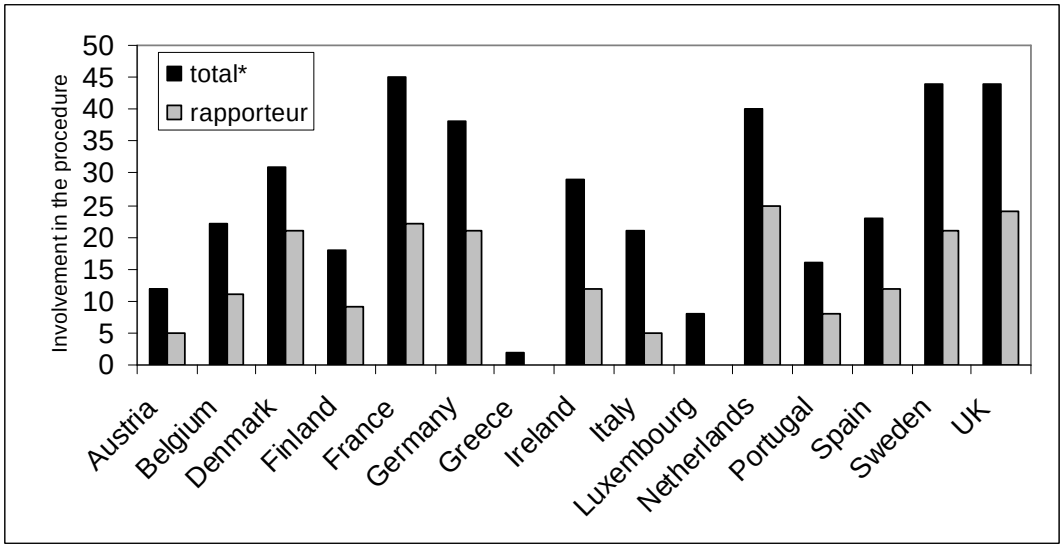
[233] In contrast, the discussion of the regulatory framework in the previous chapter rather suggests a levelling up of standards. This position is unsurprisingly shared by industrial representatives interviewed by Abraham and Lewis, while regulators either stated a constant or slightly decreasing level (Abraham & Lewis, 1999: 1657).

[234] In many instances, companies want to market a product in some of the Member States and unless it is a product for which the CP is mandatory, the decentralized procedure might represent the more fitting approval procedure (Janse-de Hoog, 2007).

[235] Since the EMA no longer publishes statistics on the RMS/CMS status, annual reports of national agencies were consulted. Depending on the sources, the ranking of national agencies after 2000 differs.

2004: 85) and it has been the official policy of the EMA to strive for a balanced representation of the CHMP members in taking the lead role in evaluation (EMA, 1998a: 24).[236]

Graph 20: Involvement in centralized procedure in the EU 15 1995-2000**

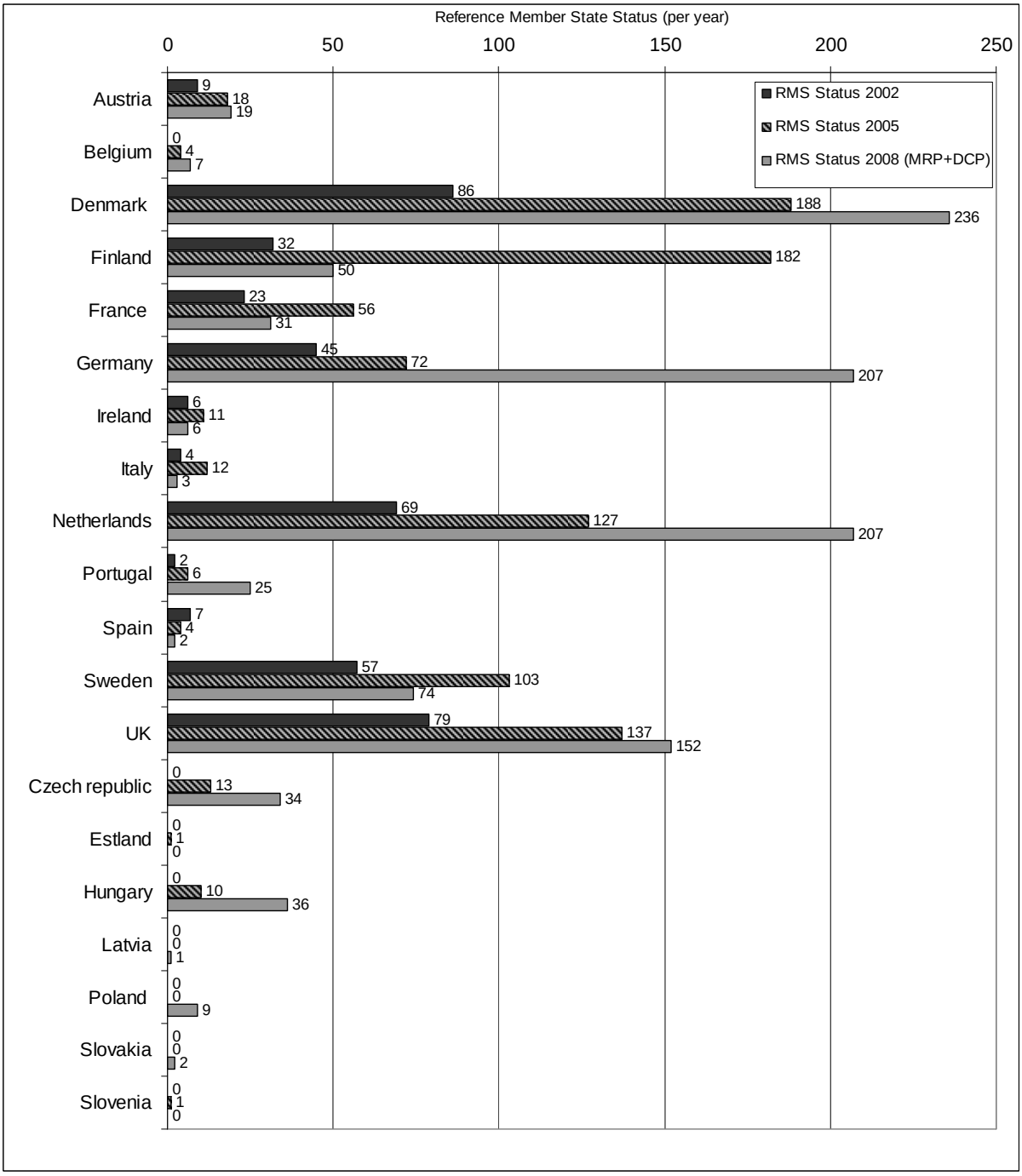


Source: EMA annual report 2000; * *total* includes participation of member states as a rapporteur and co-rapporteur; ** Data was replicated from graph values might partially differ from original numbers.

Considering the situation in the mutual recognition/decentralized procedure (DP/MRP) the picture is quite different. Some of the agencies dominating the evaluation of new application in the centralized procedure show a weaker performance in the decentralized procedure and there is a higher degree of fluctuation across time. It seems that applicants, having complete discretion in the selection of the regulatory agency, apply different criteria in selecting agencies in the different procedures. As it was highlighted above, competition is not only traceable in the selection of the assessing agencies but in the approval process as well. Compared to the centralized procedure emphasizing cooperation, the procedural set-up of the mutual recognition procedure, specifically before the review in 2004, stimulates conflicts. The agency serving as an RMS forms its position and consequently a legally binding national authorization, which in case of dissent is challenged by another authority.

[236] The EMA has recently proposed a new selection procedure for rapporteur status, increasingly considering the different national regulatory capacities (Anon, 2006b).

Graph 21: Inter-agency competition in the decentralized procedure (EU 27)*



Source: HMA annual reports 2002, 2005, 2008; Note: * values represent the number of finalized procedures (new applications), only those countries participating as a RMS in at least one of the three years have been included.

In fact there are little incentives and substantial barriers for the two agencies to relinquish their position:

> "It is difficult for a dissenting CMS to retract its opinion and adopt the RMS's position once it has refused automatic mutual recognition because of 'serious concerns' to public health in their countries. The other possibility of finding a compromise position would require a change in the RMS's initial authorization. This is no less complicated since a legally valid national authorization already exists

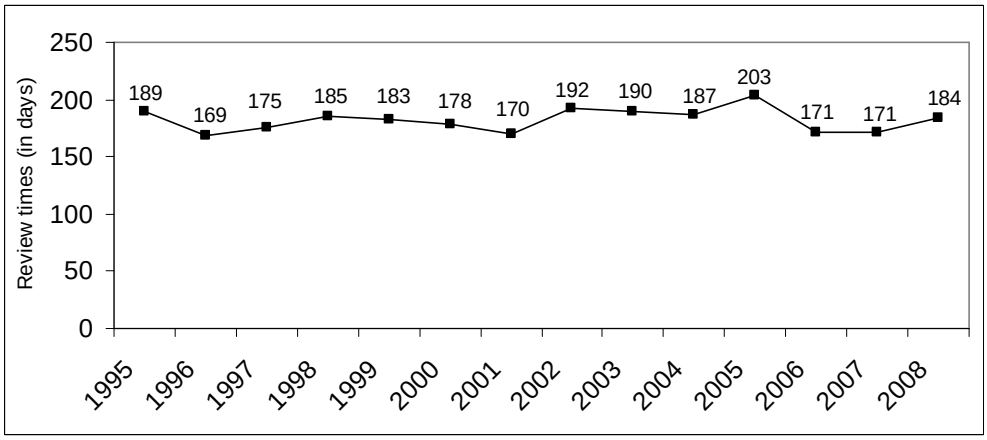
> furnishing the authorization holder with a right to market in the RMS.[original emphasis]" (Feick, 2002: 19).

Based on the logic of reputation agencies serving as a CMS, might even challenge the assessment of the leading agency to prove their own capacity (Feick, 2002: 46). While the arbitration procedure within the CHMP was intended to solve such conflicts

> "most applicants considered the duration of such a referral procedure too long (on average 9 months). Because of commercial interests to market the product as soon as possible in the Member States that could approve it, in most cases the application was withdrawn in member states that were negative." (Janse-de Hoog, 2007: 250)

Turning to the competition of standards it is assumed by some authors that the Europeanization of pharmaceutical regulation and the increased financial dependence of regulators has caused a watering down of approval standards in order to attract applicants (Abraham & Lewis, 2000; Wille & Schönhöfer, 2002). This assumption is mainly based on the fact that the European procedures and especially the CP introduced stricter timelines, significantly lower than most national approval times, forcing national regulators to rationalize their assessments.

Graph 22: Assessment times within the Centralized Procedure (1995-2008)



Source: EMA annual reports (1995-2008)

It seems noteworthy that approval times started to converge before the new European system was introduced and several agencies already conducted their national assessments based on very strict timeframes (Abraham & Lewis, 1999; Feick, 2002; Thomas et al., 1998). It is true that the European procedures intentionally rationalized national approval procedures, but a prevailing tendency towards shorter assessment times is not traceable considering the development of average review times in the CP. Instead, the former trend of convergence regarding review might have reached the baseline. Accordingly, the perceived watering down

of standards rather corresponds to the watering down of regulatory discretion and pressure to adapt national regulatory cultures.

The emergence of a European regulatory culture in the pharmaceutical sector

The instalment of the European agency and the new regulatory procedures did not only stimulate changes in national regulatory structures, but emphasized a new regulatory approach that challenged existing national regulatory traditions. This is the impression one could get, drawing on the study on the harmonisation of drug regulatory standards in Europe of Abraham and Lewis (1999: 1657-1659). While interviewees argued that standards might erode through Europeanization mainly due to the shortage of review times, national regulators from Germany, UK and Sweden perceived the application of standards by other less experienced agencies as the real challenge to safety within the European system. From this perspective, the main problem was not the erosion of standards but the lack of trust in regulatory capabilities of other agencies. However, the new European regulatory approach was based on the idea of mutual trust and increased cooperation between national agencies and between regulators and regulatees as well. The instalment of the CHMP and its procedural significance especially after the creation of the new regime played a crucial role in the diffusion of this new European regulatory approach and the neutralization of the predominant national approaches. In contrast to the decentralized procedure, where regulatory agencies were competing against each other, the CHMP was composed of individuals and therefore personnel interaction helped to adapt to the new way of conducting regulation. Boris Hauray and Philippe Urfalino in their qualitative study on the work of the CHMP concluded:

> "European committees progressively became the very places in Europe where top medicines specialists (regulators and industrialists) could engage in exchanges about pharmaceutical knowledge and rules. […] First of all, delegates developed deliberative norms and mutual trust. […] National delegates' support for positions that went against the opinions of their national committee, or against the interests of 'their' national firms, was of course critical in this process. But the development of direct personal ties and even friendship were also of great importance […] A European regulatory network was structured around the members of the 1970s working parties and, in 1995, most of the leaders of the 'new' European system had been working together for many years.[original emphasis]" (2009: 441-442)

An important change and possible conflict with national regulatory cultures must be seen in the emphasis of cooperation with the regulated industry within the European context. Within the centralized procedure, the traditional relations between regulators and regulatees shifted.

While the traditional understanding of the regulatory role in most countries was that of a gatekeeper, the new regulatory approach intentionally fostered a much more collaborative approach emphasizing the mutual goal of regulators and regulatees to achieve market access of safe products. The new regulatory culture was reflected in several respects. A manifestation of this new European regulatory style can be seen in the ever growing role of scientific advice preceding new applications (Dejas-Eckertz & Schäffner, 2005), increasing from only 7 in 1995 to 263 in 2008. Applicants can ask the EMA and more specifically the CPMP for advice before an application procedure is started and optimize their applications dossiers.[237] A second characteristic can be seen in the increased use of soft law instruments and most notably the importance of guidance provided to applicants. As it has been argued in the previous chapter, the European regulatory framework is marked by a considerable degree of vagueness, resulting in uncertainty how to best comply with regulation. To reduce this uncertainty, the issuance of guidance documents initialized by the CPMP has been continuously expanded,

Table 18: EMA guidance documents (1995-2008)

	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008
Quality Chemical	2	7	2	10	11	11	8
Biologicals	8	8	5	13	21	9	6
Non-Clinical	5	5	3	5	6	8	8
Clinical Efficacy & Safety	6	5	9	19	20	36	27
Multidisciplinary	1	1	1	6	6	14	16
Total	**22**	**26**	**20**	**43**	**64**	**58**	**65**

Source: http://www.EMEA.europa.eu/htms/human/humanguidelines/background.htm (25.3.2009); Note: Only adopted guidelines not under revision were counted, using the effective date (guidelines to become effective).

While collaborative relationships were common in some member states, most prominently in the UK where regulatory relations were marked by an "informal negotiation-based interdependency alongside a formal licensing structure" (Smith, 1991: 7), others like the German authority had developed a more cautious approach towards the pharmaceutical industry (Hohgräwe, 1992: 196-198). In order to succeed within the European system, national regulators facing the need to generate fees had to adapt to these new requirements.

[237] The practice of *scientific advice* has been criticized by Silvio Garratini and Vittorio Bertele arguing that: "it is uncommon for an organization, and in effect the same group of people […] to be responsible for giving advice to industry about the best way to proceed with the development of a drug, and also be responsible for approving drug authorization" (2004: 88-89). This perspective can be challenged considering the perspective of regulatory efficiency and increased access, since compliance with scientific advice has been found to increase the chances of approval (Regnstrom et al., 2009).

This adaption has led to the progressive adoption of a more professionalized and NPM inspired approach on behalf of the regulatory agencies: most European agencies began to publish annual activity reports roughly since the year 2000, highlighting their achievements and regulatory performance. A contributing factor to the professionalization of the regulatory network must be seen in the strong external scrutiny of the regulatory network both by the Commission and the industry.[238] While the European Commission used the regulatory revision to analyse regulatory performance and has recently commissioned an external auditor to assess the work of the EMA (Ernst&Young, 2010), the industry and the EFPIA more specifically conducts various studies and surveys on the regulatory network, for example, regarding the performance in providing scientific advice (Mayer-Nicolai et al., 2008).

7.2.3.2.3 Potential for regulatory capture: EMA & Approval regime

While the emergence of a common regulatory culture on the European level and the adaption of national agencies contributed significantly to the functioning of the approval regime, considering the centralized procedure and to a lesser degree the decentralized procedure, the resulting *efficiency regime* (Abraham & Lewis, 2000) has raised serious concerns about close relationships of the EMA and regulatees (Abraham, 2002; Garattini & Bertele, 2001, 2007; Li Bassi et al., 2003). In light of this criticism, an assessment of regulatory principles and control mechanisms regarding the European agency and the approval process is necessary at this point.[239]

The realisation of *participation* within the approval regime and the EMA

Considering the participation in the approval regime, the privileged role of industry compared to the public is obvious and less surprising, given the underlying regulatory interest of regulators and regulatees regarding the mode of governance.[240] As it has been argued before, the participation of the public within the actual regulatory decision-making processes can have a distorting rather than beneficial effect. It is hard to imagine, how personal participation in the decision process and in the discussions of the CHMP would contribute to the

[238] The external review is complemented by internal benchmarking and evaluation activities, for example by the HMA (2005).

[239] A separate assessment of the *subsidiarity* principle seems unnecessary, since the regulatory network in the pharmaceutical sector clearly reflects a sufficient realisation of this principle.

[240] The lack of public participation is not confined to the approval regime, but is traceable in the post-authorization stage as well. Public participation however constitutes a general problem in health care and its governance (Hart, 2004).

effectiveness and efficiency of the regime.[241] Nevertheless, it might be beneficial to increase public input on general risk perceptions from the perspective of (input-) legitimacy (Löfstedt et al., 2009).[242] Judging on the general involvement of the public beyond the participation in the scientific body (CHMP), it must be acknowledged that while the situation during the founding years has been disappointing (Collier et al., 1997), it improved significantly especially after the second revision of the framework. Patient groups are now represented with two seats on the management board supervising the executive director and the overall strategy of the agency and participate in the *Committee for Orphan Medicinal Products* (Georges, 2006). In addition, the EMA developed a strategy to improve and identify new aspects for patient and public involvement and started several activities in this respect. Even though participation remains selective, as the EMA only considers patient organisations which were identified based on a framework, the external perception of this initiative has been overwhelmingly positive (EMA, 2007b: 3-9).

The realisation of *transparency* within the approval regime and the EMA

Given the dominant regulatory interest of regulators and regulatees, *transparency* does not necessarily rank high on the national regulatory agenda. While the Commission emphasized the need for greater transparency and openness and the EMA compared to most national regulators seemed to be more open to the idea of transparency (Anon, 1994: 90), the first years of the European approval regime were marked by a highly secretive regulatory approach (Abraham & Lewis, 1998; Anon, 1996). Despite legally binding transparency obligations, greater openness regarding the workings of the agency and the actual assessment process was rejected based on the obligation to protect *commercially sensitive* information. Interestingly enough, this claimwas used to shield the regulatory work of the EMA from public scrutiny in general (Abbasi & Herxheimer, 1998). The first notable attempt to change this was the publishing of European public assessment reports (EPAR) for all products approved under the CP after January 1, 1995. Unfortunately, the EPARs proved to be a promise unfulfilled. Availability of the first generation of assessment reports was severely limited and the entailed information was of limited use. A study by the International Society of Drug Bulletins (ISDB) covering 9 EPARs found that the reports were lacking a clear and uniform structure, dealt

[241] For a concurring view see Abraham & Davis (2005), Abraham & Sheppard (1997) and Liberatore & Funtowicz (2003).

[242] Theoretically, it is possible for the EMA, the CHMP and the Commission to consider the position of experts during the assessment process and before the final decision, as it has been stated by the ECJ, regarding the *Olivieri* case (T-326/99) (Alemanno, 2008b; Savulescu, 2004).

with important details in a superficial manner and were generally hard to understand even for health professionals. Above all, the commitment to withhold sensitive commercial information resulted in the blackening of considerable parts of the reports (ISDB, 1998). Reacting on the accusations of the ISDB, the EMA promised to improve EPARs (EMA, 1998b), but a follow up study of the ISDB in the year 2000 showed little signs of improvement (Kopp, 2000). The situation was even worse considering the transparency of the decentralized procedure, as the field experience of Abraham and Lewis suggests:

> "We found it impossible to get basic information from the EMEA about mutual recognition applications, such as names of products, RMSs and CMSs. The EMEA referred us to the Mutual Recognition Facilitation Group of the national regulatory authorities; the chairman of that group, Dr D Lyons, told us in a letter dated Sept 5, 1996, that only 'the applicant, the RMS and the CMSs need to know' such details.[original emphasis]" (1998: 480).

The situation did only start to improve with the advent of the second legislative revision in 2000, leading to more stringent and detailed EPARs and for the first time introduced similar requirements regarding assessments under the decentralized procedure, contributing significantly to the overall transparency of the approval process (Pimpinella et al., 2007).

Considering transparency from today's perspective it must be acknowledged that the EMA has significantly improved its own transparency policy. Access to documentation is much easier than it was at the beginning of this decade especially compared to the transparency policy of national regulatory authorities within the field (Slijkerman, 2009) and most notably other European agencies (Vos, 2005: 131). In fact, the EMA publishes an abundance of documents in order to make its own work transparent. Despite this positive account, problems regarding transparency remain. First, officials working at the agency are still subjected to outmost secrecy even after leaving their position. Second, despite increased access to documents and information, large parts of the data and dossiers used in approval decisions are excluded from public access for confidentiality reasons. This creates a paradox situation as the decision to disclose information is not taken by the regulator but "the decision with respect to what information should be regarded confidential hence lies with the industry" (Garattini, 2003: 1078). Third, transparency is limited to the administrative work of the EMA and the approval procedures, but is lacking regarding clinical trials and post-authorization controls (Garattini, 2003; Kenny, 2004). While the situation regarding clinical trials has improved with the introduction of EudraCT, the lack of transparency regarding post-authorization monitoring has resulted in a recent complaint by the EU Ombudsman

(Pharmaletter, 2010). Fourth, the new found transparency of the EMA does not expand to the times before 2005.

The realisation of *accountability* and control within the approval regime and the EMA

Since the EMA represents a regulatory agency and therefore has a certain level of independence, the need for external control mechanisms arises. External control after delegation is achieved mainly by two mechanisms. First, ex-ante controls shape the agency's mandate and the more general zone of discretion defined in the course of delegation. Second, the behaviour of the agency is regulated by ex-post mechanisms and the power (and ability) to hold the agency to account. Given the interdependence of the two mechanisms it must first be discussed how strongly the agency is controlled (Busuioc, 2009: 10-14).

Ex-ante and ex-post control of the EMA

Considering the provisions establishing the EMA, several ex-ante mechanisms can be identified.[243] First, the Commission has the right to recommend a new executive director serving a five year mandate, who has to be accepted by the respective management board. Under the new regulation (after 2004), the candidate can be asked to give a presentation before the *European Parliament* (EP) and answer questions. However, the EP has no power to influence the selection of the new executive director. Another change introduced by the second revision provides the Commission with the right to propose the suspension of the executive director. The actual decision has to be taken by the management board, deciding with a qualified majority. An additional constraint can be seen in the competence of the Council, to set the fees that the EMA collects (Winter, 2004: 138).

Turning to the ex-post mechanisms, several instruments were developed to hold the EMA accountable. The EMA has adopted a code of conduct, and the management board has published rules of procedures to ensure the adherence to procedural standards – advancing *procedural* accountability – in decision-making (EMA, 2005, 2009). Board members have to provide a declaration on possible *conflict of interest* on an annual basis (EMA, 2006). Considering its *political* accountability, the Commission has significant powers in holding the

[243] This section refers to the founding regulations of the EMA, regulation EEC No. 2309/39 and EC No. 726/2004 respectively.

EMA and regulatory agencies in general to account.[244] It can ask for periodic evaluations of the regulatory performance, as it has recently done in case of the EMA (Ernst&Young, 2010). The composition of the management board ensured a continuous involvement of the member states and the Commission. Under the new legislation, external control and accountability is expanded by the inclusion of EP representatives. The management board approves the annual reports and the working plans for the following years. Annual reports are forwarded to the Commission, the Council, the European Social and Economic Committee, the Court of Auditors and the Member States. Working plans are forwarded to the Commission the Council and the Member States. The *financial* accountability (and control) of the EMA is ensured by the internal budget control mechanisms, carried out by the respective accounting officer and the external review of the European Court of Auditors. Furthermore, the Parliament and the Council in their role as the *budgetary authority* can re-examine the Community contributions to the agencies budget and the European Anti-Fraud Office (OLAF) serves as a mechanism to prevent the agency from drift. *Judicial accountability* of the EMA plays a vital role in securing agencies compliance. It has been argued by the Commission, that the agencies are responsible before the Court of Justice of the European Communities for the decisions they take (European Commission, 2005a). The provisions founding the EMA, however, remain silent on the issue of judicial review (Winter, 2004: 147). In a strict sense, the decisions of the EMA and more precisely the scientific assessments by the CHMP cannot be challenged. However, since the formal approval decision is (regularly) taken by the Commission and the Standing Committee – on a regular basis within the CP and in case of binding arbitration within the DP as well – the agency at least indirectly can be held accountable and the resulting Commission decisions can be challenged before the *Court of First Instance* (CFI) and subsequently the ECJ (Collatz, 1996; Winter, 2004).[245] In fact, the ECJ as in other European risk regulatory fields (Alemanno, 2008b), has had a significant influence on the regulatory work of the EMA, as the Court has proven at several instances that he is willing to "scrutinise the substantive reasons for authorisation decisions in detail" (Krapohl, 2008: 98). The possibility to hold the EMA accountable judicially however is confined to those actors directly affected by the Commissions decision, reducing the number of eligible plaintiffs. This has been recently demonstrated in the *Olivieri* decision. The Court of First Instance dismissed an individual complaint of a doctor involved in the clinical trials

[244] See, for example, the *Draft on Interinstitutional agreement on the operating framework for the European regulatory agencies* (2005a).
[245] Effective from December 2009, the CFI is called General Court.

of an authorized drug, arguing that she was not individually concerned by the Commission decision (Best, 2004). Apparently, the lack of direct involvement renders most claims against authorization decisions – except those of applicants – void. This surely constitutes a problem form the perspective of accountability, despite the fact that every member state, the Commission or the EP can bring nullity claims before the Court (Krapohl, 2008: 99).

The effectiveness of control mechanisms

While it can be argued that except the apparent asymmetric access to judicial accountability, the control and accountability of the agency is ensured based on the cited mechanisms, there is reason to believe that their effect is limited. Starting with the control of personnel, even though the Commission could threaten the agency to use its *suspension right* regarding the executive director, it seems questionable that it has an interest in doing so. Since its creation, the EMA has been marked by a remarkable continuity regarding its personnel. Ferdinand Sauer became Head of the Pharmaceutical Products Unit within the Commission in 1984. After serving 10 years in that position, he was appointed the first executive director of the EMA in 1994. In 2001, Sauer left to join the DG for Health and Consumers as a director. While his successor and recently reappointed executive director Thomas Lönngren, did not serve within the Commission's service, he worked for the Swedish MPA since 1990 and, given the importance of the agency within the European network, can be expected to have a strong standing within the management board.

Turning to the *financial* control of the agency, the usefulness of the existing controls can be challenged. Judging from its financial basis, the EMA has become increasingly independent from Community subsidies, even though a reverse trend has been traceable, with the contribution of the Community nearly doubling in 2007. This development could either be interpreted as an increased commitment to patient safety, an acknowledgement of the increased workload on behalf of the agency, or the attempt of the principals to regain some control over the workings of the agency. Considering the controlling function of the Management Board, the recent changes in composition might have somewhat improved the situation, since oversight by the European Parliament and public stakeholders has been strengthened. Still, the current composition of the management board exemplifies a potential lack of control. The board is dominated by representatives of national agencies. While this will ensure, that the agency is prevented from adopting a strategy that collides with national regulatory interests, it must be asked, if the current composition and size really allows for an

independent supervisory role. In light of the previous discussion, the differences in formal independence and de facto independence (Gilardi & Maggetti, 2009; Maggetti, 2007) in case of the EMA become apparent. While the formal control mechanisms would suggest a moderate level of formal independence and thus a high degree of compliance and accountability, the de facto control over the agency can be expected to be less strong than the formal mechanisms would suggest.[246] This situation is aggravated by the lack of de facto independence from the industry exemplified in the high degree of financial and informational dependence, supporting the raised assumption that the political independence of the EMA might translate into a situation of private capture. However, as it has been suggested by Martino Maggetti in the context of national independent regulatory agencies, a lack of political control and accountability does not necessarily translate into regulatory capture (Maggetti, 2007: 282). In addition, it must be noted that capture in case of the EMA does not necessarily relate to the agency as a whole but the approval procedures and the respective scientific committees. In assessing the potential capture of the regulatory regime, it is the control of the approval process that is decisive.

Control of the centralized procedure and the CHMP

While the EMA represents the central actor within the regulatory regime as a whole, the CHMP represents the key institution in the approval regime. Considering the ex-ante controls of the scientific committee, the initial directive on which the CHMP is based, does not specify measures of control.[247] The committee was expected to draw up rules of procedures governing its activities, in accordance with the legal provisions. However, this document does not entail additional control measures despite the selection of members (CHMP, 2007). Each member state appoints a member after consultation with the management board, serving for three years. Under the new legislation, five additional *co-opted* members are part of the Committee, proposed based on their expertise either by the agency or the member states. Since the majority of the CHMP are representatives of national regulatory agencies, it might be tempting to believe, that national agencies can exert control over the centralized procedure. However, national agencies are obliged to refrain from giving instructions to their representatives, which highlights the independent character of the scientific committee.

[246] This finding is in line with the current research on agency independence of national regulatory agencies (Gilardi & Maggetti, 2009; Hanretty & Koop, 2009; Vos, 2005).

[247] The only requirement specified in regulation EC No. 2004/726 is, that the Committee is expected to forward all decisions and necessary information to the *budget authority* (Council and EP).

Because of the personalized character of the CHMP, members are obliged to give annual conflict of interest declarations, available through the EMA homepage.[248] A possible lever for external control of the committee is the possibility to invite applicants and establish contacts with interested parties. However, such contacts remain within the discretion of the CHMP. Even if no clear external control mechanisms exist, the procedural requirements serve as an additional control lever. The regulatory framework clearly structures the assessment process and sets out the criteria on which the scientific assessment is ought to be based. Given the higher degree of formalisation, the significant regulatory discretion existing in previous (national and European) regulatory procedures is effectively reduced. This reduction does not imply that discretion and thus the possibility for deviating or captured decisions is fully excluded (Gehring et al., 2005: 133). Since the decision criteria remain vague to a certain degree, different interpretations remain possible at least in principle. Given the underlying preferences of the regulators, most importantly those charged with the regulatory decision, the authorization might be skewed, as long as the regulator can convince the scientific committee that his decision is in line with the underlying criteria. In order to prevent the CHMP from drift, the development of guidance documents plays a key role. While these soft law instruments issued by the CHMP were previously considered as a mechanism to facilitate the authorization process, they have an important function for the control of the actual assessment within the committee:

> "Authorization decisions that deviate from these rules will thus require particularly convincing justification. This is all the more true because guidelines as the most reliable guidance documents are not only published by the EMEA, but also by the Commission […] Instead of exploiting its informally powerful status under the authorization procedure, the EMEA expert committee limits its margins of discrete choice through the elaboration and publication of numerous guidance documents. […] By committing itself to decisions that follow its own rules, the committee reduces the number of options that could be chosen and voluntarily cuts the room for manoeuvre for internal bargaining." (Krapohl & Gehring, 2007: 221-222)

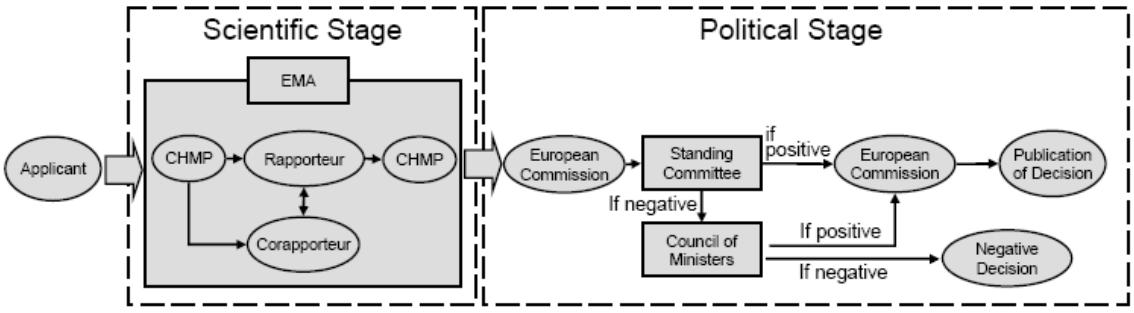
While the voluntary limitation of discretion plays an important part in the control of the independent committee, it seems to be questionable at first sight why members would voluntarily reduce their room to manoeuvre. However, this could be explained by at least two factors. First, the agreement on certain interpretations creates a common understanding of regulators and reduces remaining scientific uncertainty regarding the right assessment of products (Abraham, 1994: 494). Second, the mutual understanding of interpretation is a

[248] http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000002.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c7c (last accessed July 6, 2010).

prerequisite for the efficient work of the CHMP. While the initial assessment is conducted by the rapporteur and co-rapporteur, the committee as a whole discusses and decides on the final report. Given the personalized character of the body, the individual independence from their own organisation in the decision-making process and the consensual orientation (Hauray & Urfalino, 2009; Metcalfe, 2000), individuals will try to reduce the potential for conflicting assessment wherever possible. As the committee is expected to decide anonymously and this has been the case in the majority of decisions (Krapohl & Gehring, 2007), it is necessary for the group to agree on how evidence is interpreted. Furthermore, the committee serves as a peer-review mechanism in case the rapporteur overstepped his or her boundaries.

Beyond these internal reasons, the two step assessment process does contribute to the CHMP's willingness to limit its own discretion. While the committee provides the scientific assessment, the final political decision to authorize the product is taken by the Commission and the Standing Committee, which (in principle) are allowed to deviate from the initial proposal. Based on reputational considerations of the CMHP vis-à-vis the Commission, decision-making within narrowly defined corridors reduces the potential overhaul of a decision, since it becomes harder for the Commission to challenge the decision on procedural grounds.

Graph 23: Scientific and political stage of centralized procedure (illustration)



Source: author's own

The adherence to the approval criteria and the predefined approval process is advanced by the credible threat of the Commission and the Standing Committee to challenge the decision. In case of the latter, this threat has become even more credible, since under the new regulation the Standing Committee can challenge a decision with a qualified majority, These political ex-post controls are supplemented by the European courts serving as an additional external control mechanism. While the ECJ effectively evaluates the political decision by the Commission, this will indirectly affect the CHMP, since the court would need to prove that

either the Commission or the Committee did wrongly apply approval criteria. In light of these mechanisms, it seems that the CHMP and the centralized approval procedure, despite a lack of extensive ex-ante control mechanisms is sufficiently controlled (Krapohl & Gehring, 2007). This assumption must, however, be qualified.

While actors within the CHMP only have a limited zone of discretion and will have little incentive to take a decision that clearly reflects a (public or private) bias, the current structure can have negative implications. First, the approval process might lead to the adoption of a risk-averse regulatory strategy, as (new) products for which little guidance exists are more likely to receive a negative decision. This risk is counterbalanced by the credible threat of judicial review. The likeliness that a scientific assessment and the following political decision are challenged judicially is unequally distributed and thus represents an incomplete control mechanism. While negative decisions most likely will be challenged, the challenge of a positive decision must be seen as an exceptional case. Even if Krapohl and Gehring (2007: 217) argue that an outvoted member of the CHMP could inform the Commission that a positive scientific assessment should actually be negative, this is highly unlikely. Since the work of the CHMP has a strongly personalized character, such behaviour would negatively impact on the personal reputation within the body. No alternative external public control is possible, since data restrictions prevent independent scientists from reviewing false positive assessments. Judicial review will therefore not necessarily result in effective control of the process, but serves as an additional mechanism to hold the committee accountable to the industry. This problematic aspect of the approval system could be mitigated, since the Commission and the Standing Committee can challenge a regulatory decision. Again, such corrective action is unlikely. The Commission would have to prove, that the scientific assessment of the CHMP was not based on the substantive criteria. Since the EMA was created with the intention to provide the Commission with the necessary expertise to effectively govern the sector, the Commission does not posses scientific capacities to challenge the initial expert assessments. In fact, it must be asked in how far the Commission and the Standing Committee are interested in challenging the CHMP assessment. This assumption can be drawn from the actual behaviour of the Commission in the political stage of approval:

> "in analysing the practice, one notes, for instance, that EMEA recommendations are systemically rubber-stamped by the Commission […]. This is hardly surprising. If an institution pooling the best expertise available at the European level warns against the dangers of a given pharmaceutical, the

> ‘political power’ could not ignore its advice without taking substantial risks.[original emphasis]”(Dehousse, 2008: 799).

While data on the decision practice of the Standing Committee are lacking due to confidentiality, there is no reason to believe that the Committee will deviate from the initial decision. As in the case of the Commission, the body does not posses scientific resources and does not meet regularly, but decides on the Commission proposal in a written procedure. While the centralized procedure provides applicants with a stronger position in challenging negative decisions and can lead to insufficient consideration of false positive decisions this situation should not be confused with regulatory capture. A rapporteur is not able to bypass the underlying criteria, because such assessment would be challenged by his peers: the procedure does reduce regulatory (and unfortunately political) discretion in general and therefore the potential for capture irrespective of its nature.

Control of the decentralized procedure and national regulators

While the CHMP serves as the key actor in the governance of the centralized procedure, the decentralized procedure initially lacked a clear governance structure. *The Mutual Recognition Facilitation Group* (MRFG) was no formal body, but rather an ad-hoc group in charge of the arbitration process. In fact, this leaves the member states and more precisely the national regulatory agencies in charge of the process. The situation has been improved slightly with the introduction of the CMD(h). Comparing the two European procedures, CP and MRP/DP, the prevailing lack of governance and procedural steering becomes apparent.

Control of the mutual recognition/decentralized procedure until the second revision

Similar to the CP, the behaviour of national regulators is subjected to procedural rules and the underlying decision criteria. However, it lacks the self-binding instruments that the CHMP developed under the CP. While the MRFG developed comparable guidelines (Janse-de Hoog, 2007: 347-348), these documents lack authority. Furthermore, these ex-ante controls are not supplemented by ex-post mechanisms, ensuring the same general level of compliance traceable in the centralised procedure. Considering the standard assessment process, national authorities are for the most part left by themselves. Only in case of arbitration the CHMP and subsequently the Commission and the Standing Committee interfere with the decision making process. Considering the comparatively low levels of arbitration under the MRP/DP procedure, this ex-post political control function is rarely activated. The element of European

judicial control and accountability is lacking as well. Licensing decisions under the MRP/DP are taken on the national level and therefore remain outside of the scope of the European courts, unless a decision has been made under the arbitration procedure. The lack of controlling mechanisms could lead to the assumption that the potential for capture increases. However, just because national regulators are not controlled by the ECJ and the Commission, this does not mean that they could sidestep the approval criteria. Heightened regulatory discretion under the MRP/DP procedure is still bound to the approval criteria, even though national regulators might find it easier to consider additional reasons in deciding on approval. Since the chance that a procedure reaches binding arbitration is relatively small, their assessments are not under ex-post scrutiny. It can be assumed, that the lack of external control would make it easier for an applicant to convince a Reference Member State (RMS) to license his product. Still he would have to convince the regulators of the Concerned Member States (CMS) to accept the initial assessment. While it is theoretically possible that an applicant will benefit from the lower level of control, regulatory discretion can easily turn against him. Not only the RMS, but the CMS as well can use regulatory discretion to block an application on other reasons that he officially claims and must not fear to be held accountable, even though the possibility for such behaviour has been reduced by the second revision, making arbitration mandatory. From this perspective, the underlying regulatory competition that hinders the smooth functioning and efficiency of mutual recognition, might serve as an additional lever of control and unintentionally contributes to the avoidance of capture.

Control of the mutual recognition/decentralized procedure after the second revision

While the changes of the decentralized procedure do not alter the underlying logic of the approval process when a product has already been approved in one member state (MRP), it strengthened the control and governance of the approval procedure. The newly created CMD(h) group provides a forum resembling the CHMP in the centralized procedure. Contributing to the overall mutual understanding of the approval process and by using the soft law approach it can reduce potential discretion in the decentralized procedure. Furthermore, the clarification of the potential serious risk claim by the European Commission (2006) reduces regulatory discretion of the CMS, even though it is unclear which consequences such crossing of boundaries will have. Another change is the fact, that ex-post control has been strengthened, since every potential serious risk claim will now be referred to the CHMP. While the creation of the CMD(h) can help to facilitate consensus between national regulators

it can not solve the underlying dilemma within the MRP: as soon as a CMS is convinced that he must claim a serious risk to health, there is (still) little incentive for him to revise his position after discussion in the newly founded committee. Nevertheless the revision of the MRP/DP has strengthened control and efficiency of the European approval regime. Control is strengthened, because national regulators now have the chance to develop a common position on applications rather than being confronted with a final decision. The new procedure is thus much closer to the centralized procedure. Even though the RMS will still be in charge of the assessment, he will not take his decision before he has engaged in dialogue with his peers (Broscheid & Feick, 2005: 24) and as in the case of the centralized procedure this peer-review mechanism will reduce the potential of agency drift.

7.2.3.2.4 Intermediate result: effective approval procedures or captured regime?

From the perspective of effectiveness, the new European approval system represents a mixed blessing in many respects. Starting off with the instalment of the EMA it must be acknowledged that it contributed significantly to the sectoral integration beyond mere legal harmonization. With the establishment of the EMA and the strengthening of the CHMP, the previously informal network of agencies has been aligned. With the instalment of the CP, for the first time a truly Europeanized application procedure is available. Despite remaining procedural problems, the MRP/DP, especially in case of a newly submitted product must be seen as a clear improvement to the previous procedures based on mutual recognition. Comparing the three possible authorization procedures regarding participation, transparency and accountability a clear rank order can be established. The CP represents the most advanced procedure, even though issues of participation remain. While the MRP/DP procedure has been improved during the second revision of the regulatory framework it still falls short compared to the CP, considering reduced transparency and accountability.

Table 19: Regulatory principles within the approval regime (illustration)

	Participation	Transparency	Accountability
National	+	+	+
MRP/DP	+	++	++
CP	+	+++	+++

Source: author's own, Note: (+) low; (++) intermediate (+++): advanced

Nevertheless, both European procedures are superior to purely national procedures given the (traceable) lack of transparency and accountability measures. The European approval regime thus represents a clear advancement to the fragmented governance approach before 1995.

These improvements are outweighed by several critical aspects. As it has been shown, the alignment of national regulators has not only been the result of the emerging European regulatory approach and the creation of a European peer group (Metcalfe, 2000: 136-137), but was forced through an increase in competition and financial dependence from the regulatees. Furthermore, the strong position of the CMHP within the regulatory process raises serious concerns regarding the legitimacy of the current regulatory regime. While regulators on the national level already enjoyed considerable discretion, this seems to be even more so the case within the centralized procedure. Given that under the current regime the only chance to stop a regulatory decision by the CHMP is based on scientific grounds, and this regulatory game has to be played against a body that has been created to concentrate pharmaceutical expertise on the European level, a sufficient level of political control and therefore legitimacy is called into question. While the new regime surely is efficient, it comes at a high price. Decisions are made by an isolated regulatory body based on an approval process with a potential authorization bias towards unsafe products, insufficiently tamed by political control mechanisms.

7.2.3.3 The governance of manufacturing

As in the case of clinical development, the governance of the manufacturing phase is based on licensing and monitoring mechanisms supervised by the EMA. The monitoring capacities of the European agency have been strengthened recently, with the instalment of the EudraGMP database, providing national agencies with the data on authorization holders administered by the EMA. In order to manufacture pharmaceutical products, producers must have a manufacturing license, granted through the EMA or the respective national agency. The production process is regulated through the respective legal provisions, the good manufacturing practice (GMP) guidelines compiled in Volume 4 of Eudralex and the specifications of the production process that have been submitted in order to obtain a manufacturing authorization. The regulatory framework clearly delineates the standards that manufacturers have to meet, but regulatory compliance is largely delegated to the respective producer. Manufacturers have to have a qualified person at their services and develop a fitting quality management system (QMS). While the continuous control of manufacturing is thus delegated to the regulatee, regulators can use the instrument of inspections, mandated by the EMA or the national competent agencies, to monitor compliance. In case of EMA inspections, inspections are mostly requested in context of a centralized authorization procedure and as a

general rule will be conducted by the RMS. The need for national inspections may either result from obligations under the decentralized procedure or represent routine or triggered inspections. Given the importance of GMP requirements for the quality assurance of pharmaceutical products inspections represent an important instrument to achieve compliance. Based on the comparatively elaborate regulatory framework, the monitoring function of regulatory authorities and the self-regulation and monitoring of manufacturers the risks stemming from production seem to be regulated adequately. On closer inspection, this finding must be corrected based on two main arguments.

First, the effectiveness of the current monitoring approach must be questioned both on quantitative and qualitative grounds. Comprehensive data on the frequency of nation inspections is lacking and those European agencies issuing annual reports do not specify their inspection activities in most cases. A notable exception is the British regulatory agency MHRA. In 1998-99, the agency conducted 243 national inspections and 57 inspections in third countries (non EU/EEA) (J. Taylor et al., 2000). The general distribution of inspections remained stable with 214 national inspections and 42 in third countries in 2001/2002 (J. Taylor et al., 2003). Given that the UK is one of the member states with relatively strong national pharmaceutical production capacities, a strong agency and a fairly stable level of initiated approval procedures, it can be assumed that national GMP inspection levels will be lower in most of the other member states. While the focus of national authorities is on national inspections, inspections issued by the EMA show a reverse pattern. Between 1995 and 2005, the EMA issued 35 inspections within the EEA and 400 in third countries (EMA, 2007a). This amounts to an annual EMA inspection activity of 3.5 within the EU and 40 within third countries, indicating a modest level of continuous monitoring.[249] These inspection activities only involve products licensed under the centralized procedure, representing only a fraction of products currently on the European market. In addition, the current level of inspections of third countries can hardly be considered as sufficient given the increased trend of relocation of production capacities to China and India (Erdmann & Gabriel, 2005: 41). More stringent monitoring and increased cooperation with local authorities based on mutual recognition agreements seem to be necessary given the higher level of critical

[249] No reliable data on the number of European production sites exists. According to EFPIA figures, approximately 518,000 people (excluding R&D) worked in the pharmaceutical industry in 2009, pointing to a fairly large number of production sites (EFPIA, 2009a: 12-13).

deficiencies in these countries.[250] An additional drawback of the current regulatory practice must be seen in the fact that inspections are conducted on a regular and notified base, while spontaneous inspections remain the exception. The lack of supervision does not necessarily constitute a problem, given that pharmaceutical producers have an intrinsic interest in compliance in order to achieve the necessary product quality. While this (might) ensure that the production process is regulated sufficiently, this does not imply that a holistic regulation of possible quality problems is achieved.

The second problem diminishing regulatory effectiveness regarding production must be seen in the lack of control of the pre-manufacturing phase and the production of active pharmaceutical ingredients (API), representing input factors of pharmaceutical manufacturing. Under the current regulation, the quality control of API is effectively delegated to the respective QP of the manufacturer. It is the manufacturer and more specifically the QP who must ensure that no inferior APIs are used in the production process. This regulatory approach is based on an outdated conceptualisation of the pharmaceutical sourcing process, ignoring the fact that sourcing became increasingly competitive and globalized. Private capacities to monitor the compliance of API producers, by inspecting those companies themselves, will vary tremendously, especially in case of SMEs with limited resources. Instead, they will rely on existing certificates of API producers, issued by the local agencies, the FDA or the *European Directorate for the Quality of Medicines & HealthCare* (EDQM).[251] As recent incidents have shown, this licensing mechanism – even in the case of those certificates issued by the FDA – does not prevent the entering of poor quality API into the manufacturing process (Kaufman, 2008).[252] The quantity of FDA inspections has been lacking (Barnes, 2006) and the effects of national inspections in China must be questioned as well.[253] The impact of this insufficient self-regulatory mechanism on European manufacturers

[250] The FDA might serve as a valuable example in this matter as it recently opened up a bureau in China to conduct GMP inspections more effectively and considered to open another one in India (Erdmann & Gabriel, 2005: 44). A problem for mutual recognition of inspections is the different level of qualification, especially in China. The FDA and the EMA are currently developing a new strategy to improve the efficiency of their third country inspections.

[251] While the EDQM is mainly responsible for the European *pharmacopeia*, it has been granted the power to issue certificates for APIs. Judging from the number of conducted inspections, with approximately 30 annual inspections worldwide in the period of 1999-2009 (Keitel, 2010), the perceived lack of effective policing prevails.

[252] In the case referred to, contaminated *Heparin* entered the US market (Laurencin & Nair, 2008). The investigation revealed that the FDA confused the API producer and therefore did not inspect the right production site (Wechsler, 2008).

[253] In 2007, the head of the Chinese agency was sentenced to death, after a large scale bribe scandal was uncovered (van den Bos, 2009; Watts, 2007)

has been highlighted recently by several (industrial) interest groups, pushing the EMA and the EDQM to engage in stronger regulatory activity in the API sector as

> "the quality of our medicines is compromised and the noncompliant operator is likely to continue business in the EU undetected. Many thousands of manufacturing plants for off-patent APIs in those non-EU countries are unlikely to have ever been inspected by an EU official. For the majority of EU medicines containing off-patent APIs the authorities have not confirmed (through their inspections of the API manufacturers or traders) that the APIs are Q7A-compliant and safe. Curiously, although most of the APIs come from Asia, the majority of inspections by EU inspectors are conducted in Europe" (Villax & Oldenhof, 2007: 46).

Considering the identified deficiencies it must be concluded, that the regulation of production is only partially able to ensure the quality of pharmaceutical products. The reason for this can be seen in an inadequate problem framing and the lack of public regulatory involvement.

7.2.3.4 The governance of distribution

As the analysis of the European regulatory framework already indicated, the regulation of pharmaceutical distribution is only narrowly defined and is (still) mainly based on a directive released in the early 1990s. The European regulatory approach is based on a licensing mechanism. Wholesalers need a national license to engage in business activities. The basic requirements to obtain such a permit resemble the requirements set out in the area of pharmaceutical manufacturing. Wholesalers need to employ a QP and to ensure the appropriate storage and monitoring of pharmaceutical products. Furthermore, they are expected to comply with the requirements set out in directive No. 92/25/EEC and the guidelines on good distributional practice GDP. The most decisive requirement from the perspective of public health is that wholesalers must provide an emergency plan for the recall of pharmaceuticals in case of an authorization suspension or market withdrawal and keep detailed records of incoming and outgoing quantities. The regulatory framework thus seems to provide the necessary rules to ensure the quality and safety of the pharmaceutical supply chain.[254]

Yet the achievement of compliance in the distribution sector must be questioned. In contrast to the other regulatory phases, the EMA only recently has been granted a very limited function in the regulation of distribution and does not engage in the monitoring of

[254] National regulators are authorized to put additional requirements on wholesalers (Macarthur, 2007a).

regulatees.[255] As in the case of products authorized through national procedures, the monitoring of wholesalers remains mostly within the competencies of member states. National authorities grant wholesaling licenses and are responsible for the supervision and monitoring of the wholesalers and their compliance with regulatory requirements. Like manufacturing and clinical development, distributional activities have been increasingly Europeanized and transformed. Distribution can no longer be reduced to the transfer of products from manufacturers to dispensing units, but increasingly involves trading activities between wholesalers as well as parallel trade and parallel distribution (Chaudhry & Walsh, 1995). Such trading activities lead to repackaging and relabeling of products in order to comply with the (un-harmonized) national marketing requirements (Armengod & Baudenbacher, 2009). With an increase in trade, the number of potential actors in the pharmaceutical supply chain increases. At the same time, the capacity to monitor the quality of pharmaceuticals continuously decreases (Arfwedson, 2004). Since there are currently no regulatory obligations to use authentication mechanism in the manufacturing of products, tracking products throughout the distribution system is becoming an increasingly complex task (Lancaster, 2007: 5). The stretching of supply chains can result in potential quality risks if storage requirements are not met (Bishara, 2006). As in the case of manufacturing the probability of quality issues is aggravated by the potential lack of monitoring of wholesalers by national authorities. It remains within the discretion of member states to conduct inspections and given the lack of involvement of the EMA, the sharing of information depends on bilateral coordination. Comprehensive data on national inspection level of GDP compliance is lacking, but the assertion that the current regulatory approach is insufficient is substantiated by current incidents for example counterfeit medicine found in British pharmacies and the detection of fake drugs manufactured in Italy (Partnership for Safe Medicines, 2005; WHO, 2010a). In light of these incidents, the lack of monitoring and cooperation between national authorities does not only lead to a potential risk for the quality of pharmaceuticals, but increases the chances that counterfeit pharmaceuticals enter the (traditional) distribution channel (Walser & Mierzewski, 2008).

While counterfeit medicines have been considered a “third world problem” (Juillet & Vlasto, 2005: 461) for a long time, the topic has recently risen in political salience when Commissioner Gunther Verheugen stated that in 2008, within only two months 34 millions of

[255] Since 2004, the EMA is responsible for the supervision of parallel trade of pharmaceutical products authorized under the centralized procedure, now requiring an EMA notification.

fake drugs were seized by European customs (AFP, 2009).[256] An alternative number is provided by the IMPACT task force of the WHO estimating that around one percent of pharmaceuticals marketed within Europe are fake (Impact, 2006: 1). The amount of counterfeit medicines in traditional distribution channels seems to represent a serious public health threat.[257] Providing a more detailed perspective, the *Harper report* issued by the Council of Europe in 2006, investigated the link between counterfeit medicine and distribution.[258] The interviewed stakeholder groups identified the insufficient control of the distribution chain and the increase of trading activities between wholesalers as the main reasons for the recent emergence of counterfeit medicine in European traditional distribution chains. Beyond the insufficient control of distribution channels, the lack of criminal sanctions and the high profit margins have been identified as a reason for the attractiveness of counterfeiting pharmaceuticals (Harper & Gellie, 2006: 34-35). While improvements in the control of traditional distribution channels are important, the real threat to public health must be seen in the existence of alternative distribution channels. Bypassing regulated channels, direct internet-based trade accounts for the majority of counterfeit medicine entering the EU (Schweim & Schweim, 2009: 163).

E-commerce of pharmaceuticals has evolved slowly within Europe, but has gained speed after the decision in the *Doc Morris* case by the ECJ (C-322/01), confirming the legality of internet pharmacies (Orizio et al., 2009: 375). However, national provisions still differ resulting in an uneven diffusion of internet pharmacies in the member states. The inherent problem of internet trade is obvious: in contrast to regular distribution channels, “pharmaceutical flow via online markets is impossible to supervise effectively” (Mäkinen et al., 2005: 246) and clearly transcends the European dimension. Furthermore, effective regulation is complicated by the fact that the number of operating e-pharmacies is hard to pinpoint and subject to fluctuations. While there are legally operating internet pharmacies subjected to the same regulations applying to *regular* pharmacies and therefore not posing a specific risk to public health (Mäkinen et al., 2005: 251) the more immanent threat of counterfeit medicine does result from *rogue pharmacies* (Bostwick & Lineberry, 2007). Rogue pharmacies offer pharmaceuticals without prescription and knowledge of the medical history of the ordering

[256] This number does account for all counterfeit drugs and not only for those entering the distributional chain.

[257] It must be acknowledged that the occurrence of this phenomenon within the EU – based on the preliminary evidence available – is still limited (Macarthur, 2007a; Spielberg, 2009). The recent political discussion on the European level has been mainly stimulated by vested interests and must be interpreted in context of the latest (ongoing) revision of the pharmaceutical framework started in late 2007.

[258] As in the case of manufacturing inspections, only few national agencies publish their inspection activities and in those cases where data is available no distinction between GMP and GDP inspections is made.

person. The distinction between lawfully operated e-pharmacies and rogue pharmacies is often blurred rather than clear cut and even more so from a consumers' perspective (Schweim & Schweim, 2009). The problems with the majority of internet pharmacies are manifold. In analyzing 104 internet pharmacies out of which 67 percent delivered internationally, Tracey Bessell and her colleagues (2002) identified several shortcomings compiled in the following table.

Table 20: Common problems of e-pharmacies (n=104)

Issue	Percentage
Displayed addresses	61%
Displayed any health information	60%
Promoted the availability of pharmacist's advice	42%
Displayed privacy statements	40%
Unidentified country of origin	21%
Advertised prescription-only medicines	20%
Sold prescription-only medicines without a prescription	19%
Displayed quality accreditation seals	12%
Offered online prescribing	12%
Displayed last date of update	12%

Source: adapted from Bessell et al. 2002

Results from a more recent European study by a research team led by Grazia Orisio (2009) surveying 118 online pharmacies does amplify raised concerns: less than half of the pharmacies did provide a physical address, one third did not ask for medical history of the ordering person and health information, most importantly concerning potential side effects, was lacking in general. In addition, 81,4 percent of e-pharmacies were delivering prescription medicine without asking for prescription (2009: 375-376).

Reconsidering the governance of pharmaceutical distribution it must be concluded, that the comparatively narrow requirements entailed in the regulatory framework are not mitigated by a strong governance approach. While the pharmaceutical supply chain is regulated based on national licensing mechanisms, continuous monitoring accounting for the changing nature of distribution is not possible under the current regulatory approach. Increased trade of pharmaceuticals can negatively impact on the quality of pharmaceutical products and the multiplicity of actors along the distribution chain increases the chances of counterfeit medicine entering distribution channels. The current approach suffers from a lack of cooperation between national regulators, the EMA, manufacturers, wholesalers and pharmacies. Beyond the lack of regulatory activity connected to the traditional supply chain,

the current regulatory regime does not address the public health threats outside traditional supply.[259]

7.2.3.5 The governance of information

In assessing the changes in the governance of information, two aspects need to be considered: the information on the work of the agency network (1) and the information provided to patients (2).

7.2.3.5.1 Information on agency operations

When the EMA was installed in 1995, the mandate of the new agency included a strong commitment to an active information policy. This commitment did not only cover the work of the European agency, but expanded to the national authorities as well. Increased involvement and adaptive pressure within the regulatory network led to the adoption of a more active national information policy: the publication of annual reports by national agencies, for example, today is considered a standard but this has not been the case before 1995. Nevertheless, different levels of information on national regulatory activities prevail. While some agencies take a very proactive information approach on their regulatory activity, others provide only minimum information. National differences are exemplified by the level of detail of annual reports. Some agencies do not publish annual reports but merely statistics (Germany), or no reports at all, as in the case of Greece. If national agencies publish reports, the number of pages in the document range from 5 (Luxembourg) to 120 (France).[260] While these differences are influenced by the respective scope of the agencies and national information laws, they still reflect different and prevailing approaches to information and transparency of national agencies within the European governance structure.

The availability of information on agency operations depends on the degree of European (and EMA) involvement. Under the centralized procedure and regarding the work of the CHMP, the availability of information is much better, compared to the activities under the decentralized procedure.[261] Despite improvements, it must be acknowledged that the governance approach is still reactive. Much information remains disclosed and is only

[259] Moreover, the lack of cooperation between regulatory agencies and European customs authorities represents an additional challenge (Cockburn et al., 2005).

[260] These numbers are based on the annual reports published in 2007 and 2008.

[261] The Heads of Medicines Agencies group at least provides additional information on the functioning of the procedures based on mutual recognition on its website (http://www.hma.eu/).

revealed on a *need to know* basis, with the EMA acting under considerable discretion (Anon, 2010a). This deficiency is reconfirmed by the recent investigation of the European Ombudsman into the information policy of the agency. Based on a complaint by an Irish citizen, whose request for reports on the adverse reactions of an authorized drug was refused by the EMA, European Ombudsman Nikiforos Diamandouros asked the agency to revise its current approach and adopt a more proactive information policy (Anon, 2010a: 1753). Considering the reluctant position in the past, however, it remains to be seen in how far the EMA will adopt such a proactive approach in face of increased public pressure (Sukkar, 2010).

7.2.3.5.2 Provision of product-related information

The consumption of pharmaceuticals involves the risk of unwanted side effects. A second risk from the perspective of public health is wrong consumption. Advice by dispensing physicians and pharmacists plays a decisive role in reducing these risks. While the doctor-patient and patient-pharmacist relationship is still vital, the traditionally hierarchical constellation seems to erode gradually, with more demanding and critical patients increasingly searching for alternative sources of health information (Ball & Lillis, 2001; Deccache & Aujoulat, 2001; Visser et al., 2001). Reliable information beyond the advice of doctors and pharmacists regarding pharmaceutical products is important because pharmaceuticals are normally not consumed under supervision. Accordingly, written medical information accompanying the product serves as an important additional lever to inform patients and achieve compliance.[262] European regulation has been instrumental in their introduction and the improvement of information entailed in these leaflets. Notably, the most recent revision of the pharmaceutical code has made prior testing of package leaflets mandatory in order to achieve a higher usability of such information (Fuchs et al., 2007). Beyond the provisions entailed in the framework, the EMA and the respective ad hoc group support the continuous improvement of patient information by developing guidelines for package information. The expansion of European activities and the involvement of the EMA improved the availability of product information, but problems with written information remain. Current European standards result in lengthy and complex leaflets, hard to understand for the lay public and overemphasizing negative information resulting in potentially reduced patient compliance instead of safer

[262] Another important aspect of product related information has been the reduction of potential confusion of drug names, and the EMA has played a crucial role in this matter as well (Hoffman & Proulx, 2003).

consumption (Fuchs et al., 2007; Pander Maat & Lentz, 2010; Verdú & Castellá, 2004).[263] Additionally, leaflets only reflect the information available at the time of writing. In light of these findings, the reliance on package leaflets as the main mechanism to inform patients seems to be insufficient and does not necessarily satisfy patient's informational needs (Dickinson et al., 2003: 861). In this context, the internet plays an increasingly important role, representing an invaluable source of information for patients (Benigeri & Pluye, 2003; Närhi, 2007; Trotter & Morgan, 2008).

7.2.3.5.3 Providing pharmaceutical information through the internet

As in the case of rogue pharmacies, it is virtually impossible to control product related information available on the internet (Valverde, 2001). Hence, it is necessary to provide reliable and unbiased information to the public and ensure that people can distinguish between reliable and misleading sources of information. This task goes well beyond the provision of information on pharmaceutical products but is relevant regarding e-health in more general terms as patients are "both too much and too poorly informed" (Deccache & Aujoulat, 2001: 13). Focusing on pharmaceutical product information, national regulatory agencies and the EMA play a crucial role. While product information by producers – considering the fact that advertising for prescription medicine is not allowed under the current regime – always is potentially biased, regulatory agencies can assume the position of a *neutral arbiter* of information: beyond the provision of updated product information, regulatory agencies could advance the understanding of pharmaceutical risks in more general terms and provide contextual information on the risks and benefits of certain products. The current European regulatory approach and most national regulatory philosophies pose an obstacle to the fulfilment of this role. Regulators only reluctantly involve the public, affecting the potential to proactively communicate with the public (Schofield, 2009; Slijkerman, 2009; Vitry et al., 2009). Given this long standing practice and the shortage of regulatory capacities, especially outside the field of *application* management, the majority of agencies do not have the organisational capacities to communicate proactively. While the introduction of the EudraPharm database and the equivalent database for products authorized under the decentralized procedure provides the public with basic and updated product information, the provision of information in more general terms depends on national capabilities and an

[263] An important reason for the complexity of leaflets must be seen in the necessity from the perspective of producers to formulate leaflets in order to reduce the risk of liability (Fuchs et al., 2007).

according regulatory culture. The role of communication functions seems to focus on the processing of standard informational request rather than providing the public at large with information. This reflects the lack of public orientation of pharmaceutical regulators, not necessarily viewing the provision of information to patients as one of their core tasks. This assertion is supported by the current practice of national regulators regarding the provision of information through their websites considering both data availability and accessibility.

7.2.3.5.4 Provision of information on national regulatory agency websites

The following table provides an overview on basic data available on national agencies websites.[264] Five indicators were used to assess the level of information. The first two indicators assess the *accessibility* of the homepages from the perspective of the lay public: the availability of a specific patient portal (1) and the certification of the website as a source of trusted information (2).[265] The following three indicators assess the *availability* of standard information on pharmaceutical products: a register of marketed drugs (3), the *Summary of Product Characteristics* SPC (4) and the *Package Information Leaflet* (PIL) (5).[266] Most notably, the majority of national agencies and the EMA do not employ certificates which would make it easier for the public to identify the homepages as a source of trusted information. In addition, specific sites for the public are no common feature of regulatory websites. From the perspective of information availability, the majority of national agencies provide basic information to the public. Comparing these findings to previously conducted studies, the situation did improve, at least regarding the availability of information (Närhi, 2006; Vitry et al., 2008). Despite these improvements, the comparatively low level of accessibility of the regulatory agency websites reduces patients' ability to find necessary information.

[264] Data was compiled based on the *regular* and the English sections of agency websites. No data was available for Cyprus.

[265] The *Health on Net* Code (HON) was used, representing an established standard in health care (Boyer et al., 1998).

[266] To determine the availability of PIL and SPC, the search function of databases was used. *Paracetamol*, a pharmaceutical commonly used to treat headache, was used as a search term. Results thus do not indicate that the same level of information on PILs and SPCs is available in all member states.

Table 21: Provision of information on national authorities' websites

	Accessibility		Availability		
	HON Code	**Consumer site**	**Product Register**	**SPC**	**PIL**
Austria	No	Yes	Yes	Yes	Yes
Belgium	No	Yes	Yes	Yes	Yes
Denmark	No	Yes	Yes	Yes	Yes
Finland	No	Yes	Yes	Yes	Yes
France	Yes	Yes	Yes	Yes	Yes
Germany	Yes	No	Yes	Yes	Yes
Greece	No	No	No	No	No
Ireland	No	No	Yes	Yes	No
Italy	No	Yes	Yes	No	No
Luxembourg	No	No	No	No	No
Netherlands	No	No	Yes	Yes	Yes
Portugal	No	Yes	Yes	Yes	Yes
Spain	No	Yes	Yes	Yes	Yes
Sweden	Yes	Yes	Yes	Yes	Yes
UK	No	Yes	No	No	No
Bulgaria	No	Yes	Yes	No	No
Czech republic	No	Yes	Yes	Yes	Yes
Estonia	No	No	Yes	Yes	Yes
Hungary	No	No	Yes	Yes	Yes
Latvia	No	No	Yes	Yes	Yes
Lithuania	No	No	Yes	No	Yes
Malta	No	No	Yes	Yes	Yes
Poland	No	No	Yes	Yes	Yes
Romania	No	No	Yes	Yes	Yes
Slovenia	No	No	Yes	Yes	Yes
Slovakia	No	No	Yes	Yes	Yes
EMA	No	Yes	Yes	Yes	Yes
Ratio Yes/Total	**3/27**	**13/27**	**24/27**	**21/27**	**21/27**

Source: national agency websites (accessed 23 December, 2009); Note: SPC: Summary of Product Characteristics; PIL: Package Information Leaflet

7.2.3.6 The monitoring of pharmaceutical risks

While national monitoring systems existed prior to 1995, no stringent governance of pharmacovigilance was traceable throughout the European Union. In light of insufficient alignment, one of the reasons for the creation of the European agency has been the strengthening of the European pharmacovigilance system, resulting in a comparatively strong formal role in the monitoring of pharmaceutical risks.[267] The EMA is responsible for the pharmacovigilance of pharmaceuticals authorized under the centralized procedure and has a comparatively strong supervising function regarding products authorized under the

[267] This strong role reflected the change in regulatory philosophy shifting from the pre-market towards the lifecycle perspective of pharmaceutical risks (Laporte & Rawlins, 1999).

decentralized procedures. Three different governance aspects of pharmacovigilance can be separated: the collection of pharmacovigilance data (1), the evaluation and decision (2) and the regulatory actions (3). Building on the national pharmacovigilance systems, the new European governance approach is based on shared responsibilities between the competent national authorities, the EMA and market authorization holders. The monitoring of pharmaceutical risks is achieved by relying on organisational requirements as well as monitoring and reporting obligations. In addition, private and public stakeholders are involved in the collection of pharmacovigilance data.

7.2.3.6.1 Detection of safety issues and regulatory action

The gathering of pharmacovigilance data is based on several different mechanisms. The most important one is spontaneous reporting of adverse events. Reports are generated by patients or doctors, encountering adverse events related to pharmaceutical consumption. The reporting of such signals is organized differently in the member states.[268] Market authorization holders (MAH) are obliged to collect ADR signals as well. While the EMA does not operate an additional reporting scheme, it collects the reports gathered by national authorities within the EudraVigilance system, allowing for the rapid exchange of signals between MAH and national authorities. This system is supplemented by the *rapid alert system* (RAS) based on the Eudranet system. The RAS is used by national authorities to share their perspective concerning a specific product and developments altering its risk-benefit profile, making a subsequent decision necessary. The partial delegation of monitoring tasks to pharmaceutical manufacturers is based on the same concept employed in the other governance fields. Companies are required to employ a *qualified person* (QP) responsible for the development of a system to track and process pharmacovigilance data and the implementation of reporting requirements. Moreover, producers are obliged to compile *Periodic Safety Update Reports* (PSURS) in defined intervals, perform literature researches and conduct voluntary or mandated safety studies (Härmark & van Grootheest, 2008). These requirements are supplemented by the competence of national agencies and the EMA, for centralized products, to conduct pharmacovigilance inspections. In case of non-compliance, agencies are authorized to penalize regulatees. With the adoption of the new risk management strategy, the stringency of the different mechanisms and requirements has been strengthened further. Authorization

[268] While some member states, as Ireland, allow for direct reporting of patients, the majority of member states restrict the generation of signals to doctors (Blenkinsopp et al., 2007). In addition, some countries authorize pharmacists to report events (van Grootheest et al., 2004).

holders now have to provide detailed plans how to ensure, that the risks and benefits associated to a newly authorized product is constantly evaluated and which additional steps they will take to safeguard public health (Andrew et al., 2008; Hagemann, 2009).

7.2.3.6.2 Evaluation of signals and decision on regulatory measures

Based on the available information, national agencies, the EMA and market authorization holders engage in activities to detect safety signals, necessitating a re-evaluation of the previously established risk-benefit ratio of a pharmaceutical product.[269] Based on detected safety signals, assessments must be conducted. For products authorized under the centralized procedure, the (original) rapporteur is responsible for the assessment of safety signals. Under the decentralized procedure, the reference member state will conduct this assessment. Under both procedures, the CHMP's *Pharmacovigilance Working Party* (PhVWP) can be asked for additional (non-binding) scientific advice. The CHMP forms an opinion, which is subsequently referred to the Commission for a decision. This decision has to be implemented by the member states. Under the centralized procedure, the rapporteur based on his assessment asks the CHMP for an opinion, leading to a Commission decision. While regulatory authorities can initiate such an assessment, the current regulatory approach provides the market authorization holder with the possibility to take voluntary measures.

7.2.3.6.3 Regulatory actions, implementation and communication

If a signal is detected and regulatory action is necessary, different instruments can be applied. The market authorization holder can be asked to apply for a variation of the market authorization, modifying the existing authorization. If this does not suffice, the market authorization can be suspended, revoked or withdrawn. During the decision process, competent authorities are authorized to take *urgent safety measures* in order to protect the public health, for example by conducting pharmacovigilance inspections or restricting prescription status. If the market holder forestalls regulatory intervention, he can either apply for a variation of the market authorization or withdraw the product voluntarily. While a swift decision on safety matters is important, the clear communication of the decision is vital in order to prevent more patients from exposure to a dangerous drug. Again this is a shared

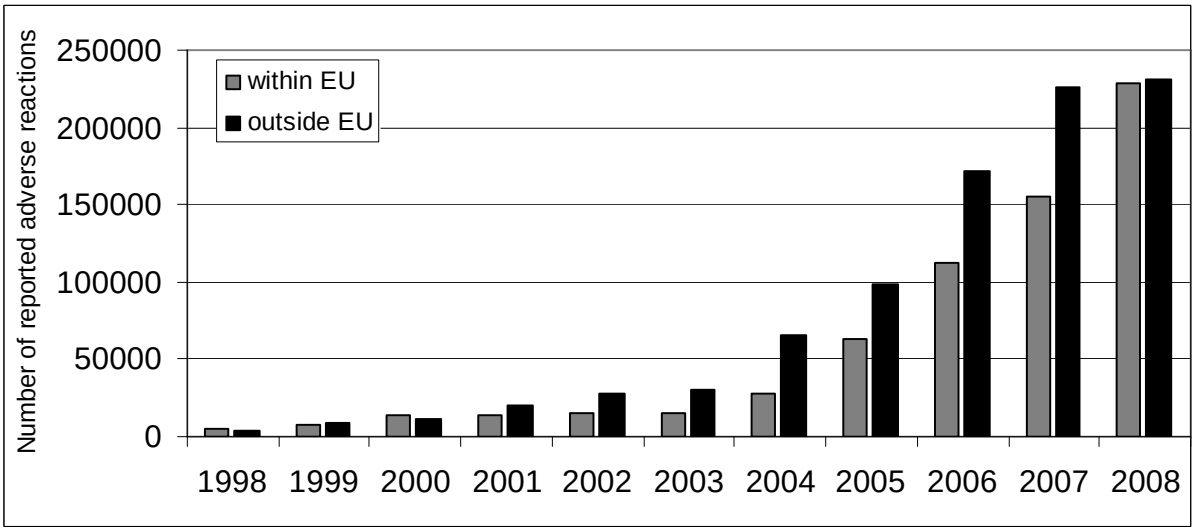
[269] Different methods and tools are used to detect safety signals employing for example data mining techniques and additional studies. For an overview see (Hauben et al., 2007; Lindquist et al., 2000; Meyboom et al., 2002; Segal et al., 2005)

responsibility between the EMA, competent national authorities and the market authorization holder. The MAH is obliged to publish a *dear doctor letter* informing health professionals while regulators can provide information on their homepages or in specific publications (drug bulletins).

7.2.3.6.4 Effectiveness of post-authorization safety monitoring

The new European governance approach to post-authorization monitoring built around the EMA represents a remarkable shift from the predominantly national and voluntary system. While the new regulatory regime builds on existing national spontaneous reporting systems, harmonized and more stringent reporting requirements as well as the improved exchange of information within the regulatory network improved the monitoring capacities. Notwithstanding these important changes, the predominantly positive assessment of post-market monitoring of pharmaceutical risk within the European Union must be corrected. Regulatory developments have mainly resulted in improvements in the collection of new ADRs, while the following aspects of post-market monitoring remained outside the scope (de Abajo, 2005). Judging from the trends in ADR reporting, the introduction of more stringent reporting requirements has led to an increase of reported incidence over time. The reasons for this trend and the conclusions to be drawn regarding the effectiveness of post-market surveillance are, however, unclear. Moreover quantity does not necessarily translate into quality. The more information is collected, the more the analysis of the data is complicated, reducing the value of ADR reporting (Waller & Evans, 2003: 19-20). Even though the limitations of ADR reporting have been recognized by regulatory authorities, it remains the corner stone of the current monitoring approach. It has been increasingly supplemented with alternative methods to detect adverse reactions, including literature research, prescription event monitoring and (mandatory) post-marketing studies (Rupalla & Jarrett, 2003). The usage of such tools has been strengthened with the introduction of risk management plans in Europe (Kermani, 2009), requiring pharmaceutical producers to propose activities to establish a sound risk-benefit ratio after market approval. Yet the responsibility to perform such investigations rests mainly with the producer (Ladds, 2007).

Graph 24: Reported adverse drug reactions 1998-2008



Source: EMA annual reports

7.2.3.6.5 Delegation of post-market surveillance and the regulatee's dilemma

Even though the delegation of signal detection to the pharmaceutical industry represents a flexible regulatory approach, the current practice must be viewed as problematic. It puts considerable regulatory costs on pharmaceutical producers, adding to the already substantial expenditures in order to comply with regulatory requirements. Evidently, it is the pharmaceutical industry that should pay for the monitoring of pharmaceutical risks, yet it must be asked if the current approach is efficient and specific enough. This problem is exemplified in the employment of PSURs. The current approach does mandate the regular compilation, irrespective of the already established risk-benefit ratio of a given product (Klepper, 2004). In addition, it is based on the assumption that pharmaceutical manufacturers will voluntarily comply with regulation and reporting requirements. The regulatee is however confronted with a potential dilemma: prolonging the timeframe of continuous safety monitoring increases the time of unrestricted marketing of the product. If it turns out that the producer was aware of a risk and harm could have been prevented, this will lead to a reputation loss. Current changes in the European pharmaceutical framework and the introduction of risk management plans surely contribute to the minimization of such behaviour, but there is still reason to believe, that compliance regarding post-market commitments is lacking. Evidence from the US market shows, that compliance with post-market commitments is at least suboptimal (Avorn, 2007; Okie, 2005; Sharma, 2009). While no comparable assessment of compliance for the European market and products under the centralized procedure exists, data from 2005 compiled by the UK regulator showed

comparable results as “of 115 studies in the MHRA registry, one-third have been completed, one-third are incomplete and one-third have not been started” (Breckenridge et al., 2005: 3). Despite the introduction of the risk management concept during the second revision of the framework, making post-authorization requirements more stringent, the compliance issue is still prevalent (Breckenridge, 2008). The potential problems cannot be solely attributed to a perceived lack of willingness of regulatees. Two contributing factors stemming from the governance approach must be acknowledged as well: a lack of active surveillance and limited enforcement capacities on behalf of the regulators.

7.2.3.6.6 Delegation of responsibility without monitoring compliance

National regulators are expected to monitor the reporting requirements of pharmaceutical companies and ensure that manufacturers comply with the organisation requirements. Despite these legal obligations, national regulators did not pursue proactive monitoring, especially in the first years of the new European regime:

> “In general time frames for reporting are relatively loosely handled […] Although Competent Authorities are concerned about time frames we are not aware of any company that has received a formal warning or has been questioned for untimely reporting by European Competent Authorities unless reporting time frames were consistently and significantly exceeded months from first notice.” (Koster et al., 2000: 476)

Similar problems were experienced regarding pharmacovigilance inspections. In a survey of sixteen European countries, Gysele Bleumink and her colleagues found that the majority of member states did not conduct inspections. Countries employing pharmacovigilance inspections focused mainly on organisational aspects and conducted such inspections irregularly (2001: 339-340). A follow-up study in 2005 by Maria Koster and Anita van den Oetelaar showed little improvement, with only half of the fifteen surveyed European countries conducting specific pharmacovigilance inspections (Koster & Oetelaar, 2005). Assessing the effectiveness of pharmacovigilance activities after the legislative review in 2005 is complicated by the fact that data and research on the conduct of pharmacovigilance in Europe is scarce. The MHRA represents a notable exception, making pharmacovigilance metrics since 2006 publicly available on their website. Two conclusions can be drawn from the data. Pharmacovigilance monitoring in the UK has increased significantly from 75 inspections conducted in 2006 to 121 in 2009. During the same period the average number of findings per inspection decreased (MHRA, 2009: 8). Judging from this (very) limited evidence, increased

inspection activities seems to contribute to regulatory compliance. Unfortunately, the UK experience might not reflect the European regulatory reality. The MHRA clearly represents a precursor in pharmacovigilance, both from a 'philosophical' and practical perspective. Members of the agency, most notably Alisdair Breckenridge, have continuously contributed to the scientific discussion of pharmacovigilance and compliance (Breckenridge, 2004, 2008; Breckenridge & Woods, 2005). More decisively, the agency dedicated considerable resources to pharmacovigilance activities. While the reluctance to adopt a more proactive approach to post-market monitoring can be partially attributed to the differences in regulatory culture, difference in resources must be considered as well.

Traditionally, national regulators dedicated their resources almost exclusively to the pre-market aspects and approval, while post-authorization activities including monitoring, pharmacovigilance and the issuance of variations have been largely treated as an administrative process. While more recent data on the distribution of resources within agencies is not available, a report of the *Fraunhofer* institute, assessing the strengths and weaknesses of the European pharmacovigilance system, provides data for 2005. Drawing on interviews with national agencies, the report identified considerable variation regarding the pharmacovigilance resource.

Table 22: National pharmacovigilance resources (2005)

	Pharmacovigilance staff in national regulatory authorities (FTE per million capita)
Minimum	0,2
Median	0,772
Maximum	4,6

Source: adapted from Bührlen et al. (2006)

The numbers correspond with the findings of a survey conducted by the HMA group in 2004 highlighting the imbalanced staff situation "with less than 10% monitoring industry compliance and very few engaged in audit of pharmacovigilance action." (HMA, 2005: 2). Both the relatively low level and the national differences of regulatory resources do point to the fact that the increased importance of pharmacovigilance within the lifecycle approach to drug safety is not reflected in staffing levels.[270] Moreover, the lack of pharmacovigilance resources points to a general understaffing of national agencies negatively affecting the conduct of post-authorization monitoring and the regulation of the sectors as a whole (Anon,

[270] The improvement of pharmacovigilance does not only depend on staffing but better trained experts and the increased employment of statisticians in regulatory agencies more specifically (Eichler et al., 2010; Jones, 1992; Skovlund, 2009).

2006c).[271] The lack of effective sanctioning mechanisms, or a reluctance to use these mechanisms on the national level reduced effectiveness (Wiktorowicz et al., 2008: 18). It remains to be seen, if the recent changes in the regulatory framework granting the EMA with sanctioning powers in case of non-compliance with regulatory obligations will fulfil its purpose or ”may prove to be a big stick that is rarely used” (Killick, 2007). While the lack of regulatory resources aggravates the compliance problems in post-authorization monitoring, it also decreases regulatory capacities to engage in analysis of potential safety signals, supplementing industrial activities. As in the case of pharmacovigilance inspections, the capacities to carry out post-authorization research, for example, data mining, prescription event monitoring and meta-analysis, are unevenly distributed throughout the Union. Many agencies do not have sufficient pharmacoepidemiologic resources to conduct independent research and signal assessment.[272] Furthermore, the conduct of meaningful post- authorization research is contingent upon the respective infrastructure and databases. Independent academic research can play an important role in supplementing information for risk benefit assessment, but limited resources and data shortages due to confidentiality prevail. Furthermore, study results are often criticized on theoretical grounds by the respective market authorization holder. On the other hand, safety studies conducted by independent experts and sponsored by pharmaceutical companies, have been found to produce positive results downplaying safety concerns (Blumsohn, 2007). Problems of data generation result in a problematic decision basis for regulatory agencies, drawing largely on evidence from spontaneous reporting systems (Clarke et al., 2006). Since this data represents a lower level in the hierarchy of evidence, the quality of resulting decisions, is potentially biased and subjected to a larger margin of interpretation rather then scientific evidence.

7.2.3.6.7 Problems of post-market decision-making

While the quality of decision-making is hampered by the limitations of data underpinning regulatory decisions in the post-market, additional problems from a procedural and institutional perspective exist. The regulatory decision process is confronted with a problematic constellation of interests, resembling the regulatee’s dilemma regarding the identification of signals. Regulators are confronted with the public perception that authorized

[271] The problem of understaffing has been raised by industrial officials highlighting the increased complexity of the regulatory task and the possible negative effects on the efficiency and speed of the regulatory process (Anon, 2008b).

[272] This problem has been recognized lately and triggered the creation of a new European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP).

drugs are (absolutely) safe. Notwithstanding the fact that this is an unrealistic perception, regulators will try to support the safety claim. If a regulator is confronted with a safety signal, he has the ethical and moral obligation to react. At the same time, the withdrawal of a product can potentially undermine his public reputation, especially if he is exposed to media attention. Obviously, a lack of action can potentially lead to more severe consequences in the long run and even higher levels of public criticism, if a regulatory failure is detected. As a result, a rational regulator might adapt a specific regulatory strategy in the governance of post-authorization surveillance: he will try to accumulate as much evidence as possible before far reaching regulatory measures (withdrawal) will be invoked and rather employ softer measures to regulate post-market safety (variations). The possibility to pursue such a strategy is supported by the institutional set-up of the process and the prevalent low level of transparency. In contrast to the centralized authorization procedure, accountability measures as well as clear decision criteria are largely absent from the post-authorization decision process (Hughes et al., 2007; Meyboom et al., 2002). Considering the fact that the decisions will be largely based on spontaneous reporting, providing the regulator with even more room for interpretation, regulatory discretion in the assessment of risk-benefit ratios is increased. Since information on potential risks as well as information on the decision process is, based on confidentiality arguments, either not publicly available or only available in highly aggregated form, external control is reduced even further.[273] Drawing on the available data on regulatory action in the post-authorization stage, supportive evidence for the assumption of an *expectant* approach to post-authorization decision-making can be found. While the number of safety related referrals to the CHMP in the post-authorization stage has remained fairly constant, the regulatory network increasingly employs the instrument of safety reviews to establish a more sound understanding of product risks.

Table 23: Post-market regulatory activities

	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008
Referal CHMP*	4	11	10	15	10	15	12
Finalized safety reviews	n.a.	n.a.	n.a.	n.a.	2	10	19

Source: EMA annual reports; Note:* Started referrals based on articles 107, 31 and 36 of directive 2001/83/EC as amended

Turning to the product withdrawal data available at the EMA website, covering only products authorized through the centralized procedure suggests, that withdrawal is regularly used. Out

[273] Lately, the situation has improved but only gradually. Considering the availability of risk-benefit data, the recent activities by the European Ombundsman have called for more transparency. For the centralized procedure, actions after authorization for any specific product are now published on the EMA website.

of the 551 products included in the EPAR database, 70 products were withdrawn after authorization.[274] Yet, the majority of these withdrawals were voluntary and because of commercial reasons.

Table 24: Drug safety incidence and regulatory action since (1995-2008)

Name	Type of Approval	Regulatory action
Trovofloxacin	Centralized	Withdrawal
Tolcapone	Centralized	Suspended
Cisapride	National	Restrictions
Bupropion	Decentralized	Restrictions
Cerivastatin (Lipobay)	Decentralized	Withdrawal
Atomoxetine*	Decentralized	Restrictions
Citalopram*	Decentralized	Restrictions
Duloxetine*	Centralized	Restrictions
Escitalopram*	Decentralized	Restrictions
Fluoxetine*	Decentralized	Restrictions
Fluvoxamine*	Decentralized	Restrictions
Mianserine*	Centralized	Restrictions
Milnacepram*	Centralized	Restrictions
Mirtazapine*	Decentralized	Restrictions
Paroxetine*	Decentralized	Restrictions
Reboxetine*	Decentralized	Restrictions
Sertraline*	Decentralized	Restrictions
Venlafaxine*	Decentralized	Restrictions
Celecoxib**	Decentralized	Restrictions
Etoricoxib**	Decentralized	Restrictions
Lumiracoxib**	Decentralized	Restrictions
Valdecoxib**	Centralized	Restrictions
Parecoxib**	Centralized	Restrictions
Macrolide	Centralized	Restrictions
Rosiglitazone	Centralized	Restrictions/review in progress

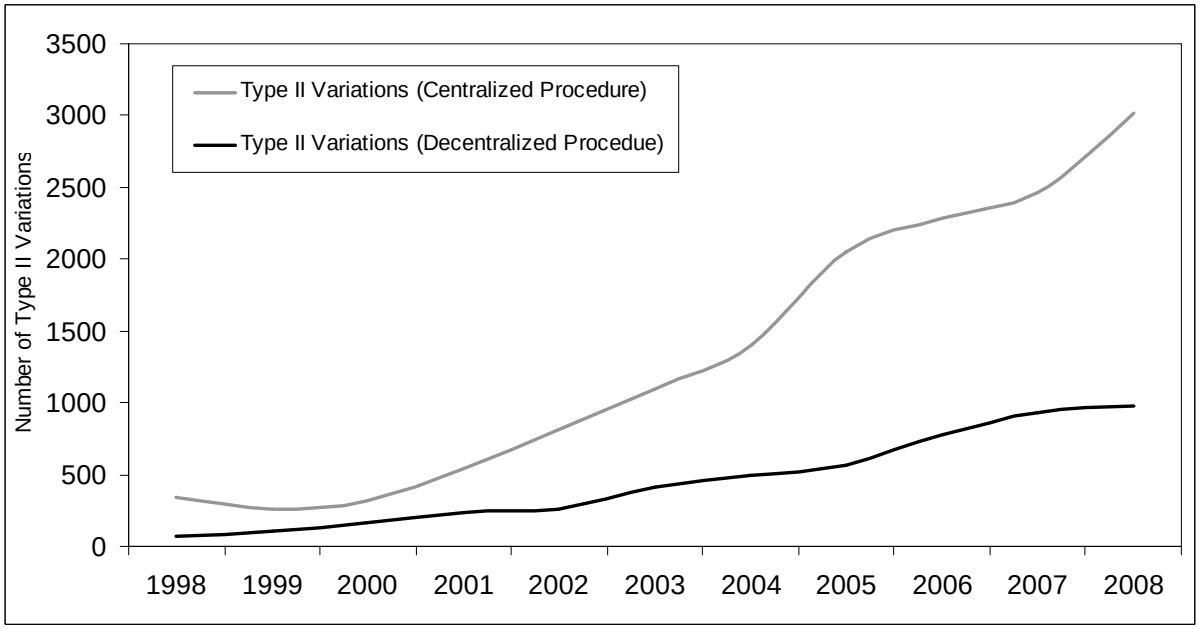
Source: adopted from *Härmark, 2008 #2289'; *: SSRis (Class review); **:Cox II (Class review)

In fact, only 10 of the 70 withdrawals were enacted because of safety reasons, based on the fact that the products were suspended prior to the withdrawal. While no comparable data for products authorized under the decentralized procedure is available, recent studies suggest that withdrawal is reluctantly used for those products as well. Based on a list of recent drug safety incidence within Europe, identified by Härmark and van Grootheest (2008), the respective authorization procedure and regulatory measure was identified. Based on this limited sample,

[274] See the appendix (A.9) for a full list of withdrawn products. Database was accessed in June 2010.

the reluctance to withdraw products is reaffirmed.[275] Instead, European regulators resort to a less intrusive approach applying restrictions to the use of the respective product. Accordingly, the level of type 2 variations, covering clinical and quality changes to an existing product, has been constantly rising.[276]

Graph 25: Type II variations between 1998-2008



Source: EMA annual reports

Comparing the use of the different regulatory measures the assumption of an expectant regulatory approach seems to be a valid and drawing on regulatory behaviour in two recent safety incidents, involving *Lipobay* (Cerivastatin) and *Vioxx* (Rofecoxib), is substantiated further. [277]

7.2.3.6.8 Regulatory behaviour during drug safety incidents: Lipobay and *Vioxx*

Lipobay was authorized in Europe in 1997 via a decentralized procedure, with the UK as a reference member state. After several adverse events with lethal consequence in the US market, the market authorization holder, Bayer, voluntarily withdraw the product from the global market in August, 2001. Even though the withdrawal was voluntary, the decision

[275] Another important finding is the fact that safety concerns seem to be more common in products authorized under the decentralized procedure.

[276] It is important to note that the level of type II variations does not exclusively reflect changes of the risk-benefit ratio, but in most cases is the result of voluntary adaptation of the product to the newest available scientific knowledge.

[277] The two cases were selected based on the high media attention. Other examples supporting the reluctance of European pharmaceutical regulators could be seen in the recent *Rosiglitazone* controversy (Bloomgarden, 2007; Misbin, 2007; Moynihan, 2010) or the case of *Alosetron* (Moynihan, 2002).

resulted in substantial attention in the (lay) media. Bayer was accused of informing investors before regulatory officials, while at the same time withholding information to European regulatory agencies, specifically the German *Bfarm* (Zylka-Menhorn, 2001). It was claimed that additional risks were already known in 1998, but neither the Bayer AG and the German regulator nor the UK authority, saw the need for regulatory action beyond variations to the existing authorization. Only after the product withdrawal and the increased media attention, the EMA started a class review of Lipobay and similar products. The behaviour of the German regulator in the Lipobay case is noteworthy. Faced with increased public criticism, the regulator first blamed Bayer for withholding information and shortly afterwards argued that an investigation of adverse incidence was not possible, since the responsibility for the regulatory assessment rested with the UK authority. However, nothing would have prevented the Bfarm from referring the matter to the CHMP (Tuffs, 2001). Instead of pursuing a proactive pharmacovigilance approach, for example the request of Phase IV studies or additional literature studies, European regulators waited for more evidence to re-evaluate the risk-benefit profile of Lipobay.

As in the Lipobay case, first evidence on the negative side effects of Vioxx was detected in the US. Vioxx sold by Merck, was withdrawn voluntarily in September 2004, after a study revealed that it doubled the risk of heart attacks and stroke in those who took it for longer than 18 months. While the information on the long-term effects leading to withdrawal could not have been collected before authorization, the withdrawal has resulted in a massive turmoil in the US media. Both the producer and the FDA were exposed to massive criticism, when it was revealed that a study commissioned by Merck in 1999 already hinted towards the safety issues leading to withdrawal (only) four years later. Information to regulators was effectively suppressed (Mathews & Martinez, 2004). The so-called VIGOR study was published, but obscured cardiovascular risks, while independent research into the risk-benefit profile of the drug was actively prevented by the producer (Krumholz et al., 2007: 121). Questions about the passive role of the FDA in the Vioxx scandal resulted in an in-depth analysis of the American regulator. Despite mounting evidence, the regulator did not request any additional investigations. Moreover, internal organisational structures amplified the negative effects of the regulatory dilemma:

> "Once a licensing approval has been made it is naturally in CDER's own interests to stand by its original decision. CDER's reputation would be damaged if its licensing judgments were constantly challenged by its own staff. This understandable but dangerous tendency to discourage dissent makes

> the Office of Drug Safety, which sits lower in the hierarchy of CDER than the Office of New Drugs, weak and ineffective." (Horton, 2004: 1996)

Unsurprisingly, the Office of Drug Safety lacked the regulatory powers to effectively govern the post-authorization stage (Dohrman, 2005; Waxman, 2005). Public and media attention surrounding the Vioxx incident in Europe have been more moderate. Vioxx had been authorized in 1999 through a decentralized procedure with the UK serving as a reference member state. In contrast to the Lipobay case, European regulators in light of the emerging evidence from the US and after referral by the French Agency engaged into the investigation of the risk-benefit profile of Vioxx and other COX-2 inhibitors in 2002 (Arznei-Telegramm, 2004). However, the practical conduct of the investigation remained largely secretive and took nearly two years, reflecting the expectant approach of European regulatory agencies. This impression is shared by Silvio Garratini, a longstanding member of the CHMP and the Italian agency:

> " 2 years to make a decision on whether a class of drugs used by millions is safe or dangerous is certainly too long. (…)The EMA depends on the fees paid by industry much more than the FDA does, and is much less transparent — of the above referral procedure, only a onepage document can be traced on the EMA web site." (Garattini & Bertelé, 2005: 24).

In light of the current governance approach and regulatory behaviour, the current surveillance of post-market risks must be described as both expectant and reactive. At the same time, it is important to note that the reluctance to withdraw products must not be equated with the wilful endangering of public health. The public has to understand that risk/benefit decisions are complex and take (some) time. Moreover, withdrawing a product can have severe consequences for those patients successfully treated, calling for a careful evaluation of less intrusive measures. In light of a functioning approval process withdrawal must remain the exception and not become the routine. Higher levels of product withdrawals should thus not be confused with a higher level of public health protection. However, it is not the rate of withdrawal or the number of suspensions that is problematic, but the fact that it remains unclear, which steps have been taken by regulators in the post-market to evaluate products in a proactive way.

7.2.3.6.9 Communication of risks in the post-authorization stage

The reactive governance approach characterizing the monitoring of post-market risks unsurprisingly affects the communication of product risks as well. The task of communicating product risks is shared between regulators and regulatees. Companies either voluntarily or mandated by the regulatory authorities issue dear doctor letters. In addition, regulatory authorities will take supplementing measures through the distribution of drug bulletins or information on their websites. In case of product variations, updated product characteristics are published. This communication approach is problematic from at least two perspectives. The approach focuses mainly on health professionals. It is frequently legitimized based on the claim, that the public is not able to evaluate product risk information, resulting in wrong assessments. However, it is questionable how such an understanding should ever be developed, if only limited information is communicated to the public. Furthermore, unregulated information on the internet could have a much more detrimental effect (Tatsioni et al., 2003). Accordingly, a more proactive communication approach to the public is necessary. By educating the public about the general risks of pharmaceutical consumption and the role of patient compliance and a more continuous approach to risk communication, differences in informational needs and the risk of information *overload* can be reduced (Goldman, 2004). While the pharmaceutical industry frequently claims, that such continuous education would be possible if advertising was allowed, such claims should be interpreted with caution (Anon, 2006d; Hugman, 2006). Instead, regulatory agencies should be responsible. Most regulatory authorities do, however, not have the resources and, judging from their behaviour, not the will to assume such a role. A second argument for a more inclusive communication approach must be seen in the fact, that physicians despite their medical training do not necessarily possess the skills to interpret the information entailed in the product risk communication in a much more reflected way than the public. Pharmacology and pharmacovigilance represents only a small fraction of medical education (Cox et al., 2004; Hauben & Reich, 2005; Orme, 2003). Additionally, the information received by health care professionals about changes in the risk-benefit profile of a specific product, as in the case of product information, is not easy to understand, lengthy and not written in a manner that easily translates into clinical practice (Mazor et al., 2005; Seligman, 2003).

7.2.4 The European regulatory regime from the perspective of effective risk governance

Drawing on the findings of the previous analysis, the regulatory regime can be briefly re-evaluated from the perspective of risk governance, focusing on the approval procedure and post-authorization monitoring process.

7.2.4.1 Approval regime

The three stages of risk assessment, risk management and risk communication are traceable in the European approval regime, even though differences in the centralized and mutual recognition/decentralized procedure exist. In general, the current regulatory approach to approval represents a science-based risk regulatory model. Risk assessment is based on expert advice and even though decision making is subjected to clear decision criteria and transparency as well as accountability is safeguarded under both procedures (CP and MRP/DP), the current process does arguably not allow for adequate and mandatory risk framing. Even though this might still be achieved informally, the lack of an institutionalized option to consider the public regulatory interests represents a shortcoming of the current regulatory approach.

Turning to the risk management stage, two main issues can be identified. First, the dominant position of the CHMP within the assessment process blurs the clear separation between a scientific opinion and the actual (political) regulatory decision. The CHMP occupies an agenda-setting position within the CP and to some degree in the MRP/DP and the challenging of the initial scientific assessment is highly improbable. The political control function that risk assessment should normally provide is levered out by the current regulatory set-up. Second, the risk management stage does not allow for additional consideration of public risk perceptions, but is organized as a closed regulatory process.

Considering the risk communication efforts of the pharmaceutical approval regime, the quantity of information compared to national approaches has increased. The introduction of mandatory assessment reports clearly helps to retrace regulatory decisions. Moreover, the communication of risks based on package leaflets has been improved under the European regime. From the perspective of quality, however, the current approach does not necessarily improve the understanding of pharmaceutical risks in general and specific terms, as the potential negative effect of leaflets on compliance demonstrates. The effectiveness of risk

communication is hampered by the formulation of leaflets amplifying concerns and serving the commercial interest to reduce potential liability.

7.2.4.2 Risk governance during post-authorization

Risk governance of the post-authorization stage reflects a science based approach. Risk assessment is conducted by experts, but in contrast to the approval regime, transparency, accountability and control is much more limited. While the underlying regulatory criteria apply in post-authorization assessment as well, the external scrutiny and transparency of the process seems to be much more limited. In addition, the quality issues of scientific evidence underlying risk assessment increases the zone of discretion of regulators. As in the case of approval, no institutionalized form of risk framing is traceable. Similar to the approval regime, risk management in the post-authorization stage hardly serves as an independent political assessment, since the same procedural limitations for challenging an initial assessment apply. A positive aspect of the current risk communication approach can be seen in the dissemination of information through physicians serving as a "credible source" (Maule, 2004: 26). Yet the effectiveness of risk communication is potentially reduced by the lack of physicians' education regarding the interpretation and communication of pharmaceutical risk information, as well as the limited information that is provided by regulatory authorities and manufacturers. While the approach thus avoids the perils of direct risk communication to the lay public, its effectiveness is reduced by insufficient consideration of context.

7.3 Conclusion: The merits of European governance

The aim of this chapter was to evaluate the impact of the Europeanized regulatory regime on regulatory effectiveness in the pharmaceutical sector. While no uniform and simple answer is possible several conclusions on governance and regulatory effectiveness in the European pharmaceutical sector can be drawn.

7.3.1 Aligned regulatory interests and conflicting pharmaceutical risk cultures

In the field of European pharmaceutical regulation, aligned interests between the three main actors – regulators, regulatees and the public – do exist. The equilibrium of interests converges around the provision of safe medicines in the pre-authorization and the maintenance of access in the post-authorization stage. Paradoxically, the post-authorization

situation is still characterized by aligned interests, but can still negatively affect public health as it confronts regulators and regulatees with a fundamental dilemma and far reaching consequences for the effective governance of post- authorization safety. Even though the sector is characterized by an equilibrium of interests the analysis of public interests revealed the existence of distinct national pharmaceutical risk cultures, impacting on the perception and acceptability of pharmaceutical risks and (indirectly) on the regulatory behaviour of national competent authorities. Linking the existence of risk cultures to the performance of the regulatory regime until the fundamental changes in the mid 1990s, an immanent conflict between the principle of voluntary mutual recognition and the underlying risk perceptions of national regulators was identified, serving as well-grounded explanation for the regulatory patchwork and under-performance of the regulatory regime.

7.3.2 The EMA, new European regulatory culture and adaptive pressure

The creation of the European agency and the shift from voluntary to facilitated mutual recognition has had a fundamental impact on the effectiveness of sectoral governance and the compliance of national regulators. The mind change within the regulatory network is explained by the emergence of a new European regulatory culture, emphasizing cooperation both within the established regulatory network and between regulators and regulatees, as well as increased experience and development of mutual trust within the regulatory network. Moreover, the agencification, economisation – understood as an increased dependence of regulators on industrial fees – and professionalization of the network were identified as the main reasons for improved governance effectiveness. The new governance approach is marked by an increased respect for the principles of transparency and accountability regarding agency operations and authorization procedures. While the EMA has been instrumental in this regard, its creation raises questions of accountability, control and legitimacy. The EMA and its scientific committee the CHMP more specifically, effectively dominates the authorization of innovative products, even though the Commission, together with the Standing Committee, is officially responsible for the issuing of authorizations. The current situation provides the EMA with significant regulatory powers, only partially controlled by external actors. While this regulatory set-up can be legitimized both from the perspective of increased effectiveness and efficiency, the current regulatory regime does not necessarily represent an optimal institution from the perspective of public participation and input legitimacy.

7.3.3 Regulatory governance: the pre and post-authorization divide

Even though the emergence of a European approach and governance structures increased the effectiveness of governance, the discussion of the different aspects of the regulatory lifecycle pointed to several weaknesses.

The authorization process has been found to be potentially biased towards early access and providing disproportionate representation of industrial interests.[278] Furthermore, the different authorization procedures result in different levels of transparency and accountability. Under the decentralized procedures, regulatory discretion is significantly increased allowing for a black box approach to regulation. Turning to the post-authorization governance aspects, several general shortcomings of the regulatory approach were revealed. The regulatory burden is increasingly shifted to the pharmaceutical manufacturers, without ensuring that compliance with regulatory requirements is achieved.[279] The insufficient guidance and reactive monitoring, resulting from a lack of resources and potential lack of willingness, is traceable in all aspects of the post-approval. Furthermore, the current approach to the governance of production and distribution does not account for the fundamental changes affecting the sector. This finding points to a remarkable and almost ironic paradox. While European regulation was initially created to establish the internal market, increased trading is mainly responsible for the counterfeiting of medicine, one of the most pressing regulatory problems in the pharmaceutical sector. While the quantity and quality of information on the performance of the regulatory network as well as product-related information has improved under the European regulatory framework, the availability of information still suffers from selectivity bias and confidentiality. Product-based information, largely confined to package leaflets, has been found to be too complex and at times even negatively affecting patients' compliance. In addition, the current information governance approach does not seek to advance the general understanding of pharmaceutical risks. While the strengthening of the regulatory network could have been expected to improve post- authorization surveillance, the positive impact must be described as limited. The current approach relies heavily on information provided by the regulated industry and the institutional design does not account the identified dilemma in post-market monitoring. Regulators and regulatees seem to adopt an expectant approach, potentially impacting negatively on public health.

[278] Yet this situation does not represent a state of capture as sufficient checks and balances under both procedures, especially in the case of the centralized procedure seem to exist.

[279] The tendency to delegate could be seen as an attempt to reduce regulatory uncertainty on behalf of the regulator (Beck, 1992; Power, 2007).

8. Regulatory outcomes: industry, the single market and public health

Three interrelated and potentially conflicting goals have been identified in the European pharmaceutical sector: the protection of public health, the competitiveness of the European pharmaceutical industry and the completion of the single market. The present chapter will assess in how far regulatory goals are met and which impact regulation has had in this regard. The following section will start with an assessment of the current state and previous development of the European pharmaceutical industry, focusing on the innovation capacities from a European perspective. Subsequently, progress towards a single market in pharmaceuticals will be discussed. The third section will assess the impact of the European regulatory regime on public health and pharmaceutical safety more specifically.

8.1 A competitive European pharmaceutical industry

Changes in the European pharmaceutical industry since the early 1960s have been substantial. While national companies focusing on domestic operations dominated the industry early on, German, French, Swiss, British and Italian companies increasingly started cross-border operations exporting their products within Western Europe in the 1970s (Casper & Matraves, 2003; Taggart, 1993). Increased demand, rising development costs and globalization trends of the pharmaceutical sector helped to grow and expand their businesses: in 1977, several European-based companies were ranked under the world's top 30 companies, with the German *Hoechst* company leading the group. By the mid-80s, six European companies were under the leading 15 pharmaceutical producers (Taggart, 1993: 32-33). Beginning in the late 1980s and early 1990s, the pharmaceutical industry has been dominated by even stronger globalization and consolidation leading to several waves of mergers and acquisitions (M&A) both on the national, European and global level affecting the position of European pharmaceutical companies (Busfield, 2003; Chaudhry et al., 1994).

8.1.1 Consolidation in the pharmaceutical industry

The first wave of consolidation in the sector was largely connected to changes in pharmaceutical development and economy of scale considerations (Jungmittag, 2000). Fundamental changes and improvements in the drug discovery process in the 1980s resulted in rising development costs. In an attempt to consolidate R&D activities and increase the chances to regain development costs, companies looking for external growth engaged in

M&A activities (P. Danzon et al., 2007). These activities were concentrated regionally during the first wave. European companies merged with other European-based companies and US competitors focused on targets based in the US (Busfield, 2003: 587). While economy of scale arguments are still invoked in more recent merger decisions, the filling of the product pipeline in light of patent expiry of blockbuster products now plays a major role as well (Frantz, 2005, 2006). The altered motive has lead to a change in M&A strategy in recent years: besides horizontal mergers between large pharmaceutical manufacturers, producers in attempt to increase their R&D competitiveness increasingly target biotechnology companies (Munos, 2009). M&A activity in the generic industry has recently gained momentum as well, both between generic producers and between innovative and generic manufacturers (Karwal, 2009). While the volume of M&A decreased after 2004, a new wave of consolidation started in 2007 culminating in the recent mega-mergers between Pfizer and Wyeth as well as Merck&Co and Schering Plough (KPMG, 2009). Consolidation trends have changed the industry in several respects. The number and position of companies leading the industry has changed fundamentally in the last 15 years. Most of the top 30 companies of the 1990s did cease to exist as they were bought by their competitors, resulting in increased market concentration: In 1989, the leading 10 companies had a market share of roughly 30 percent (Busfield, 2003: 588).[280] In 2007, the same group had a market share of 44,9 percent and the leading 20 companies even controlled 62,6 percent of the global market (ABPI, 2008). From the perspective of the European pharmaceutical industry, consolidation has strengthened the position of US based pharmaceutical manufacturers. US based companies expanded their market shares on both sides of the Atlantic and dominated recent M&A activities (KPMG, 2009). As a result, "the 'pharmacy to the world', once located at the intersection of Germany, Switzerland, and France, today is found in the United States [original emphasis]"(Daemmrich, 2009: 17). In light of these developments, it must be asked in how far the current regulatory regime impacted on the position and competitiveness of the European pharmaceutical industry.

8.1.2 Competitiveness of the European pharmaceutical industry

The pharmaceutical industry both from a national and European perspective has traditionally represented a key industrial sector. Despite national differences within the European Union,

[280] The Herfindahl index (Wagschal, 1999: 143-146), would provide a more adequate measure of market concentration. Unfortunately, the relevant data for the pharmaceutical industry is not publicly accessible.

the pharmaceutical industry, in comparison to other manufacturing industries, has been characterized by high added value, productivity and continuous growth, resulting in considerable direct and indirect employment effects (Vekeman, 2005). Moreover, the sector is of strategic importance and positively contributes to the European trade balance.

Table 25: Employment and trade balance of the European pharmaceutical industry

	1985	1990	1995	2000	2005	2006	2007	2008
Employment	437,613	500,879	504,014	538,438	634,546	643,138	636,403	633,056
Trade balance (in mio. €)	5,130	7,067	13,849	22,094	35,794	44,375	48,128	52,000

Source: EFPIA annual reports 2000-2009

While the European pharmaceutical industry has been deemed one of the most competitive ones in comparison to other industrial sectors, previously mentioned global trends have resulted in mounting concerns and a heated debate on the global competitiveness of the European pharmaceutical industry (Anon, 2004; Charles River Associates, 2004; Gambardella et al., 2000; Tsipouri, 2004).[281]

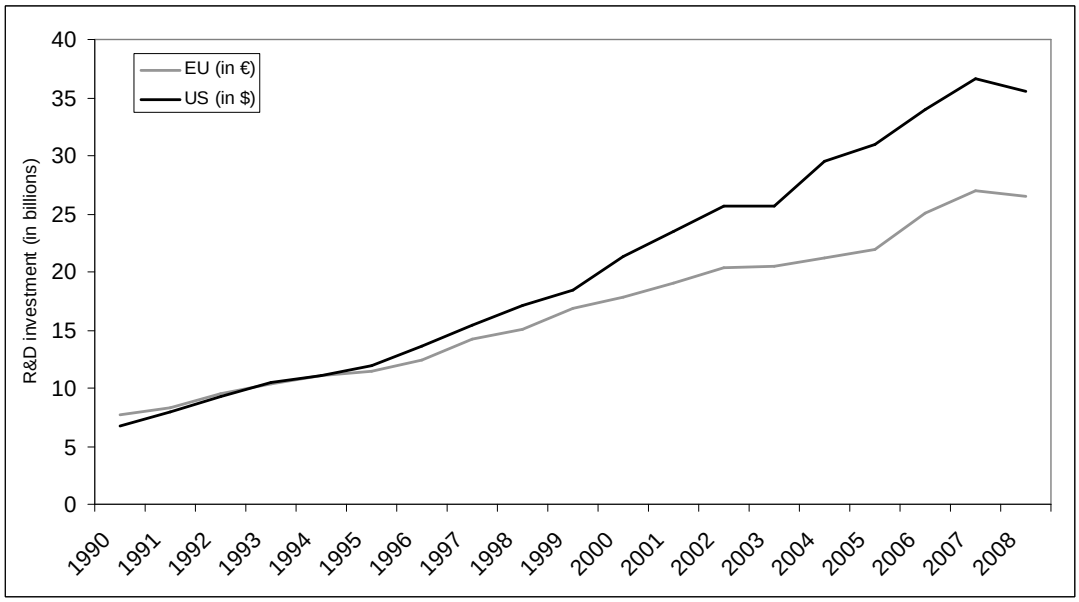
8.1.3 The innovation gap

Previously mentioned sectoral developments have altered the European research-based pharmaceutical industry. The German pharmaceutical industry, despite still representing the biggest market within Europe (Jim Gilbert & Rosenberg, 2004), has lost ground to French and UK based companies. As a result, the breadth of the European industry compared to the US has decreased. The competitiveness discussion, however, goes well beyond the market shift. While the claim was based on economic arguments and the lack of productivity (Gambardella et al., 2000: 20-23), the main concern has been the reduced innovation capability of the European pharmaceutical industry. The survival of the pharmaceutical sector – even more so than other industries – depends on innovation. While the European industry historically contributed significantly to the development of new drugs, a declining trend in comparison to the US industry has been highlighted both by European officials and industrial associations. Comparing absolute European research and development (R&D) spending to the development of US-based investment, an innovation gap is becoming apparent. According to the EFPIA,

[281] It should be noted, that the discussion of competitiveness is no recent phenomenon, but has been raised constantly since the late 1980s (Grabowski, 1989) and represents a fundamental and general problem for the whole industry (Coombs & Metcalfe, 2002; Ganuza et al., 2009).

"between 1990 and 2008, R&D investment in United States grew 5.6 times whilst in Europe it only grew 3.5 times" (2010a). Further structural challenges impeding European competitiveness are connected to the biotechnology revolution (Nightingale & Martin, 2004) in the pharmaceutical industry, the resulting changes in research and development and the prevailing problems to establish a competitive European innovation system (Owen-Smith et al., 2002). Furthermore, collaboration between academia and industry, instrumental in developing a strong biotechnological innovation system, is still underdeveloped in Europe (Jason et al., 2002; Owen-Smith et al., 2002; Riccaboni et al., 2003). As a result, the diffusion of biotechnology has been largely confined to the US industry (EFPIA, 2010a). Divergence in input factors translates into a corresponding shift in innovation output. Based on the number of new *chemical* and *biological entities* (NCE/NBE), the perceived loss of competitiveness on behalf of the European industry is substantiated (Grabowski & Wang, 2006). While the European industry dominated drug discovery during the 1980s and 1990s, the US has taken over the lead in the new millennium. Judging from the available data, the European industry indeed has lost competitiveness, as both the industrial capabilities and the innovative outputs decreased.

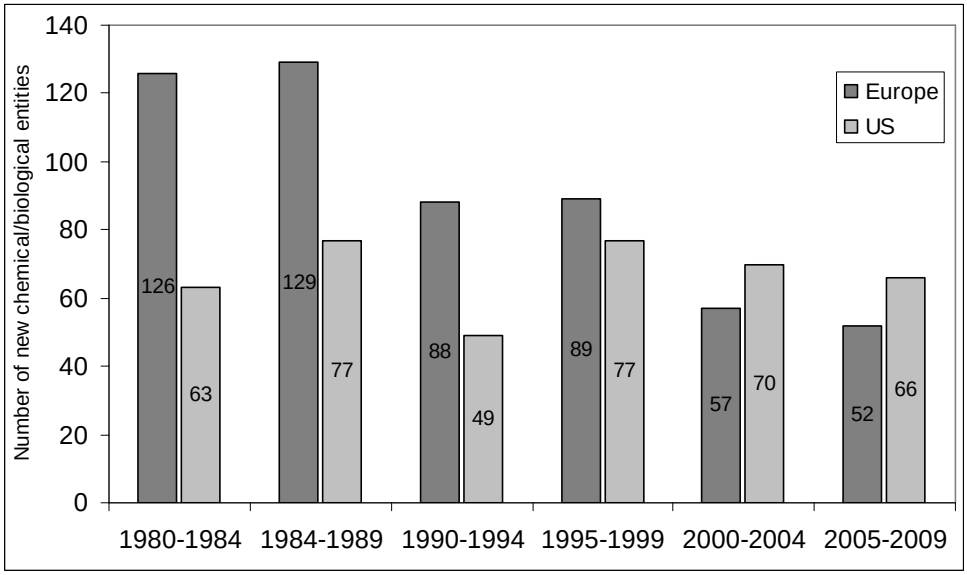
Graph 26: European and US R&D investment (1990-2008)



Source: EFPIA (2010c)

However, the severity of this development must be interpreted in context of a globalized pharmaceutical industry. First, even though it is true that the US industry has been more productive, the distance between European and US NCE/NBE output is closer compared to the situation in the 1980s.

Graph 27: Discovery of new chemical and biological entities by the US and European pharmaceutical industry (1980-2009)

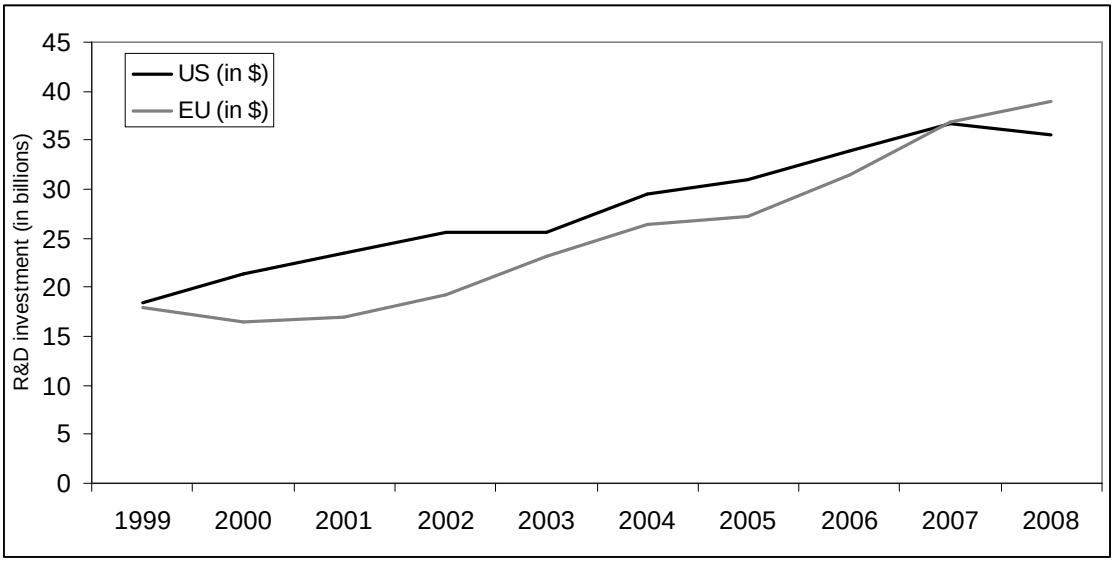


Source: Data from 1980-1989 Permanand (2006), Data from 1990-2009 EFPIA (2010c)

In fact, the pharmaceutical industry as a whole seems to suffer from a productivity crisis: R&D investment has multiplied but the relative number of innovations is decreasing. It is therefore uncertain, if significantly higher European R&D investment had resulted in a corresponding sharp incline of NCE output. Second, the validity of the widely used comparison of innovation outputs has been called into question since "counting which country discovers the most new molecular entities is irrelevant in a global market. Companies know that where a good drug is discovered does not matter and often a discovery comes from research in several countries" (Light & Lexchin, 2005: 959). Third, the extent of the competitiveness gap partially depends on the data used. Reconsidering the comparison of R&D investment, it seems striking that the figures provided by the EFPIA are not based on the same currency, effectively amplifying the volume of US R&D investment. Recalculating the estimates by the EFPIA based on annual exchange rates provided by the European Central Bank (2010) for the period of 1999-2008, the investment gap decreases significantly. Fourth, using total R&D spending as an indicator tends to obfuscate differences regarding industry size, market share and consumption (Keyhani et al., 2010; Donald W. Light & Lexchin, 2005).[282]

[282] A recent study by Donald Light (2009) using productivity ratios even concludes that the competitiveness of the European industry did not decrease but increased in certain therapeutic areas.

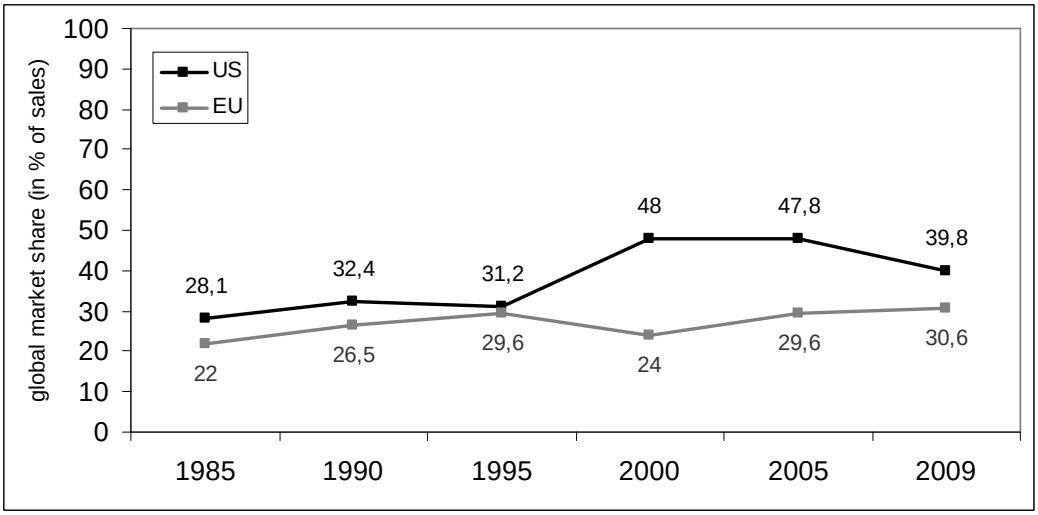
Graph 28: Recalculated US and European R&D investment (1999-2008)



Source: EFPIA (2010c); For the calculation of exchange rates see ECB (2010)

From this perspective, the gap mainly reflects changes in the global importance of the European market and the industry. Considering the US share of the global pharmaceutical market, its importance has risen significantly between 1995 and 2000 and despite a moderate convergence of European and US shares, the US continues to represent the largest national market.[283]

Graph 29: Global market share of EU and US market (in % of sales)



Source: Data from 1985-1995 (Gambardella et al., 2000), 2000-2009 (EFPIA, 2010c)

In light of these changes, the decision to relocate R&D investment and register new chemical entities in the most important domestic market might be related to other factors, for example

[283] Unfortunately, no reliable estimate for 2008 was available. While graph 30 suggests, that the US share of the global market has been always above European level, an alternative estimate by the WHO (2006) suggests, that the European market in 1990 was bigger than the US.

increasing the chances of successful market approval and quicker return on investment. While these counter-arguments point to the potential dramatisation of the European competitiveness gap, it must be acknowledged that the European industry has lost ground vis-à-vis its US counterpart. At the same time, the impact of European pharmaceutical regulation in this regard seems to be unclear.

Regulatory impact on innovation and competitiveness

Focusing on the issue of innovation as a major component of competitiveness, research on pharmaceutical innovation has singled out a broad range of distorting and supporting factors.[284] Unsurprisingly, regulatory burden has been identified as an important negative external influence (Reed et al., 2006). Robert Ruffolo, former head of R&D operations of Wyeth, for example, identified raised regulatory requirements, a lack of harmonization and a tendency of regulatory conservatism, depicting an overly cautious approach to drug approval, as important reasons for decreased R&D productivity and output (Ruffolo, 2006: 100-101). The impact of changes in the European regulatory framework on the reduced competitiveness of the European industry might however not be as decisive as Ruffolo with regard to the global industry suggests. The creation of the new European approval regime was intended to reduce regulatory burden and stimulate innovation by providing one approval route for new and innovative products. Considering the rising number of applications und the centralized procedure, a positive impact of regulation can be constituted. Moreover, the introduction of orphan drug regulation as well as increased support for small and medium enterprises (SMEs) supports innovation activities.

At the same time, the evolution of the regulatory framework has increased regulatory burden by introducing stricter and more extensive requirements. Reaching definite conclusions on the impact of such changes on European competitiveness is problematic, especially in context of a globalized pharmaceutical industry. First, regulatory changes did not affect the European industry per se, but all companies applying for product approval within Europe. Only if the European market was dominated by European companies realizing the majority of their earnings within Europe, a negative impact of (safety) regulation on European competitiveness can be constructed. While the European industry is partially made up of SMEs, the market and therefore the centralized approval procedure is dominated by large companies (Regnstrom et al., 2009). Considering the current distribution of European market shares, US-based as

[284] For an overview see (Hu et al 2007).

well as European-based companies use the procedures. Second, the levelling-up of regulatory requirements has been a global rather than a European phenomenon. Only if European requirements did exceed US standards, providing US companies with a home advantage, this could have translated into higher competitiveness of the US industry. Moreover, this would largely affect competitiveness from the perspective of realizing profits. Moreover, regulatory requirements outside the European market have not remained stable but moved towards stricter requirements as well (Anon, 2008a). Third, considering actual regulatory behaviour, *regulatory conservatism* hampering innovation seems to be a US rather than a European phenomenon. Drawing on the average approval times between 2000 and 2006, the EMEA approved drugs faster than its US counterpart, even though differences have been marginal (Wilsdon et al., 2008).[285] Moreover, the success rates of new drug approvals indicate that the European system seems to outpace the FDA in terms of access (B. Hughes, 2008a; Regnstrom et al., 2009).

These arguments point to the limits of regulation in steering innovation capacities, but it must be remembered that regulatory requirements impact on the development strategy of companies. If regulatory standards are too high, companies might have fewer incentives to invest in specific therapeutic areas. Considering the development of the European framework, it could be argued that standards are probably too low and too high at the same time. Standards are (probably) too low when the concept of innovation under the centralized procedure and approval standards are considered. The centralized procedure was gradually opened up to new product groups. As a result, the initial idea of the centralized procedure, rewarding innovative products with uniform market access, has been somewhat corrupted. Since an increased number of product categories can now use the centralized procedure, the concept of innovation is watered down. This perception is supported by the analysis of Domenico Motola and his colleagues (2006). Evaluating products authorized during the first decade of the centralized procedure, the study concluded that only 32 percent of the authorized products constituted a real innovation. While this number must be interpreted carefully, it points to the fact that it is becoming easier for products to be considered as innovative. Moreover, current approval criteria potentially do not serve as an incentive to stimulate innovation. New pharmaceuticals are predominantly assessed on its own merit instead of comparing their efficacy to existing therapies (Eichler, Bloechl-Daum et al., 2009).

[285] This might have changed in the post Vioxx area, with approval times increasing again on a global scale (Ruffolo, 2006).

Despite the lack of relevance in approval decisions, concepts of relative efficacy are increasingly impacting on drug development because of the heightened relevance in the context of reimbursement (Hughes, 2008b; Miller, 2005; Syrett, 2003).[286] While current regulatory standards might be considered as too low to stimulate innovation, they could at the same time appear too high from the perspective of regulatees. Pharmaceutical development is marked by uncertainty. This does not only relate to the development process but to the approval decision as well. Facing the trade-off between a product that carries a high risk of failure regarding development and approval and a product that has been developed for a known indication, risk-averse producers can be expected to choose the latter.[287] In fact, most European producers have been found to employ risk-averse R&D strategies focusing on established product categories, providing an alternative explanation for the European innovation gap (Pammolli et al., 2010). The contribution of regulation in stimulating innovation can therefore be seen in a reduction of regulatory uncertainty through increasing the predictability of regulatory decisions. Furthermore, adjusting incentives for drug development – demonstrated in case of the orphan drug development and the introduction of new pricing regulations even though outside the scope of European regulation – can contribute to the development of new and better drugs (Hughes, 2008c; Jayadev & Stiglitz, 2009; Light, 2009).[288] While regulatory uncertainty and incentives do play a role for innovation, such contextual factors play a minor role in strategic considerations in the development of R&D strategies. Instead, shareholder value, demands for short-term profits and a corporate strategy focusing on the development of me-too drugs and few (lucrative) therapeutic areas contribute significantly to a more conservative R&D approach (Hu et al., 2007). Judging the performance of the European regulatory framework in light of these findings, the impact of the European framework on industrial competitiveness is ambiguous. The centralized procedure has potentially stimulated innovation by providing companies with a streamlined access point to the European market, but this impact must be understood in

[286] Incorporating such concepts into market approval can be expected to reduce duplication of efforts, market delays and revitalize innovation The need to readjust approval criteria will however depend on what is considered as an innovation (Hughes, 2009). The current European debate is divided between the industry position focusing on incremental innovation (Cohen, 2005; EFPIA, 2010b) and more critical authors advocating stricter innovation concepts (Abraham, 2002b; Ahlqvist-Rastad et al., 2004; Light, 2009).

[287] Economic theory would suggest that high risk development would result in greater benefits in the long-term most important a lower level of competition (Pammolli et al., 2010: 8). Moreover, the importance of reimbursement should motivate producers to develop superior products. The strong trend of producers to focus on me-too products, however, supports the assumption of a short-term orientation and a conservative approach to R&D (Angell, 2000; Markovitch et al., 2005; Pauly, 2007).

[288] Another area of activity can be seen in the adjustment of IP protection and the expansion of market exclusivity for innovative products (Hughes, 2008c).

context of a globalized industry: Not only European but all companies using the approval route have profited from the rationalization of regulatory procedures. The same holds true for the incentives introduced under the orphan drug regulation as well as the negative impact of increased regulatory burden. Against this backdrop, it seems to be considered to conclude that the new regulatory framework increased the incentives to develop innovative products. Yet both the global productivity gap as well as the innovation gap of European companies must be viewed as influenced by regulation but determined by other (and predominately internal) factors.

8.2 Creation of a single pharmaceutical market

In determining the regulatory impact on the completion of the European pharmaceutical market, the supply and demand side of the pharmaceutical market have to be considered. Starting with the supply side, a functioning (pharmaceutical) market should be marked by a certain degree of competition (Makowski & Ostroy, 2001). While the benefits of competition have been discussed regarding innovation capacities of originator companies, it is expected to contribute to higher efficiency and more favourable market conditions for customers as well (Haucap & Coenen, 2010). The creation of a single market should result in as broader choice for customers and contribute to a convergence or even lowering of pricing levels (Armstrong & Bulmer, 1998; Cecchini et al., 1988). Drawing on the general benefits of market integration, a single pharmaceutical market should result in improved and European-wide access to pharmaceuticals (Bungenstock, 2010).[289]

8.2.1 Competition in the European pharmaceutical market

Competition in pharmaceutical markets can take two main forms: competition between originator companies and competition between originator and generic companies.[290] In determining the level of inter-originator competition, general industry trends and the specific market structure have to be considered. As the previous section highlighted, a comparatively

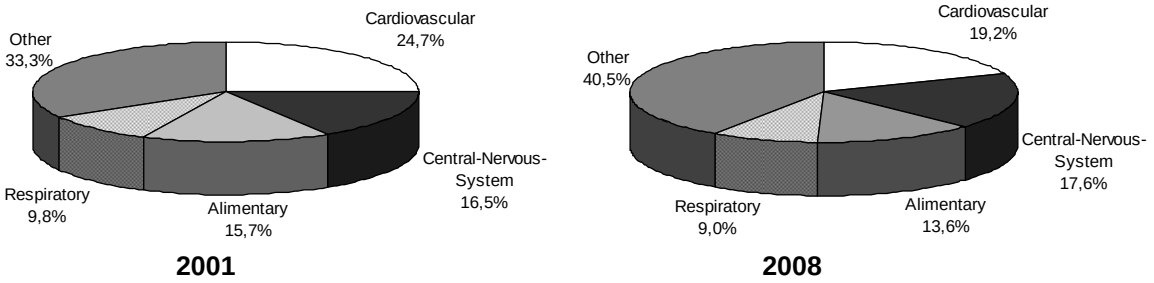
[289] The convergence of prices is not considered in this study, since it represents an ambivalent indicator. While convergence can be interpreted as an indicator for market completion, complete convergence does not necessarily translate into benefits for customers, but can result in welfare loss (Towse, 1998).

[290] Competition between generic producers and within the OTC sector is important as well. However, the impact on the performance of the sector as a whole is much more limited in this regard. Furthermore, the practice of parallel imports has been discussed in context of (supply side) competition. While the issue of parallel trade is beyond the scope of this study, the impact on competition has been thoroughly discussed without reaching definite conclusions (Anon, 2004; Panos Kanavos & Costa-Font, 2005; Kyle, 2007; Macarthur, 2007b).

small number of companies dominates the global pharmaceutical industry and this groups is strong in the European market as well. The comparison of respective market share of the leading three companies on the US, European and global level however suggests that the general dominance of big pharma has eroded and since 2005, has been less pronounced in Europe in comparison to the US market. Sufficient competition thus seems to exist in the European pharmaceutical market. Yet this aggregated perspective does not take the specific structure of the pharmaceutical market into account. Pharmaceutical markets are characterized by a specific structure, consisting of several dynamic submarkets (Amisanoy & Giorgetti, 2009).

While market dominance on the aggregate level might in fact be not as pronounced as commonly referred to, the situation within submarkets can be expected to be quite different. Submarkets are dominated by a small group of producers, which in most cases will partially consist of market (share) leaders, forming an oligopolistic core (Bottazzi et al., 2001: 1163) dominating the submarket for as long as IP protection is intact. The diabetic care market effectively shared by the two companies Eli Lilly and Novo Nordisk serves as an example for the oligopolistic structure (HAI, 2010). Considering recent strategic shifts within the European pharmaceutical market from blockbuster to niche buster portfolios (Anon, 2006d), manufacturers pursuing a specialty strategy will be increasingly able to realize market shares that exceed those on the aggregate level. A recent example has been the emergence of the therapeutic class of oncology (McCabe et al., 2009; Pollack, 2009), with Roche gradually developing a dominant position on a global scale (Anon, 2009b). The general characteristics of limited competition in sub-markets are traceable in future markets – therapeutic classes where most products are still in clinical development – as well (Karlberg, 2008). While the relative importance of therapeutic classes is subjected to changes based on the described mechanism, the most important European market segments have been rather stable over time. Again, this supports the assumption that competition within the originator market is not as pronounced as it could be. While the importance of cardiovascular treatment has decreased, the remaining market segments remained largely stable and despite growing originator-generic competition over time, oligopolistic structures within market segments are highly likely.

Graph 30: European sub-market shares 2001 and 2008



Source: Datamonitor

An additional factor undermining competition between originator companies within the European market has been identified by a recent sector inquiry conducted by the Directorate General Competition (DG Competition). The analysis spanning the period from 2000 to 2007 found that originator companies use defensive patent and publication strategies to prevent other research-based companies from developing new drugs in the same sub-market.[291] In addition, IP infringement claims were used to protect one's development strategy (DG Competition, 2009: 379-440). However, the report as well as responses of industry during the consultation stressed, that the dimension of such behaviour is hard to quantify exactly (Killick & Dawes, 2009). Judging the degree of competition between originator companies in light of the available data, it is concluded that the specific market structure as well as company behaviour will lead to oligopolistic structures within submarkets.[292] Economic theory suggests that such structures result in inefficiencies (Craig & Malek, 1995), but it can be argued that the negative impact is limited and even represents a necessary incentive to stimulate future innovation. In addition, the oligopolistic structure is temporary since generic pressure will impact as soon as the market turns off-patent (Magazzini et al., 2004). Therefore, the safeguarding of originator – generic competition is vital from the perspective of single market completion and the stimulation of competition (Perry, 2006; Simoens & De Coster, 2006). Aggregated data supports the assumption that originator-generic competition has grown in the European Union. While in 2002 generics had a value share of 7.4 percent recent figures for 2008 estimate a European sales volume of roughly 20 percent (Datamonitor, 2003; IMS Health, 2009).[293] Focusing on sales volume conceals the growing importance of generics in

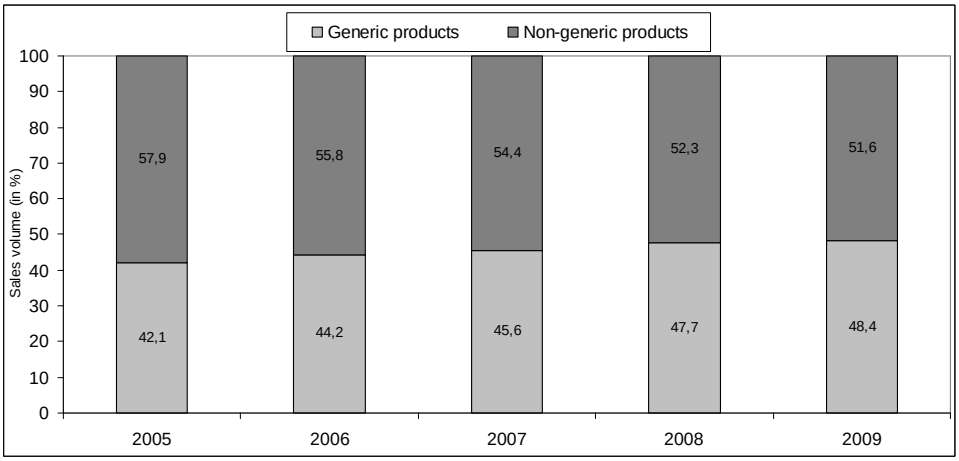
[291] Defensive strategies are no European phenomenon, but have been discussed as a general problem negatively affecting R&D productivity (Heller & Eisenberg, 1998).

[292] This finding must be interpreted carefully, since the situation can vary on the national level and between therapeutic classes. Furthermore, previous studies emphasized strong competition in originator markets (Pammolli et al., 2010).

[293] Unfortunately, reliable estimates regarding the European generic market during the 1990s are not available. Since the rising shares are mainly the result of large-scale expiry of blockbuster drugs, the numbers can be considered considerably lower (IMS Health, 2009).

terms of sales volume and thus the contribution to fulfil pharmaceutical demand in Europe.[294] Given the expiry of IP protection of many blockbusters in the next years (Anon, 2007) and a high percentage of generics currently seeking approval (EGA, 2007) this trend is sustainable, potentially reaching US levels were generics made up 90 percent of volume sales in the off-patent market and 65 percent of total pharmaceutical volume sales in 2008 (IMS Health, 2009; Larkin, 2008). Moreover, the rising importance of *biosimiliars* and the strong involvement of the European generic industry in this field can be expected to contribute significantly to future growth (DiCicco, 2006).[295] While the present level of competition in *off-patent* submarkets resulted from the cited internal factors, the role of national policies must be acknowledged. Policies to stimulate generic substitution have been employed to a varying degree by national governments, in an attempt to consolidate health budgets (Andersson et al., 2007; Garattini & Tediosi, 2000). The data suggest an increase of competition in the European *off-patent* pharmaceutical market. Yet there is ample evidence that generic competition in the European single market is still far from a social optimum.

Graph 31: Share of generic products in Europe 2005-2009 (volume sales %)



Source: IMS Health (2009)

To protect submarkets from generic competition, originator companies apply similar tactics as to prevent me-too products from market entry. Companies use patent cluster and defensive patenting, which, given the much more limited resources of generic producers, can have a detrimental effect on generic development costs. A related strategy has been the so called evergreening, depicting minor variations of existing products, the creation of second generation or follow-up products and the patenting of processes in order to extend the patent

[294] While the EU average does suggest a homogenous distribution, market penetration of generic products within the European Union differs widely on the national level, ranging from six percent (Italy) to nearly eighty percent (Latvia) (EGA, 2007).

[295] *Biosimiliars* are generic versions of biopharmaceutical products.

life cycle and impede generic development (Bansal et al., 2009; Whitehead et al., 2008). The legitimacy and extent of this practice is heavily contested and the discussion within Europe has become much more controversial in light of the findings of the sectoral enquiry (Becker, 2009; Jorge, 2009; Mooney & Parker, 2007). While the inquiry found that the aforementioned strategies are applied regularly, several additional measures to prevent generic competition were identified. Originator companies have increasingly used patent litigation as a means to delay generic entry and the number of cases "rose nearly fourfold from 36 in 2000 to 132 in 2007" (DG Competition, 2009: 214). Litigation is prolonged, since patents are granted on the national level resulting in multiple separate law suits. Given an average duration of 2.8 years, such action can have a decisive impact on generic competition (DG Competition, 2009: 228). Interim injunctions are used during litigation to prevent generic companies from realizing profits, while the originator company is not affected by this measure. In addition, manufacturers have threatened wholesalers selling generics with legal proceedings. Beyond legal measures, companies apply communication strategies to defame generic products by raising legal and quality concerns. This includes communication to authorizing agencies, reimbursement bodies and doctors as well as negative advertising in medical journals (DG Competition, 2009: 312-342). While the findings of the inquiry must be interpreted cautiously (Killick & Dawes, 2009), the claim of restricted competition in the European pharmaceutical sector is substantiated further by legal proceedings against originator companies. The AstraZeneca decision by the European Commission in 2005 has been a prominent example in this regard (Lawrance & Treacy, 2005).[296] Drawing on the presented data, competition in the pharmaceutical sector must be considered as restricted.

8.2.2 Access to pharmaceuticals

From the perspective of consumers, a single pharmaceutical market should result in better access to treatments. Harmonization of regulatory criteria and processes should have impacted positively in this regard both from a qualitative and quantitative perspective. Drawing on the rising application numbers, new and innovative treatments have become available to all citizens of the European Union. However, not only innovative treatments authorized under the

[296] In 2005, the Commission found the Swedish company AstraZeneca guilty of abusing its dominant position when it decided to withdraw the market authorization for the capsule form of Losec shortly after introducing the tablet form, to prevent generic producers from entering the market. In addition, AstraZeneca was accused of abusing the patent system and Supplement Protection Certificates (SPC) to extend market exclusivity (Manley & Wray, 2006).

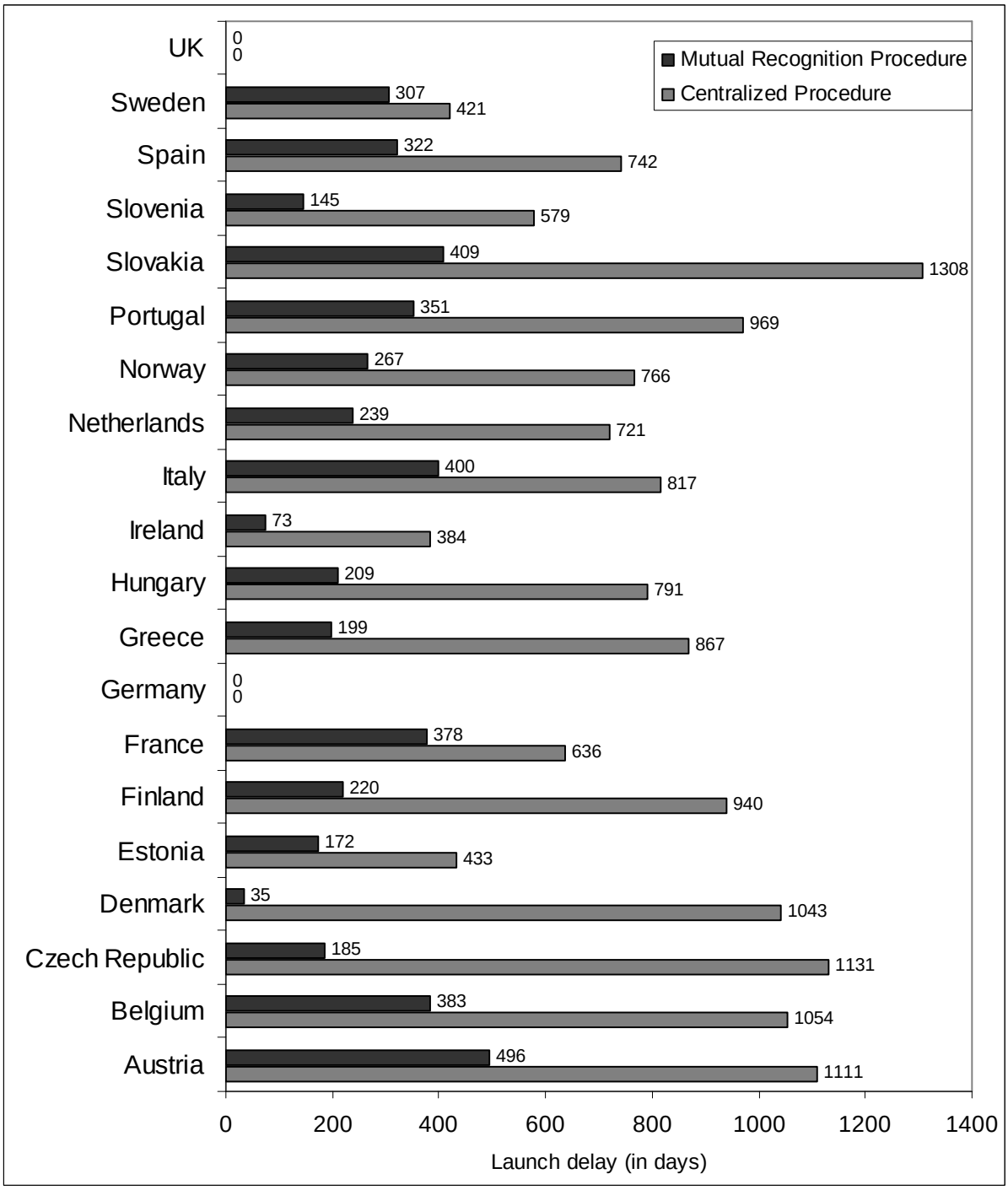
centralized procedure contribute to the increase of access. While products authorized under the decentralized procedure do not represent therapeutic innovation in a strict sense, they represent alternative treatments with potential additional therapeutic benefits, for example less side effects or higher efficacy. Access to generics has been improved as well, by opening up the centralized procedure. In light of these developments, the creation of a single European pharmaceutical market has delivered on its promises. At closer inspection, this positive account has to be reconsidered. First, an increase of authorized products does not necessarily meet the specific distribution of demand for products and result in different access for different patient groups. Given the focus of most manufacturers on certain therapeutic areas and risk-averse development strategies, access will be uneven in different indications. Therapeutic areas promising little financial incentives attract fewer products, as the development of the European orphan drug market shows.[297] While over 500 orphan designations have been defined under the European orphan regulation, only 45 products were authorized in 2008 (Heemstra et al., 2008). This clearly represents an improvement to the situation before the new regulation entered into force and orphan drug development seems to gain momentum (Heemstra et al., 2008), yet access to orphan drug treatment still is severely limited (Joppi et al., 2006, 2009). Second, general access is limited by the occurrence of different drug lags, depicting a delay in treatment. The first type of drug lag relates to the availability of new treatments in major pharmaceutical markets. Since the 1990s, the US has regularly been chosen for first approval and launch of new products, with subsequent launch in the European market (Grabowski & Wang, 2006; Tsuji & Tsutani, 2008, 2010).[298] In addition to this *Atlantic* drug lag, the single market is hampered by the existence of an internal drug lag between member states. The timing of access and the availability of specific treatments differs widely. Considering the extent of the temporary drug lag within Europe for products authorized under the centralized procedure, Heuer, Mejer and Neuhaus (2007) estimated a variation between 3.5 (Germany) and 18.9 months (Belgium). A report by IMS health commissioned by the EFPIA, covering 20 European countries reconfirms these assessments (2007). Access delays do represent an impediment to the completion of the single market, yet the persistence of permanent differences in drug availability does constitute a more fundamental problem. Regarding the uniformity of access within the EU 15 a study by Folino-Gallo and his colleagues found that “only 7% of all the active ingredients are available

[297] The same argument can be applied on the global level, with companies not dedicating enough R&D resources on treatments for neglected disease, mainly affecting people in low-income countries (Trouiller et al., 2002).

[298] *Drug launch* depicts the actual marketing and availability of a drug on the market.

in all the participating countries" (2001: 444).[299] More recent data compiled by the HMA covering the whole European market point to continuous national disparities.

Graph 32: Average launch delays in selected European countries (in days)



Source: adapted from IMS Health (2007). Note: In Germany and the UK no delay can *occur*, since pharmaceuticals can be marketed instantly after market approval (IMS Health, 2007).

[299] Even though completion of the single market could be interpreted extensively, it must be asked if all products have to be available in all member states. However, if essential medicines are missing from several member states as in the current situation (Task Force on Availability of Human Medicinal Products, 2007) this points to a lack of regulatory effectiveness.

Unsurprisingly, the differences in access mainly affect the group of accession countries, even though variation within the EU 15 is traceable as well. Many smaller member states experience problem of access to essential pharmaceutical products. While access delay can be of *temporary* nature, with some countries experiencing significant delays and shortages, in other instances products never were brought on the market resulting in a permanent access problem (Task Force on Availability of Human Medicinal Products, 2007: 6-15). In light of these findings, the uniformity of access both from a temporary and permanent perspective within the European Union has not been achieved so far, pointing to a clear lack of single market completion.

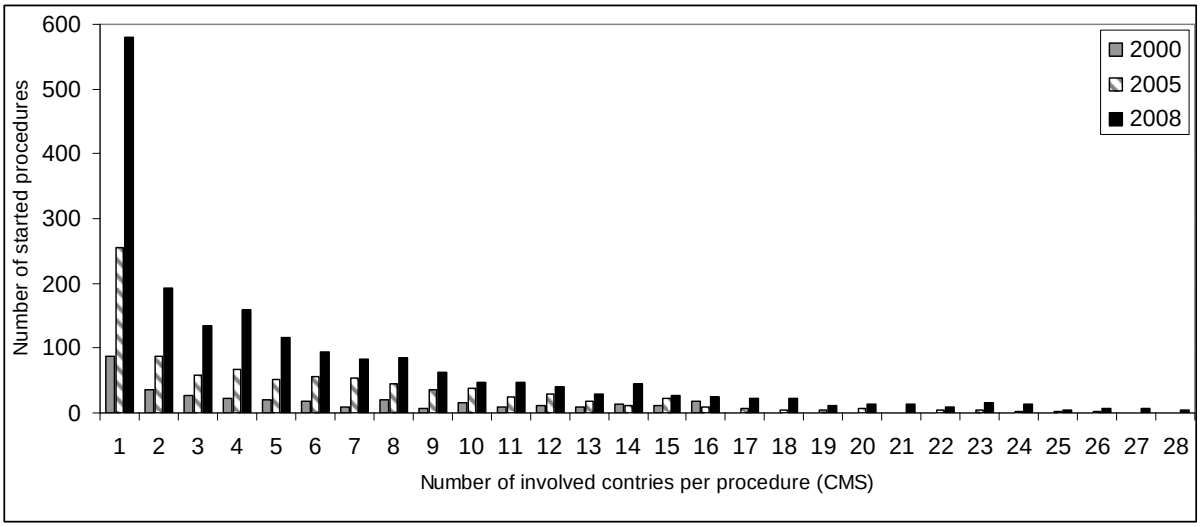
8.2.3 Impact of the approval regime on the completion of the single market

As in the case of innovation, it must be asked how European regulation impacted on the completion of the single market and the stimulation of competition and access. Considering the impact on inter-originator competition, the creation of a European approval regime and more specifically the centralized procedure clearly represents a reduction of regulatory costs and therefore a reduction of regulatory barriers for companies entering the European market. However, the reduction of entry barriers does not suffice to stimulate entry of originator competitors into submarkets, requiring substantial R&D investment. Such decision will mainly depend on the prospective market size, the number of existing competitors, entry barriers (e.g. defensive patenting) and companies' experience (Nerkar & Roberts, 2004; Pauly, 2007; Vernon, 2005). While *regulatory conservatism* can reduce the probability of actual market entry, the impact of the current regulatory setting on inter-originator competition compared to other strategic considerations should not be overstated. This assertion must be corrected when the contribution of regulation to originator-generic competition is considered. As in the case of inter-originator competition, the introduction of the European framework has streamlined the approval requirements depicting a reduction of entry barriers for generic substitution. Most notably, the introduction of the *8+2+1* provision leading to a harmonization of data exclusivity and the introduction of the *biosimiliar* regulation (Roox, 2006), facilitated generic competition. At the same time, the prevailing lack of generic competition in Europe calls for a reconsideration of the regulatory impact. As in the case of originator producers, generic manufacturers, despite substantially lower R&D expenses, will have to weigh the options before market entry. While approval has become easier under the European regulatory framework, generics still face entry barriers. Product

launch is hindered by the various strategies originator companies apply to prevent market entry. While the identified mechanisms clearly affect generic entry, the main barrier must be seen in the fragmented nature of national pricing and reimbursement approaches and respective national generic policies. European member states adopted distinct policies, approaches and structures to regulate generic entry, directly affecting market penetration. Despite the variety and associated regulatory costs, a general reason for the lack of generic competition must be seen in the increased pressure on generic prices, reducing existing and already comparatively small margins (Simoens, 2008). Following from this, the limited impact of (approval and safety) regulation on generic competition is revealed. Generic competition is mainly influenced by national policies, "because of European harmonisation, patent legislation and approval procedures no longer affect much the development of generics"(Garattini & Tediosi, 2000: 149).

In contrast to the facilitation of supply side competition, the impact of the regulatory framework on access is much more intuitive. Both European procedures theoretically allow for the marketing of pharmaceuticals throughout the single market. A closer look reveals the impact of the regulatory framework and the decentralized procedure more specifically on the prevalent access problems within the European Union. Only a small number of countries, serving as concerned member states, are normally involved in the decentralised procedure.

Graph 33: Number of involved countries (CMS) within the mutual recognition/decentralized procedure



Source: based on monthly MRFG/CMD(h) meeting reports; Note: calculation based on *new applications*

Applicants using this procedure do obviously not pursue a strategy of uniform marketing, but target a limited number of European countries.[300] It can be argued, that the focus on a limited number of countries represents only a minor problem since drugs authorized through the decentralized procedure in most cases target established therapeutic classes.[301] Nevertheless, this constellation negatively affects customer choice and aggravates the existing national differences in product availability. While the selective character of the MRP/DCP explains variations in permanent availability of pharmaceuticals, it does not explain the *Atlantic* drug lag and temporary drug delays within the European Union. As previously discussed, market approval times have converged both within the European Union and on the global level. While remaining national differences in the implementation of approval decisions as well as different organisational capacities of national regulatory authorities may serve as an explanation, such differences cannot be responsible for the considerable delays.[302]

Again, the reasons for these developments are for the most part beyond the scope of the regulatory framework. Drug delays within the European market have been largely attributed to the distinct national pricing and reimbursement processes. While it is tempting to blame these regulatory burdens for the drug delays, it tends to downplay the role of strategic behaviour on behalf of the launching companies (Garattini & Ghislandi, 2007). This argument is connected to the interdependence of national pricings system and the phenomenon of parallel trade. Since certain member states use cross-reference pricing – based on prices in other member states – companies have an incentive to delay drug launches in some member states in order to maximize total profits (Danzon et al., 2005). Furthermore, pharmaceutical producers delay or even refrain from launching products in countries with low pricing levels, since this will reduce the negative impact of parallel export from these countries on revenues in high price countries (Ganslandt & Maskus, 2004).[303] Unfortunately, the European market structure is conducive to such strategic considerations. While the biggest five markets – France, Germany, Italy, United Kingdom and Spain – account for roughly 73 percent (DG Competition, 2009: 20), most European member states represent small market shares and in combination with lower price levels and specific pricing regulation, strategic considerations

[300] Note that the *new procedures* underlying the calculation can include reapplications and therefore might overstate the focus on few countries. However, the data do not allow for a verification of this assertion.

[301] 80 percent of pharmaceuticals under the MRP/DP procedure are generics (Kenny, 2008).

[302] Industrial representatives are increasingly criticizing the insufficient regulatory capacities and specific national selection criteria for accepting RMS status, resulting in long waiting times for review timeslots of national agencies (Costa & Barea, 2009; Senior, 2010).

[303] Parallel trade itself can lead to availability problems even in bigger markets if large quantities are exported from *cheaper* countries as the recent experience of drug shortages in the UK has shown (Pagnamenta, 2008).

of companies will result in delayed or no access at all.[304] Put differently, while a drug may be authorized this does not mean that it will be marketed.[305] The HMA report on the availability of medicines reaffirms the causal relationship between access, market attractiveness and companies' behaviour:

> "The unavailability of some medicinal products poses a real threat to public health and welfare. […] The main reason for the industry not to put their products on the market in a Member State seems to be the size of the market. Size of the market and national language are closely connected, since translation of information and labelling of medicinal products to national languages is not a problem for big markets, but is considered unfeasible for small markets. The size of a market is an obvious reason why pharmaceutical companies are not willing to accept the extra costs involved (pharmacovigilance, translations, scientific service, pricing, country specific information, etc.) for markets that cannot sustain profitability. The combination of different prices and parallel import/export may be one of the reasons for availability problems in certain markets that is not due to the size of the market. [original emphasis]" (Task Force on Availability of Human Medicinal Products, 2007: 4).

In light of these findings, it must be concluded that the current regulatory framework plays only a minor role, while national pricing regulation as well as company behaviour are crucial factors. These findings point to a problematic and asymmetric situation: While the creation of a European regulatory framework has increased choice and decreased regulatory burden for most producers, the identified shortcomings regarding access show that such positive developments are not necessarily traceable on the demand side of the market. While European regulation has helped to increase the quality and quantity of available treatments, by stimulating the development of innovative drugs, incentivizing research in orphan drugs and specific paediatric needs as well as streamlining approval for generics, this does not automatically translate into increased access and affordability.

8.3 Safeguarding of public health

The overarching goal of European pharmaceutical regulation is the provision of effective and safe drugs to the European citizens. Assessing the regulatory impact on public health should thus consider both aspects. First, effective pharmaceuticals can be expected to positively

[304] As the HMA report states, drug launch is delayed and sometimes permanent even in those countries serving as a reference member state (RMS), reducing the willingness of authorities to take over the role (Task Force on Availability of Human Medicinal Products, 2007).

[305] To a certain degree this paradox situation may in fact result from the regulatory framework, which does not provide the right mechanisms to enforce availability. On the other hand, forcing producers to launch products in all markets would conflict with European economic freedoms.

impact on aggregated health outcomes. Second, improved product safety should have reduced the occurrence and impact of unwanted side effects.

8.3.1 Pharmaceuticals and European health outcomes

To assess the development and current state of public health within the European Union one could draw on several well-established and commonly used metrics. Starting with a rather general measure, life expectancy within the European Union can be considered. A second commonly used measure is the probability of infant death (Reidpath & Allotey, 2003). While measures of mortality provide an important indicator of public health, it is important to apply a qualitative perspective as well. A higher life expectancy surely is positive from the perspective of public health, but the quality of additional life years must be considered in this regard (Jagger et al., 2008). Therefore, disability-adjusted life expectancies (DALE) can be used, measuring the (expected) number of years to be lived in full health and without serious health constraints, adding a qualitative dimension to the assessment of public health (Mathers et al., 2000; Murray & Evans, 2003). Data was retrieved from the WHO Health for all database. Drawing on the development of life expectancy within the European Union, a positive trend emerges with life expectancy of EU citizens growing roughly 6 years between 1980 (74.18) and 2008 (80.61). Unsurprisingly, growth has been more pronounced in the old member states. A comparable trend is traceable regarding the survival of infants, as the rate of children dying before the age of five has decreased continuously. While general life expectancy and at an early age has increased significantly both in the old and new member states, changes in quality have been less pronounced, even though pointing to a fairly high degree of full health within the European society as a whole. Drawing on the presented data, general public health as measured by these outcomes has improved significantly in the last four decades. While research on mortality has traditionally focused on socio-economic factors to explain life expectancy increases (Cutler et al., 2006), it can be assumed that better treatment of fatal diseases had an impact on the identified trends as well.

This assumption is supported by the overall, yet moderate, decrease of death rates for common illnesses with a potentially lethal outcome in the same period. Accordingly, changes can be partially related to differences in the management of these illnesses and improved treatments. Indeed, studies have increasingly pointed to the relevance of healthcare regarding the increase of life expectancy (Arah et al., 2005; Nixon & Ulmann, 2006). More specifically,

it is argued that changes in public health can be attributed to changes in the availability and utilisation of pharmaceuticals (Cutler et al., 2006; Frech & Richard, 2004; Grootendorst et al. , 2009). In addition, the importance of innovative drugs has been increasingly considered as a major factor in explaining decrease of standard death rates (SDR), the increase of life expectancies and the quality of life (Lichtenberg, 2001, 2009; Weisfeldt & Zieman, 2007). In light of these findings, a link between European pharmaceutical regulation and improved public health can be established, since the centralized procedure as well as the orphan drug regulation intended to strengthen the development of innovative drugs and the introduction of paediatric regulation aimed at an improvement of drug therapy for children. Moreover, the framework has had a quantitative impact: Since approval of generic drugs has become easier, access for patients suffering from common (off-patent) diseases within the European Union has partially improved. Yet, the previous discussion of regulatory outcomes regarding the single market suggests, that both the impact of pharmaceuticals on public health and consecutively the impact of pharmaceutical regulation on public health has been much more limited.

First, pharmaceuticals only represent one factor within the field of healthcare contributing to public health outcomes and their importance will vary significantly between therapeutic areas. Better diagnosis and prevention, new medical technologies and improved disease management are decisive in this regard as well (Grootendorst et al., 2009; Weisfeldt & Zieman, 2007).[306] Moreover, several studies point to the limited effects of pharmaceuticals and healthcare on life expectancy in developed societies, especially in comparison to socio-economic factors (Poças & Soukiazis, 2010; Stoddart, 1995; Ulmann, 1998) and this has been reconfirmed for the EU 15 by Nixon and Ulmann (2006). Second, the aggregated changes in life expectancy within the European Union should not be mistaken for uniform improvements (Jagger et al., 2008). Given the discussed problems of access, the possible contribution of drugs will vary between European member states and between different patient groups. Furthermore, differences between therapeutic classes both from a qualitative and a quantitative perspective remain. The public health impact of drugs will vary, for example because of a lack of generic substitution allowing for broader uptake or an outright lack of treatment, as in the case of orphan drugs.[307] Another limiting factor for the contribution of

[306] However, due to the interconnectedness of these factors, it seems impossible to quantify the exact impact of pharmaceuticals, especially on the aggregated level (Grootendorst et al., 2009; Nixon & Ulmann, 2006).

[307] Another important aspect affecting the impact of drugs on public health are the costs associated with generally increased pharmaceutical consumption and permanent medication (Moynihan & Smith, 2002).

new drugs to public health can be seen in the remaining national differences in diffusion of innovative treatments (Schöffski, 2004). Finally, the lack of fundamental innovations diminishes the aggregated impact of pharmaceuticals on European public health (Motola et al., 2005). Going back to the underlying question of this chapter, the influence of European regulation regarding the improvement of public health seems to be rather limited. Clearly, the impact of approval regulation can be decisive since a drug that has not been approved will have no public health impact at all. Apart from this fundamental gate-keeping function, the impact after approval is much more limited, since factors outside of the regulatory scope largely determine the possible public health benefit of pharmaceuticals. If new drugs are approved but access is delayed or even permanently restricted, the asserted positive impact on public health is severely impeded. Existing differences between different patient groups can only be partially reduced by the regulatory framework, for example, by developing incentives for the development of needed, but commercially unattractive, pharmaceuticals.

8.3.2 Safety of (new) pharmaceuticals

Leaving the extent of the relative impact on public health aside, pharmaceuticals clearly represent an important component of health care within Europe. While they should contribute to personal health, their consumption can negatively impact on personal and public health, if adverse drug reactions (ADR) are experienced. Accordingly, the discussion of the regulatory impact on public health must consider changes in pharmaceutical safety as well. Starting with a general observation, the absence of a major pharmaceutical crisis comparable to the extent of the Thalidomide disaster within the European Union can be interpreted as the result of improved drug safety and functioning regulation (Groenleer, 2009). Even though there have been several pharmaceutical incidences within the European Union in the last decades, with Lipobay and Vioxx being the most publicized ones, the number of severely affected European patients has been limited. While this argument has high face validity, the absence of crisis does not serve as a reliable estimate of risk levels stemming from pharmaceutical consumption. A more direct measure of pharmaceutical risks can be seen in the previously discussed reported numbers of ADRs. Unfortunately the number of (all) reported ADRs does not serve as a reliable indicator for the evaluation of drug safety.[308] Instead the discussion of

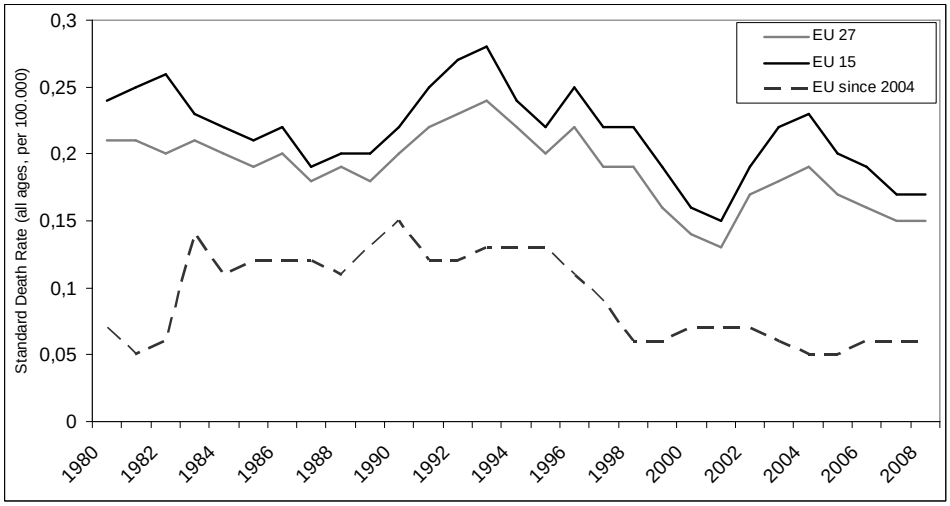
[308] Evaluating drug safety solely based on reported ADRs would imply an unrealistic perception of pharmaceutical safety. Drugs will always have some side effects and it is therefore important to focus on those drug reactions representing unacceptable risks.

drug safety should focus on serious ADRs, representing the real challenge to public health. Accordingly, both serious ADRs resulting in hospital submissions and *fatal* outcomes represent more appropriate indicators of the drug safety impact on public health (McGavock, 2004a).

Even though adverse drug reactions are a common phenomenon, no systematic research on incidence of serious ADRs within Europe exists. While the interest in the subject has grown over the last decades, there are virtually no studies comparing incidence rates between European member states. Instead, research has focused on local studies monitoring admissions in specific hospitals, multi-centred studies and national databases. While differences in sample size and methodology call for a cautious interpretation, results are comparable to a certain degree.[309] Based on this assumption, trends in hospital admissions can be charted. Drawing on the report by the *Expert Group on Safe Medication Practices* established by the *Council of Europe* (2006), selected studies from three different periods shed some light on the occurrence of serious ADRs. Between 1980 and 1990, ADR hospital admission rates varied between 0.2 – 11.5 percent. During the period of 1990-2000 rates have been between 1.0 – 10.8 percent and changed to 1.8 – 13.8 percent between 2000 and 2007. This trend is reconfirmed by the available multi-centre studies, estimating 1.1 – 3.3 percent for the period of 1990- 2000 and 2.4 – 6.5 percent after 2000. Similar but slightly higher numbers have been found for ADRs witnessed during hospitalization (Davies et al., 2007). In light of the available data, it seems that serious ADRs have been on the rise in Europe. Turning to the trends in fatal ADRs within Europe, the development is less consistent. According to data compiled by the WHO, the SDR caused by therapeutic agents has been partially declining.

[309] For a discussion of methodological differences see Beijer & de Blaey (2002).

Graph 34: Standard death rates therapeutic agents in Europe (1980-2008)



Source: Health for all database

However, there is reason to question this trend. First, the reliability of the WHO data can be challenged.[310] Second, SDR levels reported to the WHO seem to be lower than more recent European studies suggest. A prominent study by Munir Pirmohamed suggested a fatality rate of 0,15 percent for hospital admissions caused by ADR and 5700 annual deaths for the UK and even 10.000, if fatal ADRs after hospitalisation are included (Pirmohamed et al., 2004: 18).[311] Similar rates have been found for the Netherlands (van der Hooft et al., 2006, 2008), Sweden (Wester et al., 2008), Italy (Leone et al., 2008) and France (Pouyanne et al., 2000).[312] It is assumed, that incidence rates in Germany are close to these estimates (Grandt et al., 2005). Since recent admission and fatality rates are comparable to studies conducted 20 years ago (Pirmohamed et al., 2004: 18), it must be concluded that the burden of ADR within Europe has at least remained constant or even increased (Völkel et al., 2009). Putting the consequences of fatal ADRs into perspective, it has been estimated that ADRs rank 7th in Sweden (Wester et al., 2008), and 6th in Germany as the most common cause of death, accounting for 16.000 deaths in Germany each year (Wille & Schönhöfer, 2002: 478-479). Finally, an impact assessment conducted in context of the latest legislative review on the European level estimated that "197,000 deaths per year in the EU are caused by ADRs and that the total societal cost of ADRs in the EU is €79 billion" (European Commission, 2008: 1). From the perspective of public health, these developments are worrying. Beyond the

[310] National data in the database are missing for many countries and considering the constant values across time it must be asked how reliable the data really are.

[311] This number might even be too low, as it only considers identified fatal events, leaving those aside that were not detected.

[312] While most of the cited studies refrain from calculating fatality levels, they would be much lower than the 5700 annual deaths that the study of Pirmohamed and his colleagues suggests for the UK. These differences might be partially explained by different definitions of ADRs.

obvious personal implications of serious and fatal adverse reactions, their occurrence has a decisive economic impact and represents a growing financial burden for national healthcare systems (Gautier et al., 2003; Pirmohamed et al., 2004; Ritter, 2008).

The prevailing level of serious and fatal adverse drug events can be considered as an outcome of regulatory failure. Again, this would imply that the European regulatory framework is decisive in this regard. As in the case of the previously discussed regulatory goals, it is argued that both the impact of ADR on public health and the regulatory influence are limited. What constitutes an ADR is a matter of definition, implying that the level of serious events as ADRs in general might be subject to under- and overestimations. While ADRs should be limited to those reactions that result directly from the drug, more inclusive definitions are commonly used (Fernandez-Llimas et al., 2004). Rather than focusing on side effects of the drug, it includes results of potentially wrong usage and administration. ADR levels thus might reflect the prevalence of medication errors and iatrogenic illnesses to a certain degree. From this perspective, the negative health impact of ADR is not caused primarily by the respective drug. This perception is reaffirmed by the fact that the considered ADR studies estimate between 22 and 80 percent of the serious and fatal adverse events preventable (Madeira et al., 2007: 392). This shifts the focus of regulation from the pharmaceutical product towards the behaviour of actors involved in drug therapy. Considering the role of prescribers, most adverse events can be attributed to overprescribing (McGavock, 2004a) and overdosing (Pirmohamed et al., 2004). Furthermore, ADR can be the result of inadequate information regarding the risks and benefits of a given drug, individual patient data and a lack of pharmacological training leading to inadequate diagnosis (Aronson, 2009; Jonville-Béra et al., 2005; Ritter, 2008). Turning to the patient's role, ADRs are caused by the previously discussed issue of non-compliance (Raschetti et al., 1999). Finally, demographic change as well as current trends in drug therapy account for the prevailing levels of serious and fatal adverse events. It has been found that elderly patients have been affected by ADRs and inadequate prescription to a larger extent (Gallagher et al., 2007; Hamilton et al., 2009; Malhotra et al., 2001; Passarelli et al., 2005; Routledge et al., 2004). A contributing factor must be seen in polytherapy, including the simultaneous consumption of pharmaceuticals increasing the likeliness of drug-drug interaction (Becker et al., 2007; Madeira et al., 2007) and personal genomic factors (Severino & Zompo, 2004).

Obviously, many of the root causes of adverse events are well beyond the scope of the European regulatory framework. They are the result of informational asymmetries, a lack of

error culture and risk awareness in drug therapy. However, this might not only be true for prescribers but reflects a more general public misunderstanding of pharmaceutical risks and personal responsibility. As James M. Ritter regarding effective and safe drug therapy noted, "it is the balance between benefit and harm that is key, rather than an unachievable ideal of absolute safety." (2008: 451). Yet pharmaceutical risks seem to be downplayed by industry (Clark, 2003) and absolute safety seems to be publicly embraced within Europe. More importantly, most European patients do not seem to believe, that patient safety is within individual responsibility. In a recently conducted special Eurobarometer respondents were asked, which organisations, bodies or authorities were mainly responsible for patient safety. The result indicates that European citizens seem to consider personal influence as negligible (Eurobarometer 2010). Promoting public health from the perspective of pharmaceutical consumption will therefore necessitate a mind change on behalf of prescribers as well as consumers.[313] Clearly, European pharmaceutical regulation has contributed to public health by providing a sound and continuous risk-benefit assessment of the drug, the provision of information and the adoption of necessary measures in case of drug risks. While these tasks help to reduce the inherent product risks, it cannot solve issues associated to the medication process.

8.4 Conclusion: regulatory outcomes and the limits of regulation

Previous studies considered European pharmaceutical regulation and the regulatory network as a prime example of effective European governance. The identified lack of regulatory goal attainment points to the difference of de jure and de facto effectiveness and calls for a critical reassessment of these claims. The innovation capacity of the European industry has been stagnating and the global competitiveness of the industry has decreased. While some European companies are still among the group of leading pharmaceutical manufacturers, US based companies have become the driving force within the industry. After more than four decades a single market for pharmaceuticals has not been achieved. Competition remains restricted and uniform access is not realized. Finally, while the introduction of new drugs has helped to increase life expectancy and reduce the burden of illness, the prevalence of serious pharmaceutical safety issues negatively impacts on public health. However, this does not mean that the European framework has resulted in regulatory failure, but points to the limitations of the current regulatory framework instead.

[313] For recent suggestions see (Aronson, 2009; Awé & Lin, 2003).

While the competitiveness of the European industry is partially influenced by European regulation, this influence should not be overstated. Innovation may be partially connected to approval, but it is hard to believe that regulatory burden alone determines innovation capacity and competitiveness. Pharmaceutical risk regulation has a gate-keeping function and impacts on the ability of a company to recoup its R&D investments. Yet there is little reason to believe that the European framework has unduly restricted these possibilities. Instead, the reasons for the reduced competitiveness should be seen in differences in investment, innovation systems and a lack of public-private partnerships in the European pharmaceutical sector, factors that are outside the scope of European regulation.

The same holds true for the creation of the single market. While the streamlining of regulation has created a single market from the perspective of approval, the stimulation of competition, increased access and convergence of prices remains largely unaffected by European regulation. Competition result from potential gains and as the discussion of market structure revealed, the characteristics of the pharmaceutical market do not seem to stimulate competition. While the Europeanization of the approval regime has potentially eased market entry for originator and generic competitors, it does not determine strategic behaviour of companies. Moreover, it cannot influence R&D portfolio allocations, the decision to market products in specific national markets and the development of prices.[314] While producers might be morally obliged to provide access to approved drugs to all European citizens, it remains within their discretion to do so. As a result, the single market may be realized from the perspective of producers, but is still far from completion from the perspective of (many) European citizens. The solution to this paradox situation and the remaining disparities regarding access must be seen primarily on the national level and rests with the national health authorities.

While the protection of public health is connected to the provision of access, the issue of safety has been identified as vital in this regard. The development of new drugs has improved European public health considering the positive development of health outcomes, but the regulatory framework cannot ensure that all citizens get the drugs they need.[315] In addition, the prevalence of serious and fatal adverse events negatively affects the public health of European citizens. Stricter pre-market controls might have prevented some of these adverse

[314] While uniform supply could be made a mandatory requirement for market approval, it would represent a strong intervention into the economic freedoms of pharmaceutical producers.

[315] Even though drugs might be approved they must not necessarily be marketed and reimbursed in all states. Moreover, the regulatory framework does not ensure allocation efficiency of drug development, as pharmaceutical producers cannot be forced to develop drugs for indications for which prior treatments exist.

events, but at the same time would result in a delay in access for those patients potentially benefiting from the new treatment. Furthermore, the analysis of serious ADRs revealed that the majority of adverse events are related to medication errors, something that is beyond the reach of European regulatory intervention. Instead, the solution must be seen within better control of the medication process, education, information and a more critical approach to drug therapy within society.

9. Conclusion: the effectiveness of European pharmaceutical governance

The present study has attempted to provide a comprehensive analysis of the developments and current state of regulation and European regulatory governance in the pharmaceutical sector. From the perspective of regulatory effectiveness it was shown that (European) governance matters and has helped to strengthen the control of pharmaceutical risks, to use a distinction employed in this study, not only de jure but de facto. Moreover, European activities have been instrumental in the advancement of the underlying legal framework and it seems questionable if the same dynamic would have been traceable in case of predominately national initiatives. This generally positive finding should however not obfuscate the limits of regulation which were revealed in course of this enquiry. In concluding this study, several aspects therefore ought to be considered. First, the three research questions developed in the introductory chapter should be revisited. Second, the implications of the study results beyond its initial scope must be worked out. Third, limitations and further research needs will be identified. Finally, current regulatory developments and their perceived impact must be reviewed briefly and additional measures to improve regulatory effectiveness will be proposed.

9.1 European health policy, the delegation of risks and regulatory effectiveness

Three interrelated questions forming the underlying structure of the study have been raised at the beginning of this study. First it was asked, if the emergence of a European health policy can be affirmed. Second, the study tried to answer, why member states would be willing to delegate risk regulatory competencies in such sensitive policy fields as pharmaceuticals. The third and central research question has been, in how far the current regulation of the pharmaceutical sector is effective.

9.1.1 European health policy: focusing on public health and pharmaceuticals

The study started from a paradox observation. Even though the European Union has no legislative competencies in the field of health, a growing number of studies identified the emergence of an increasingly Europeanized health policy. As the discussion of previous studies revealed, this finding was developed based on qualitative approaches and comparatively broad concepts of Europeanization and health policy.

Using a more focused definition of health policy and employing a quantitative method the alleged European health policy paradox was clarified. No European health policy does currently exist since no specific legislative and judicial activity in most constitutive health policy dimensions is traceable. While the European Union has clearly tried to advance its position in the European public health discourse for example by providing information, issuing health strategies and programmes and introducing a responsible Executive Agency for Health and Consumers (EAHC), this does not amount to the emergence of a distinct European policy field.[316] Even though the emergence of a general European health policy is not supported, the analysis revealed that beyond policies related to public health, a European pharmaceutical policy has emerged since the early 1960s. The reanalysis of European health policy claims clarified the paradox of European health policy, but raised similar questions regarding the identified European pharmaceutical policy.

9.1.2 Delegation and the emergence of a European risk regulatory state

Beyond questions of legal competencies of the European Union justifying intervention in the pharmaceutical sector, the more decisive question has been why member states would be willing to share or even delegate responsibility in sensitive policy fields. Pharmaceuticals, for example, represent a significant share of national health expenditures and more importantly, their consumption is related to certain risks. Since one of the key tasks of the modern state is to protect the well-being of its citizens and its legitimacy depends on its performance in this regard, willingly giving up room to manoeuvre in such matters seems to be counter-inductive.[317] Starting from the premises of the grand theories of European integration – intergovernmentalism and neo-functionalism – the study set out to identify a theoretical explanation for the delegation of pharmaceutical (risk) regulation and risk regulation in general. Since these approaches focus on how rather than why integration and/or delegation happened, the discussion advanced to the liberal intergovernmentalism theory of Andrew Moravcsik (1993) and rational choice approaches, introducing the concept of preferences into the integration debate. Drawing on the concepts of Principal-Agent theory (Kassim & Menon, 2003; Tallberg, 2002a), several reasons for delegation were identified. While the forwarded

316 See for example the first and second *Programme of Community Action in the Field of Health* (DG Sanco, 2003b, 2007) .

317 Moreover, it was found that the issue of delegation is not limited to the pharmaceutical sector, but represents a general European development. Delegation of risk regulation expands to other risks as well, for example, foodstuff (Chalmers, 2003; Krapohl, 2003) and chemicals (Fisher, 2008).

reasons for delegation advance the understanding of European developments, their explanatory value is reduced by a "functionalist fallacy" (Krapohl, 2008: 25): the reason for delegation is solely based on the outcome that is ought to be achieved by delegation, while a sound "micro-foundation" (Kassim & Menon, 2003) is missing. Accordingly, functional reasons for delegation can hardly serve as the singular explanation for the delegation of risk regulation, since they omit the individual motivations and preferences underlying the (political) decision to delegate. Moreover, the explanatory value of functional reasons in the pharmaceutical sector is diminished by the partial character of delegation: risk aspects have been delegated while financial aspects of pharmaceutical regulation remained on the national level. Based on the concepts of blame avoidance (Weaver, 1986) and depoliticisation (Buller & Flinders, 2006; Burnham, 2001), a complementary and preference-based explanation for the delegation of risk regulation in the European context was developed. Delegation of risk regulation is conceptualized as the consequence of individual cost-benefit assessments on behalf of governments and politicians (1) and the specific characteristics of risks (2). Politicians and governments need to claim credit for their actions including regulatory activities. At times, the possibility to claim credit is comparatively low and the potential risk to be held responsible for a wrong policy decision is high, causing rational governments to adopt blame shifting strategies. Considering risk regulation, the motivation to pursue the latter is amplified, since the possibility to claim credit is hard to predict as the regulation of risks is characterized by uncertainty. The decision to delegate may however not be viewed as avoiding blame in the first place, but as a strategy to avoid uncertainty involved in the regulation of risks. Uncertainty avoidance thus provides an alternative and micro-founded explanation for the willingness of member states to delegate regulatory competencies. Delegation to the European level is facilitated by willingness of the European Commission to take over more and more regulatory responsibilities to prove its regulatory abilities (Kelemen & Menon, 2007b).[318] The urge of member states to avoid uncertainty is thus met by regulators on the supranational level, willing to try out their luck and accept the risk of taking the blame. The actual decision to delegate regulatory tasks to the European level can be stimulated by national regulatory failure and the resulting public pressure (Hood, 2002; Hood & Rothstein, 2001; Hood et al., 2004) and this has been the case in the field of pharmaceuticals and the *Thalidomide* disaster (Krapohl, 2008; Permanand, 2006). Uncertainty avoidance does not only lead to delegation but has been found to impact both on the regulatory architecture (1) and the

[318] At the same time the still prevailing bureaucratic and depoliticized character of the European Union reduces the risk aversion of European bureaucrats viewing regulation as a chance to claim public credit.

European approach to risk regulation (2). Even though the European bureaucracy may appear less risk averse as national governments, the urge to avoid blame and uncertainty does affect their behaviour as well. As a result, the responsibility for the regulation of risks is distributed between multiple actors (Beck, 1992; Hood, 2002) resulting in the creation of regulatory networks (Dehousse, 1997) and increased use of independent regulatory agencies (Everson, 1995) on the European level. In an attempt to reduce the inherent uncertainty of risk regulation, the regulatory approach is becoming more legalized, formal and is increasingly based on a risk-averse strategy, namely the precautionary principle. As a result, European risk regulation is becoming stricter, less science-based and potentially (re)politicised.

9.1.3 Regulatory effectiveness in the European pharmaceutical sector

The uncertainty avoidance argument provided a valuable theoretical explanation for the delegation of risk regulation. At the same time, it raised some concerns on the regulatory capacities of the European Union. Previous functional explanations were based on the claim of European regulatory superiority, arguing that delegation would result in better regulation. The discussion of the predominant European regulatory logic revealed that superiority is largely understood as higher efficiency, reflecting an economic and business perspective on regulation. From the perspective of European citizens however, it is regulatory effectiveness – understood as the realization of regulatory goals – that must be achieved in the first place. As a result, European regulation might not necessarily reflect public needs and preferences, as it potentially focuses on the achievement of an economic instead of a social optimum, prompting the need to reassess the performance of European regulation from a citizen's perspective.

9.1.3.1 An analytical framework for regulatory quality and effectiveness

In order to structure the subsequent analysis of European pharmaceutical regulation, an analytical framework for the assessment of regulatory quality and effectiveness accounting for the characteristics of European regulation and risk regulation was developed. Acknowledging the dual character of regulation, as a distinct type of policy (Lowi, 1964b) and a mode of governance (Baldwin et al., 1998) four different levers for the realisation and analysis of regulatory effectiveness were identified.

First, certain preconditions of regulation ought to be realized. A regulatory goal advancing the public interest justifying intervention, a legal mandate and the necessity of European intervention has to be established. Second, regulatory policies should be based on a properly specified regulatory goal, covering all aspects of the regulatory problem. In addition, certain regulatory principles, synthesized from previous research on good governance, ought to be realized within the legal framework underlying regulation. Acknowledging the federal character of the European regulatory state (Kelemen, 2004), the transposition of European rules serves a precondition for effective regulation. Based on the neo-institutionalist claim that institutions do matter, governance structures have been identified as the third and most decisive lever of regulatory effectiveness. While the legal framework is instrumental in achieving de jure effectiveness, regulatory institutions need to ensure that de facto effectiveness is realized. Institutional design of "regulatory regimes" (Hood et al., 2004) has to account for the common critique of regulation (Francis, 1993) and most importantly ensure that regulatory capture is prevented. Regulatory institutions must be able to develop the right regulatory answers and establish an "equilibrium of interest" (Walras, 1954) between key stakeholders, ensuring compliance and support for the regulatory regime. Accounting for the distinct character of risk regulation and the European regulatory context, the general framework was adapted by introducing two additional requirements. First, a risk model fitting the specific character of the risk in need of regulation (Fischer, 2009; Millstone et al., 2004; Renn, 2008) should be traceable within the regulatory governance structures. Second, national regulatory bodies must be aligned and tied in (McGowan & Wallace, 1996) within a European regulatory network. Regulatory outcomes constitute the fourth lever of analysis, since the achievement of regulatory goals represents the key concept of regulatory effectiveness. Linking the general framework to pharmaceutical regulation, the regulatory lifecycle, covering all pre- and post-authorization aspects, was introduced.

9.1.3.2 Evaluation of the regulatory framework

The empirical investigation of European pharmaceutical regulation commenced with the assessment of precondition, the regulatory framework and the transposition of European rules on the national level. Based on the need to correct negative externalities and informational asymmetries and considering that less intrusive forms of regulation have been deemed as insufficient, a justification for public intervention was established. Acknowledging the continuous character of pharmaceutical product risk, a combination of pre-market controls,

licensing (approval) and monitoring mechanisms was identified as an optimal regulatory strategy. While such measures can be organized on the national level, the transnational character of the regulated industry, the relative genetic similarity of the European peoples, the completion of the single market and economy of scale consideration in safeguarding public health necessitate a European approach.

The discussion of constitutional foundations for European intervention revealed an inherent tension between regulatory goals and the legal base. While the need for regulation results from the possible negative impact of pharmaceutical risks on public health, intervention is based on the approximation of national laws to reduce barriers to the internal market. Put differently, intervention to protect public health is disguised as a measure to reduce obstacles to internal trade, amplifying concerns whether pharmaceutical regulation strives for a social or economic optimum.

Development and Performance of the European regulatory framework

European pharmaceutical regulation has evolved into a dense regulatory framework over the course of more than four decades. Retracing the development of pharmaceutical policy, three phases were identified. The first policy phase spanning from 1965 to 1990 focused on the harmonization of standards and regulatory aspects related to pre-authorization. Beyond establishing approval criteria policies mainly affected the development process. While several attempts to Europeanize national approval were enacted, opposition of member states and more importantly national regulators hindered the institutionalisation of European approval structures. Realising the limited effect of voluntary commitment, the Commission decided to engage in a fundamental review process, marking the beginning of the second policy phase of institutionalisation. The introduction of a threefold approval regime consisting of (existing) national, decentralized and centralized procedures as well as the foundation of a coordinating European regulatory agency, the EMA, marked a critical juncture. The approval regime was changed by the introduction of binding European procedures. While national regulators before had engaged in voluntary cooperation, the supervisory and coordination role of the EMA established a regulatory network in the sector, tying in national agencies. The second phase marked an expansion of the regulatory framework previously focusing on pre-authorization aspects as more specific European rules in the field of production, distribution, information and monitoring (pharmacovigilance) were enacted. Starting with the second revision in 2000, the regulatory framework moved into the third phase of consolidation and differentiation. The

increasingly fragmented regulatory framework was integrated and the existing level of regulation was raised further, with the notable exception of distribution.

Considering the development of the legal framework from today's perspective, a predominately positive assessment can be drawn. Starting as a rather fragmented set of policies harmonizing development and approval standards, pharmaceutical policy evolved into a consistent regulatory framework throughout the different policy phases. In addition, the framework sufficiently incorporates identified regulatory principles, serving as indicators of regulatory quality. Reviewing the current state from the perspective of the regulatory lifecycle, however, the predominantly positive assessment must be qualified. The density of the framework regarding different regulatory aspects is subject to considerable variation. While pre-authorization aspects are regulated rather extensively, the regulation of post-authorization, distribution and information more specifically, remains under-regulated. This finding is puzzling, considering the market-based justification for European intervention. While the completion of the single market has been invoked as the reason for regulation, those regulatory aspects closely related to trade are not controlled sufficiently at least on the level of policy. The increased complexity of the framework as well as the lack of clarity and vagueness of most European provisions impedes the de jure effectiveness of regulation. While it is intended to reduce uncertainty on behalf of regulatees and specify regulators' expectations, the European regulatory framework does not necessarily fulfil these requirements.

Comparing the transposition performance of member states throughout the policy phases, a generally positive compliance trend is traceable. In line with previous research on compliance within the European Union, national transposition records have been found to vary within the EU 15. Despite this variation, transposition performance in the pharmaceutical sector as a whole proved to be less problematic than in other sectors and policy fields.

9.1.3.3 Regulatory governance in the pharmaceutical sector

Turning to the sectoral governance, the distribution of regulatory preferences in the regulatory arena, its impact on the conduct of regulation and the development of regulatory governance throughout time were analyzed.

Regulatory interests: pharmaceutical risk cultures, alignment and reputation

Based on the claim that the functioning of regulatory regimes depends on trust, cooperation and compliance both within the regulatory network and the regulatory arena, regulatory preferences of the public, regulatees and regulators were deducted.

Starting from the notion that the public has a general interest in *safe* medicines, this assertion was specified by drawing on cultural theories of risk perceptions. Even though safe medicines represent an overarching public regulatory interest, what constitutes *safe* and *acceptable risks* varies throughout the member states of the European Union. National cultural differences impact on the public perception of risk and therefore the valuation of safety versus access and to a lesser extent on the preferred mode of governance regarding the regulation of pharmaceuticals, forming distinct national *pharmaceutical risk cultures*. Since cultural influences have been found to persist over time, the existence of these differences has several implications for regulatory governance: a commonly accepted European regulatory approach is harder to achieve, the input legitimacy of a supranational regulatory regime is reduced and most importantly, differences in risk perceptions translate into regulatory differences affecting the regulatory network. Turning to the position of the industry, pharmaceutical manufacturers' interests have been found to converge around the reduction of regulatory costs and the rationalization of safety regulation, translating into fast and cost-efficient market access. While regulators both at the national and the European level have self-interests, the pursuance of these interests will (partially) depend on their ability to accommodate the interests of the public and the regulated industry. In ensuring organisational survival, regulators will need to regulate in accordance with public perceptions and in order to ensure compliance need to meet regulatees' expectations. As a result, regulators will need to build a reputation towards the public and the industry. The safeguarding of reputation towards the public results in a more risk-averse regulatory approach and little public exposure to maintain a positive public reputation. Building a reputation towards the industry is achieved by rationalization of approval procedures and regulatory requirements. Moreover, the regulator's preferred secretive mode of governance advances the reputation towards the industry as well.

Based on the discussion of preferences, a consensus between the three considered actors can be identified. The provision of safety is a shared goal, even though individual reasons for this consensus vary. While the public does not necessarily prefer a specific regulatory mode of governance, regulators and regulatees can be expected to prefer a science-based, secretive mode of regulation.

The identified congruence of interests proves to be positive from the perspective of regulatory effectiveness. At the same time two distorting effects can be identified. First, the shared focus on safety is limited to the pre-authorization stage, while the interest constellation moves towards access considerations during post-authorization. Given this time inconsistency, compliance with the regulatory framework of regulators and regulatees is lower in the post-authorization stage. Moreover, the potential reluctance to repeal regulatory decisions on safety grounds can negatively impact on public health. Second, the equilibrium of interest in the regulatory arena does not prevent conflicts within the regulatory network, resulting from national regulatory approaches and more importantly pharmaceutical risk cultures.

Regulatory governance before 1995: regulatory patchwork

The regulatory regime in the pharmaceutical sector before the first revision is best described as a “regulatory patchwork”. The legal framework reached a considerable level of density, but the establishment of governance structures was lagging behind. Implementation of regulation was largely shifted towards private actors and the existing European institution, the CPMP, created to stimulate collaboration and alignment of national regulators, was lacking the necessary competencies to effectively tie in national authorities. While public health was safeguarded in principle, since market authorization based on specific criteria became mandatory, a single market in the sense of functioning mutual recognition was clearly not established. The patchwork of national procedures persisted and the introduced European procedures failed to eliminate duplication of assessment efforts. The lack of collaboration and appropriate structures was even more problematic regarding the post-authorization stage. National pharmacovigilance systems existed, but little was done to streamline and rationalize the exchange of information. Instead the situation clearly represented a state of under-regulation and under-institutionalization. The prevailing ineffectiveness of the regulatory regime during the first three decades clearly reflected the previously identified imbalance of the regulatory policy framework, the impact of national pharmaceutical risk cultures and the underlying logic of uncertainty avoidance.

Governance after 1995: institutional and cultural changes

Comparing the performance of the regulatory regime after 1995 to the achievements during the first policy phase a fundamental improvement can be identified. Two institutional changes in the sector provided a more specific explanation for this advancement.

First, the introduction of European approval procedures based on a binding supranational decision (centralized procedure) and binding mutual recognition (decentralized procedure) reduced the distorting effect of deviating national positions in risk assessment. Second, the foundation of the EMA transformed the loosely connected group of national regulators into a regulatory network, aligning national regulators and increasing internal compliance. Beyond these obvious changes, two additional factors for the improved performance of the approval regime and governance in more general terms were identified. Institutional changes were not limited to the European level, but affected the regulatory network as a whole. Stimulated by the emergence of the EMA and starting in parallel to the first revision of the regulatory framework, agencification in the pharmaceutical sector led to a convergence of regulatory structures. Moreover, the institutional transformation resulted in increased external accountability of independent national regulators, as they became increasingly dependent on applicants' fees. Closely connected to the previous argument, the newly created regulatory network emphasized a new regulatory approach, challenging existing national regulatory traditions. While the understanding of the regulatory role in most member states was that of a gatekeeper, the newly created European regulatory culture emphasized collaboration and the mutual goal of achieving market access. Driven by financial pressure, increased external (and internal) scrutiny of the Commission and the industry, national regulators had to adapt to these new rules, arguably resulting in decreasing regulatory discretion.

The EMA, expert regulation, the potential for capture and social legitimacy

The positive impact of the EMA and the new European approval regime on regulatory effectiveness can not be denied. At the same time, the creation of an independent European regulatory agency with a disputable public mandate, harbouring an expert body (CHMP) dominating regulatory decision-making, raised concerns regarding participation, transparency, accountability and control. The transparency of EMA's work has clear improved since its foundation and has reached an advanced state compared to national agencies in the sector and other European agencies, even though full transparency is still not achieved. A comparable development has been traceable regarding the participation of the public, with the agency increasingly consulting patient groups and providing them with permanent representation. Several ex-ante and ex-post mechanisms to ensure (political) accountability and control of the agency were identified. While these measures should ensure a sufficient level of formal

control, the subsequent discussion revealed that de facto control of the agency is not as strong as the formal mechanisms would suggest.

Turning to the approval regime and the work of the CHMP, the result has been much more heterogeneous. Starting with realisation of participation within the approval regime, the current approach is strictly science-based and creates a reserved domain for experts, deciding on market approval. Approval processes differ regarding transparency with the centralized procedure being the most advanced one, followed by the decentralized (MRP/DCP) and national procedures. The same rank order can be established regarding the accountability and control of the approval regime. The centralized procedure is controlled by defined approval criteria, strong guidelines, a peer-review system within the CHMP, the possibility of judicial review through the ECJ – even though reduced to actors affected by the decision – and finally a political control mechanism. While these mechanisms do reduce regulatory discretion, they reduce the effectiveness of political control at the same time. The only chance to stop a regulatory decision (opinion) by the CHMP in the political phase is based on scientific grounds, and this regulatory game has to be played against a body created to concentrate pharmaceutical expertise on the European level. Even though the same underlying approval criteria apply, most of the control mechanisms applied to the centralized procedure are absent in case of the decentralized procedure, at least before the stage of binding arbitration is reached. While regulatory discretion and the potential for capture is supposedly higher in case of the decentralized procedure, regulatory competition that has been found to hinder the smooth functioning and efficiency of mutual recognition serves as an additional lever of control. In contrast to the European procedures, accountability and control is largely absent from national procedures, with most agencies still practicing a science-based *black box* model of regulation. While the new approval regime surely is efficient and reduces the potential of capture these advantages come at the price of decreased social legitimacy. Decisions are made by an isolated regulatory body, in an approval process with a potential authorization bias towards unsafe products insufficiently tamed by political control mechanisms.

Coverage of the regulatory lifecycle and the regulatory approach

While the positive impact of European governance is reaffirmed regarding the regulation of different regulatory lifecycle aspects, general as well as specific drawbacks of the current regulatory approach ought to be highlighted.

A general problem of the regulatory approach must be seen in the strong emphasis of voluntary compliance as well as a lack of monitoring, for example via inspections, and sanctioning activities. While this is partially the result of the new European regulatory culture, other important factors in explaining the lack of policing are the insufficient national regulatory resources focusing largely on the approval process and the longstanding lack of sanctioning power. The shifting of increasingly complex regulatory tasks towards regulatees without providing additional guidance how to achieve compliance represents another worrying trend. Finally, the predominately European rather than global framing of regulatory problems resulting in insufficient regulatory answers has been traceable in several aspects of the regulatory lifecycle.

Development has been one of the most regulated aspects covered by the regulatory framework. Beyond harmonizing trial registration throughout the European Union serving as a licensing mechanism, governance is exerted through monitoring activities. Considering the low level of inspections and the increased conduct of clinical trials outside the European Union, the effectiveness of this approach could be questioned. Beyond insufficient monitoring, regulatory governance of production does not account for the globalization that has affected producers of active ingredients (AI), representing the input factors for pharmaceuticals, increasingly shifting production to countries with insufficient quality regulation. The multiplicity of AI sources and increased trading further diminish the effectiveness of self-regulatory approaches mainly based on manufacturers' activities.

The limited level of regulation regarding distribution within the European regulatory framework is amplified by problems of governance. While member states employ licensing mechanisms to control wholesale activities, this intervention does not seem to provide sufficient control in an increasingly complex field. Global trade has transformed distribution from simple wholesaling into a complex trading activity involving long supply chains and an increased number of players. As a result the current approach is neither able to protect the traditional supply channels from the entering of counterfeit medicine, nor addresses the potential negative impact of e-trade and rogue pharmacies on public health. The previously identified regulatory gap therefore reflects a governance gap as well.

The governance of information both regarding the work of regulatory agencies and products is hindered by prevailing national regulatory cultures. While the Europeanization of the regulatory network has increased obligations to provide information, most regulatory agencies still do not seem to be willed or staffed to take over a more active communication role

towards the public. While the provision of product information is mainly based on package leaflets, which currently do not seem to provide adequate information and ensure patients compliance, the provision of product information through the internet is increasingly used. However, the current approach does not allow for a more fundamental education of patients regarding pharmaceutical risks and benefits which would help to strengthen regulatory effectiveness.

The governance of post-authorization monitoring has been strongly influenced by the creation of the regulatory network and the EMA, strengthening the exchange of safety information. Supported by heightened regulatory requirements for manufacturers entailed in the regulatory framework, the effectiveness of pharmacovigilance activities has been one of the key improvements of the new regulatory regime. In light of the perceived shift of regulatory interests towards the maintenance of access after product authorization, however, the regulatory approach and structure turns out to be problematic. Regulation largely focuses on the generation of information, largely provided by the industry. Acknowledging the potential dilemma of regulatees to report on product defects potentially resulting in withdrawal, the lack of independent research on behalf of regulators constitutes a decisive problem. A lack of monitoring activities and insufficient regulatory capacities of national bodies dedicated to the conduct of pharmacovigilance aggravates the situation. The dilemma of regulatees to provide all available information is complemented by a dilemma on behalf of the regulator. Since, according to the logic of reputation, a change of its initial assessment will negatively impact on its public perception, regulators will try to accumulate as much evidence as possible before far reaching regulatory measures (withdrawal) will be invoked. As a result, regulators resort to softer measures to regulate post-market safety. Drawing on available post-authorization data and the Vioxx and Lipobay example, supportive evidence for the dilemma was found. The possibility to pursue such a strategy is eased by several factors. Restrictions regarding availability and quality of safety data provide the regulator with higher regulatory discretion then during the approval decision. The institutional set-up of the process and more specifically the prevalent low level of transparency of post-authorization decision making is conducive as well.

9.1.3.4 Regulatory effectiveness and regulatory outcomes

The assessment of regulatory outcomes regarding competitiveness, the completion of a single market and public health reaffirmed the previously indentified drawbacks of the current regulatory approach. The innovation capacity of the European industry has been stagnating and the global competitiveness of the industry has decreased. While some European companies are still among the group of leading pharmaceutical manufacturers, US based companies have become the driving force within the industry. After more than four decades a single market for pharmaceuticals has not been achieved yet. Competition remains restricted and uniform access is not achieved. Finally, while the introduction of new drugs has helped to increase life expectancy the prevalence of safety issues negatively impacts on public health. Paradoxically, these findings do not necessarily mean, that the current regulatory regime is ineffective, but point to the limits of regulation in achieving these goals. The regulatory regime may influence the pharmaceutical sector and provide a supportive regulatory environment. The attainment of the identified regulatory goals is however largely contingent on factors outside of the regulatory scope. It depends on the pharmaceutical industry, the member states and in the case of public health especially on the behaviour of prescribing doctors and patients. While the competitiveness of the European industry is partially influenced by European regulation, the reasons for the reduced competitiveness must be seen in differences in investment, innovation systems and a lack of public-private partnerships in the European pharmaceutical sector, factors that are outside the scope of European regulation. The same holds true for the creation of the single market. The streamlining of regulation has created a single market from the perspective of approval, but it can not influence R&D portfolio allocations, the decision to market products in specific national markets and the development of prices. Turning to public health, the regulatory framework cannot ensure that all citizens get the drugs they need and safety of pharmaceuticals and the occurrence of adverse events more specifically are mainly related to medication errors, something that is beyond the reach of European regulatory intervention. Recalling the initial research question, it can be concluded that the introduction of a European regulatory regime has had a major impact on the regulatory effectiveness in the pharmaceutical sector, aligning national regulators and counterbalancing the distorting effect of national pharmaceutical risk culture. At the same time, a divide between de jure and de facto effectiveness is traceable, pointing to the limits of regulatory governance both from the perspective of right problem framing and the scope of regulation.

9.2 Implications of the present study

In trying to specify, what the present study adds to what is already known, three different levels should be differentiated: European pharmaceutical regulation, European risk regulation and European studies especially in the field of health.

The present study has been the first to analyse European pharmaceutical regulation from a holistic perspective, going well beyond the focus of previous studies. First, it expanded the scope beyond the analysis of the regulatory framework, by including questions of transposition, governance and regulatory outcomes. Second, it introduced the concept of regulatory effectiveness. Third and most decisively, instead of focusing on the EMA and the approval regime, the introduction of the regulatory lifecycle, allowed a more precise and inclusive analysis of regulatory performance. The study revealed that the assumed effectiveness of the regulatory regime and governance of the sector can and must be challenged. While de jure effectiveness, despite the identified imbalance of the regulatory framework can be considered as accomplished, the discussion of governance and regulatory outcomes revealed a lack of de facto effectiveness. Furthermore, the study advanced the understanding of interaction within the regulatory network by drawing attention to the existence of national pharmaceutical cultures and implications for regulatory behaviour. By introducing regulatory preferences and the logic of reputation, a more advanced model of regulatory relations within the regulatory arena and its impact on regulatory effectiveness in the pharmaceutical sector is provided. Drawing on these concepts, more advanced explanations for the ineffectiveness of sectoral governance before 1995 as well as prevailing current deficiencies of sectoral governance are provided.

The contribution to the field of European risk regulation is threefold. First, the developed explanation for delegation in risk regulation based on uncertainty avoidance provides a more fitting and micro-founded reasoning, avoiding the functionalist fallacy. Second, the identified national differences in risk perception and its general impact on the appropriateness and acceptance of European risk regulatory regimes can help to understand the functioning and effectiveness of current risk regulatory approaches. In addition, the identified dynamics within the regulatory network, sectoral agencification and the emergence of a European regulatory culture could constitute developments traceable in other sectors as well. As the discussion of risk perceptions revealed, general risk cultures do exist in the European Union and, as the discussion of the pharmaceutical sector exemplified, impact on public and regulatory

perceptions. Third, the basic analytical framework developed in the fourth chapter can be applied to other risk regulatory fields and serve as a structuring device for similar studies on regulatory effectiveness both on the European and national level.

Turning to impact of the study on European studies and on health studies more specifically, the proposed approach to assess the Europeanization of policy fields, represents a complementary research strategy to existing qualitative studies and can by applied to other policy fields as well. Another important finding relates to the creation of a European administrative space, the emergence of European regulatory agencies and a European regulatory culture. Even though research on agencification on the European level has expanded considerably in the last few years, it seems striking that questions of social legitimacy regarding the delegation to unelected bodies have not entered the debate. If the European Union is primarily understood as a regulatory state, its legitimacy depends both on the conduct and outcome of regulatory activities. In light of the dominant European regulatory logic emphasizing economic aspects, it seems at least questionable if European regulation is superior from the perspective of citizens and businesses alike. However, if the social legitimacy of the European risk regulatory state is ought to increase, it is important to frame questions of better regulation from the perspective of effectiveness. Moreover, it would be important to analysis existing European regulatory regimes in this regard. As this study tried to show, European regulatory agencies can have a fundamental influence on the conduct of regulatory governance, potentially impacting on the everyday life of European citizens. Considering the isolation and potential lack of control that is exercised over these bodies, more research on the actual behaviour and activities of these bodies seems to be necessary as well.

9.3 Current developments in the European pharmaceutical sector

Unsurprisingly, developments in the pharmaceutical sector both on the level of the regulatory framework and the regulatory regime did not cease. A fundamental change to the sector has been the recent transfer of pharmaceuticals and the EMA from the DG Enterprise and Industry into the responsibility of the DG Health and Consumers at the beginning of 2010. While it is too early to speculate on the strategic and political implications, it will be interesting to see if the relocation will result in an increasing public health turn of pharmaceutical regulation and governance. Beyond several modifications to the existing regulatory framework, the Commission engaged in a new and still ongoing revision process of

the regulatory framework in 2007 and adopted a communication in December 2008, entitled Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector sketching out the future regulatory priorities. The second major project has been the so-called pharmaceutical package, consisting of two regulations and three directives. The package covers three main topics: information to patients, pharmacovigilance and fake medicines.

The proposals regarding information to patients foresee to harmonize the provision of information to patients and grant more rights to market authorization holders in this regard. Based on a report published in 2007 and the subsequent consultations the Commission saw the need to streamline the availability of information and to clarify the borderline between (prohibited) promotion and information. Moreover, the proposal lays down measures for the monitoring of compliance with these rules.

The changes to pharmacovigilance will both affect the collection, decision and communication stage. Direct patient reporting will be allowed under the new provision, a new Committee located within the EMA supporting the conduct of pharmacovigilance will be created and the decision process on safety measures is rationalized by clarifying roles and responsibilities. The role of the EMA and the CHMP in pharmacovigilance is strengthened further, especially regarding the collection of ADRs. Responsibilities of market authorization holders are expanded and rationalized at the same time. The Commission will be allowed to mandate post-authorization studies and the use of risk management plans is encouraged while duplication of reporting efforts is reduced by reporting all cases to the Eudravigilance database and the requirements for the description of pharmacovigilance systems are rationalized by introducing a pharmacovigilance system master file. Additional rationalisation affects the requirements for periodic safety update reports are which should be made proportional to the risks and the introduction of single assessments, including all products based on the same active ingredient. Communication is strengthened by the creation of web portal for citizens and the introduction of a key information section in leaflets.

To combat the risks posed by fake medicine, the Commission proposed a number of changes to the current regulation of the distributional chain. Control is expanded to other actors (brokers) active in the trading of pharmaceuticals and by expanding licensing mechanisms throughout the distribution chain. The use of specific safety features (seals, serialisation) which not ought to be separated during distribution is proposed. Wholesalers will be obliged to certify the reliability of their business partners and product sources. The control of API production shall be strengthened by stricter import rules and audits of producers. Moreover,

stricter rules for inspections and the increased use of the EudraGMP database are highlighted as a means to improve drug safety.

The pharmaceutical package has attracted a lot of controversy during the last two years and the plans for the improvement of pharmacovigilance and information of the public have been at the centre of a heated debate. While industry associations support the provision of information and rationalization of pharmacovigilance (EFPIA, 2009b), consumer organisations have opposed to the changes negatively impacting on the provision of public health (AIM & ISDB & MiEF & HAI Europe, 2009). With the package still in the legislative process at the time of writing, the final impact on regulatory effectiveness is hard to estimate at this point. Evaluating the entailed changes in light of the previous assessment of the European pharmaceutical regulation it is nevertheless possible to identify the most significant improvements and drawbacks from the perspective of public health.

At first sight the pharmaceutical package arguably contributes to the reduction of most gaps of the regulatory framework identified in this study. Most importantly, the introduction of the measures to combat fake medicine would close the regulatory gap of distribution. The allowance of direct reporting of ADRs, increased collaboration and the extended role of the EMA in pharmacovigilance, as well as the introduction of more extensive post-authorization study requirements can be expected to broaden the (data) foundation of decision-making and potentially advance the public understanding of pharmaceutical risks. Moreover, the changes to leaflets and the creation of a safety portal will help increase the effectiveness of (pharmaceutical) risk communication. A similar effect can be expected regarding the provisions on information to customers providing both product-related information and contextual knowledge on pharmaceutical risks. However, there is reason to believe that the effect of the envisioned changes will be more limited than the Commission and proponents of the reform would like to admit.

Starting with the issue of fake medicine, the clarification of roles and expansion of licensing as well as a product-based regulatory strategy employing tracing systems is important, but the real challenge must be seen in the implementation of these new rules. As the previous analysis tried to show, the monitoring of distribution has become increasingly complex and is complicated further by the insufficient resources of regulatory agencies, hardly able to fulfil their current and less extensive tasks. While private regulatory arrangements already do exist in wholesaling, past experience suggests that many companies do not necessarily have the resources to engage in auditing activities (Avellanet, 2010). Moreover, the current proposals

do (still) not account for the challenges of alternative supply chains and internet trade (Anon, 2009a). Considering that the pharmaceutical package seems to put increasing emphasis on the responsibility of private actors in ensuring safety, distribution can be expected to remain the weak link of pharmaceutical regulation.

While providing more information to patients is a laudable goal in itself, the proposals by the Commission raise some serious concerns. While it is true that pharmaceutical manufacturers do possess an informational advantage regarding their products it is questionable in how far allowing direct information will advance the consumers' level of information:

> "What key data are pharmaceutical companies going to give to patients that have not been included on the patient leaflet or the assessment reports that are available at any time on the Eudrapharm European database and on the websites of the member states health authorities […] Countless recent examples show that pharmaceutical companies are not in the habit of divulging certain items of 'key information' which they possess, such as information on the risks associated with their drugs. [original emphasis]" (AIM & ISDB & MiEF & HAI Europe, 2009: 2-3).

The Commission seems to misapprehend the meaning of more effective informing of patients. The issue is not primarily related to product information but the provision of information allowing for informed decision-making in therapy and a better understanding of pharmaceutical risks, as well as the comparison of alternative treatments. Pharmaceutical companies can hardly be expected to provide such information, considering the inherent conflict of interest. Instead of reducing agencies' role to the control of industries' informational activities, a task that will be extremely difficult, providing them with the responsibility to inform citizens in the previously mentioned way would prove to be a better solution.

Finally turning to the proposals on pharmacovigilance, it can be argued that the changes will mostly benefit the industry while representing a modest advancement regarding public health. Beyond the fundamental improvement of involving patients, the streamlining of reporting might lead to unintended consequences. While the fear of consumer organisations that the new legislation will result in a privatisation of reporting and the crowding out of national pharmacovigilance structures (ISDB & MiEF, 2009: 3-4) is most certainly overrated, the changes in reporting will probably not only increase reporting rates but will impact on the possibilities of national pharmacovigilance experts to process and analyse these information. While improved reporting and the reduction of duplicated efforts is a laudable goal, data quality and the enabling of independent assessment by national agencies are vital in

improving pharmacovigilance. Unfortunately, this does not seem to be the main goal of the pharmaceutical package, as more sophisticated reporting requirements (PSURs) are streamlined, depicting the reduction of reporting frequencies and level of detail. In addition, the proposals do not address the identified conflicts of interest in post-authorization decision-making on behalf of regulators and regulatees and the prevailing lack of transparency and accountability.

9.4 Implications for the improvement of regulatory effectiveness

Significant progress towards more efficient and effective pharmaceutical regulation in the European Union has been made over the last fourty-five years. This study has attempted to draw a realistic picture of the current regulatory situation, highlighting progress as well as shortcomings of the regulatory regime. While the identification of possible improvements provides valuable insights, it seems to be of even greater importance to sketch out tentative solutions to increase the overall regulatory effectiveness of the regime.

In supporting the completion of the single market from the perspective of access it is important to differentiate between changes within the scope of the current regulatory regime and factors out of the scope. Starting with the first set of changes, an option to reduce remaining disparities can be seen in the expansion of the centralized procedure to all products, leading to a uniform authorization throughout the European Union. Even though this would not guarantee uniform marketing it could be expected to increase access. An additional yet highly intrusive measure would be mandatory marketing in all member states as a condition for approval. The streamlining of pricing and reimbursement throughout the European Union – even though highly unlikely given persistent national reservations – can be expected to have a positive effect on the integration of the single market. In stimulating the competition and increase of access regarding generics beyond national policies, the Commission and the respective DG would have to engage in a stricter monitoring and sanctioning of market distorting practices. While the recent sectoral enquiry shows the commitment of the Commission, it remains to be seen if misconduct by innovator companies will have legal consequences.

As the discussion of regulatory outcomes has shown, the strengthening of innovation capacities and competitiveness is largely outside the scope of the current regulatory regime. Beyond the provision of regulatory certainty as a lever to stimulate the development of

innovative instead of me-too pharmaceuticals, the provision of additional incentives, for example extended exclusivity and increased scientific support during development could be useful. A more drastic measure would be the change of approval criteria and the application of relative efficacy as a condition for market approval. However, the impact of these changes on the European pharmaceutical industry could be catastrophic and result in no innovation at all.[319] Turning to the changes outside of the regulatory scope, the creation of a coherent innovation system within the European Union represents a major area of improvement. While recent initiatives like the Innovative Medicines Initiative (IMI) represent a promising development, the European sector is still lagging behind the US regarding the creation of a conducive scientific environment.[320]

In improving public health several general and more specific recommendations can be drawn. Starting with the regulatory framework, the study showed that the body of regulation is marked by increasing complexity and vagueness at the same time. While this translates into regulatory burden, this is not only an issue of regulatory efficiency but regulatory effectiveness, as it increases regulatory uncertainty and potentially decreases compliance. It would be therefore necessary to review the framework from this dual perspective.

The regulatory network is vital for the achievement of regulatory effectiveness. Drawing on the discussion of regulatory governance in the sector, two main issues need to be addressed. First, staffing and resources represent an increasing challenge. Most national agencies are understaffed and the distribution of staffing within national bodies is still skewed in favour of approval related tasks, rather than reflecting the increasing importance of post-authorization. In addition, staffing of agencies has to be expanded in certain disciplines and uniform training across the network is necessary. While current initiatives of the network are promising (Sharma, 2009), greater efforts are necessary. Closely connected to the issue of staffing is the reform of agency financing. While agencification has increased alignment of regulatory agencies it has resulted in increased financial dependence of national regulators and the EMA. Unfortunately, the recent changes in the framework do not seem to encourage a return to greater public involvement in this area. Second, the current regulatory approach might not only foster cooperation but at the same time discourage compliance. While this study argued, that the building of regulatory relations is decisive in achieving compliance, this does not

[319] In addition, the valuation of innovation to some degree is conducted during pricing and reimbursement. However, as the recent developments in Germany show, rewarding innovation rather than reimbursing every new drug introduced to the market does not seem to be a political priority (Anon, 2010b).

[320] The IMI is a partnership between the European Community and the EFPIA intended to strengthen the research environment especially regarding the development of biopharmaceuticals (IMI, 2010).

mean that traditional mechanisms and more importantly the use of sanctions to ensure compliance are obsolete. For a long time the regulatory regime has been somewhat toothless, and the power to sanction regulatees has just been supplemented lately. It remains to be seen, if the regime is willing to bite the hand that feeds it to ensure that compliance especially in the post-authorization stage is achieved.

Improving public health will necessarily require changes to certain governance aspects of the regulatory lifecycle. In improving the approval process, the institutionalization of risk framing would improve the input legitimacy of the regime by integrating public perceptions of acceptable risks (Johnson et al., 2009). Reducing the risks to public health stemming from distribution, the collaboration between health authorities, regulatory bodies and other affected actors must be increased. Rather than shifting the responsibility towards regulatees, strengthening monitoring capacities especially in third countries will be necessary. Increased monitoring has to be supplemented by more vigorous sanctioning and criminal charges. Considering the global dimension of counterfeit medicines a joined approach between the EMA, the FDA and other regulatory bodies is inescapable and progress currently made in this area seems to be promising. However, the regulation of illegal e-trade remains virtually impossible and raising public awareness of associated risks seems to be the only option to reduce its negative impact. Repeating an argument developed in the seventh chapter, the improvement of information will necessitate a reframing of the task and a change of roles. Beyond the provision of product-related information strengthening public health needs will necessitate the provision of contextual information and education of patients. Promoting health literacy (Carmona, 2006) should be a prior task of national regulatory agencies. Embracing this role as well as creating the capacities to fulfil it will be one of the many challenges for the European regulatory framework. Finally, the monitoring of pharmaceutical risks and more effective pharmacovigilance represent the key area to advance the protection of public health. Rather than increasingly relying on industry assessments – potentially affected by the described regulatees dilemma – independent research by regulatory agencies, external experts and institutions must be encouraged and enabled. This implies improvements in data generation, training of physicians to detect signals (Durrieu et al., 2007), an increase of staffing in pharmacovigilance departments across Europe and stronger collaboration between existing national resources. Moreover, it will be necessary to improve the analytical tools and databases. A promising development in this regard has been the creation of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP). While

increasing post-authorization commitments of regulatees must be carefully weighed against the implicit regulatory burdens, it seems to be necessary to increase regulatory compliance with existing commitments in the first place. Turning to decision-making in the post-authorization stage, more transparent and faster decisions are necessary to increase public trust. Dismissing such demands on the grounds of preventing public confusion ignores the potential gains of increased awareness for the continuous character of pharmaceutical risks. A fundamental, yet potentially decisive change would be the previously proposed institutional separation of approval and post-authorization decision-making. While this would result in the creation of yet another regulatory body, it resolves the prevailing regulators' dilemma of revoking its own decision despite reputational considerations.

9.5 Concluding remarks: merits and limits of European regulatory governance

As this study has shown, the European regulation of pharmaceuticals has evolved from a fragmented patchwork into a coherent framework supporting the safeguarding of public health in the European Union. European regulation has remedied the existing shortcomings of national regulatory frameworks and the creation of a European regulatory network has resulted in effective sectoral governance. While the merits of European regulation and governance in realizing regulatory goals must be acknowledged, it also has been found that certain limits of regulation exist. Clearly, recent and future advancement in the regulation of the sector as well as in pharmaceutical development can be expected to further decrease pharmaceutical product risks. However, the current regulatory approach will not be able to reduce those risks not stemming from the product itself.

It has been said that European citizens today live in medicated societies (Moynihan & Smith, 2002). While it might be tempting to assume that increased consumption has been the result of demographic changeor an increased need and access to novel treatments, it has been stimulated as well by both private and political forces. National governments promote pharmaceutical consumption by switching drugs to over the counter (OTC) status and the pharmaceutical industry advances the "medicalisation" (Busfield, 2010) of society through lifestyle drugs. Increased consumption does, however, not lead to a more advanced public understanding of pharmaceutical risks.

Most patients refuse to acknowledge the risks associated with consumption and (understandably) want to believe that drugs are absolutely safe. At the same time, every new

public drug scandal is accompanied by accusation against regulators and mounting distrust towards the industry. This inconsistent public perception can be seen as the result of a regulatory approach effectively isolating regulators and regulatees from public scrutiny and efforts by the pharmaceutical industry downplaying the risks of pharmaceutical consumption. While public unawareness of pharmaceutical risks might be conducive to short-term business interests it represents a disruptive potential in many ways. It amplifies the impact of drug scandals and can result in the short-term repoliticisation of regulatory policy leading to stricter yet not necessarily more effective regulation. Moreover, it may lead to a more hostile public perception of the industry and a more critical stance towards innovation. Most decisively from the perspective of public health, it tends to obfuscate the personal responsibility in mitigating pharmaceutical risks.

The majority of risks involved in pharmaceuticals are not caused by the drug itself but are the result of medication errors. To react to this regulatory challenge implies an expansion of the current regulatory understanding beyond the product and towards the medication process. Producers, doctors, pharmacists and most importantly the end-user need to be aware of their respective roles in the medication process. Consumers also have to acknowledge the crucial importance of compliance to increase the benefits and decrease the risks of drug therapy. In other words, public unawareness must be replaced by a more critical understanding of pharmaceutical risks, benefits and most importantly individual responsibilities in drug therapy. Clearly, the need to increase health literacy goes well beyond the regulation of pharmaceuticals but represents a more general topic in safeguarding public health and the strengthening of individual responsibility in healthcare decisions.

While this argument could be interpreted as additional supportive evidence, that governance and regulation only matters within a limited extent in the management of pharmaceutical risks, it should rather be understood as the need to adjust the regulatory scope. While the role of physicians and pharmacists in this regard must be acknowledged, it calls for a different role of regulatory agencies as well. By providing agencies with a more fundamental mandate in informing the patients, the impact of regulatory activity at least regarding public health would be increased significantly. Beyond the broadening of regulatory scope, however, a much more fundamental change of mind and behaviour in pharmaceutical consumption will be necessary.

As a consequence, increasing drug safety will mainly depend on two factors. First, the current regulatory network involving the national agencies and the EMA, which has contributed tremendously to the protection of public health in the past, must accept a more proactive role

in drug safety, including the necessary changes in the current allocation of regulatory resources. The second and probably more decisive challenge will be to raise awareness and individual responsibility of patients and others involved in the medication process, for the benefits and risks pharmaceuticals pose. Even though representing major challenges for all stakeholders involved, it seems to represent the only feasible way, if drug safety ought to be increased in the future.

The only real alternative in reducing the risks of pharmaceutical consumption would be to take no pharmaceuticals at all. While this radical approach would practically eradicate all the risks associated with drug consumption, the same would be true for its benefits.

Appendix

A.1 Description of computation

Starting off by selecting the menu item *simple search* the search function is started. By using the option *search by date,* search is limited to the respective period or interval selected. As outlined, parameters were set for the first interval between 1970 and 1975. The database will now display all documents issued in the given period. By using the menu item *Refine* the results can be reduced further. Using the option *type of document* the respective type of document can be selected e.g. regulations. By selecting a specific type of document, the number of hits gets reduced to the specific type of document within the given period. By selecting the option *refine* again, the search can now be conducted. Either the sides' *Search Terms* or the *Key words* function can be used to search for a concrete term. While *Key words* allows the user to search the database based on a predefined list of categories (EUROVOC), using the *Search Terms* option enables free search of the data. Since the inquiry is based on a set of distinct terms, computation was conducted using the *Search terms* option. Using the entry mask, the specific search term e.g. *health* can now be entered. Finally, by selecting the option *Title* or *Title and text,* search function is either applied to document titles or title and full text.

A.2: Detailed results

Legislative activity health policy (title search)

	1970-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2008
total documents	**33439**	**38505**	**51066**	**62772**	**73444**	**86211**	**83834**	**40581**
Regulations	6246	8224	8659	10411	12114	16512	14186	6774
Health	1	0	2	5	9	6	20	28
Public Health	0	0	0	0	0	0	0	1
Prevention	0	0	0	0	0	0	0	0
Health Care System	0	0	0	0	0	0	0	0
Medical scheme	0	0	0	0	0	0	0	0
Health Insurance	0	0	0	0	0	0	0	0
Ambulatory/Outpatient care	0	0	0	0	0	0	0	0
Inpatient treatment	0	0	0	0	0	0	0	0
Health care	0	0	0	0	0	0	0	0
Medical/Medicinal	0/0	0/0	0/0	0/1	6/25	1/75	0/65	1/40/
Pharmaceutical	0	0	1	0	0	2	0	2
Directive	**385**	**644**	**653**	**793**	**1011**	**1146**	**1144**	**936**
Health	25	23	26	47	80	49	32	23
Public Health	3	0	0	2	3	1	0	3
Prevention	0	0	0	0	0	0	0	0
Health Care System	0	0	0	0	0	0	0	0
Medical scheme	0	0	0	0	0	0	0	0
Health Insurance	0	0	0	1	0	0	0	0
Ambulatory/Outpatient care	0	0	0	0	0	0	0	0
Outpatient care	0	0	0	0	0	0	0	0
Inpatient treatment	0	0	0	0	0	0	0	0
Health care	0	0	0	0	0	0	0	0
Medical/Medicinal	0/3	0/4	2/5	3/20	5/22	8/8	7/20	6/3
Pharmaceutical	0	0	0	0	0	0	0	0
Decisions	**2052**	**3485**	**3148**	**3448**	**4944**	**5950**	**6435**	**4568**
Health	9	63	109	90	197	175	265	108
Public Health	1	8	9	5	6	32	34	8
Prevention	0	0	0	0	0	3	3	0
Health Care System	0	0	0	0	0	0	0	0
Health Insurance	0	0	0	0	0	0	8	0
Ambulatory/Outpatient care	0	0	0	0	0	0	0	0
Inpatient treatment	0	0	0	0	0	0	0	0
Health care	0	0	0	1	0	0	4	0
Medical/Medicinal	3/0	21/0	20/0	14/0	15/0	17/0	14/1	2/4
Pharmaceutical	2	1	1	2	16	18	3	0

Source: EUR-lex

Legislative activity health policy (title and full text search)

	1970-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2008
Total documents	33439	38505	51066	62772	73444	86211	83834	40581
Regulations	**6246**	**8224**	**8659**	**10411**	**12114**	**16512**	**14186**	**6774**
Health	21	37	114	192	265	278	655	628
Public Health	6	5	10	5	21	31	88	114
Prevention	1	0	0	0	3	6	32	32
Health Care System	1	1	3	0	1	1	1	1
Health Insurance	1	0	1	1	2	3	8	10
ambulatory/outpatient care	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
inpatient treatment	0	0	0	0	0	0	0	0
Health care	0	0	5	2	4	17	16	27
medical/medicinal	11/2	28/10	65/16	38/0	85/47	64/101	111/130	123/105
Pharmaceuticals	2	29	59	47	75	63	84	79
Directives	**385**	**644**	**653**	**793**	**1011**	**1146**	**1144**	**936**
Health	25	123	149	247	366	357	478	330
Public Health	3	44	33	73	90	85	117	71
Prevention	0	9	8	18	17	22	38	19
Health Care System	0	0	0	0	1	0	0	2
Health Insurance	1	1	0	4	4	2	9	4
ambulatory/outpatient care	0	0	0	0	0	0	0	0
inpatient treatment	0	0	0	0	0	0	0	0
health care	0	0	0	5	10	15	25	13
medical/medicinal	17/17	27/25	29/43	43/47	80/62	80/62 ?	95/84	71/23
Pharmaceuticals	6	6	16	25	25	20	43	14
Decisions	**2052**	**3485**	**3148**	**3448**	**4944**	**5950**	**6435**	**4568**
Health	17	115	455	470	1075	1279	1762	1271
Public Health	2	19	69	64	219	230	352	227
Prevention	0	1	3	7	22	40	83	55
Health Care System	0	0	0	1	2	4	5	0
Health Insurance	0	0	0	3	11	12	21	10
ambulatory/outpatient care	0	0	0	0	0	1	1	0
inpatient treatment	0	0	0	0	0	0	0	0
health care	0	0	5	9	28	57	77	48
medical/medicinal	5/(4)	42/(4)	60/(5)	50/10	92/25	146/45	171/32	140/35
Pharmaceuticals	6	22	43	38	89	113	117	71

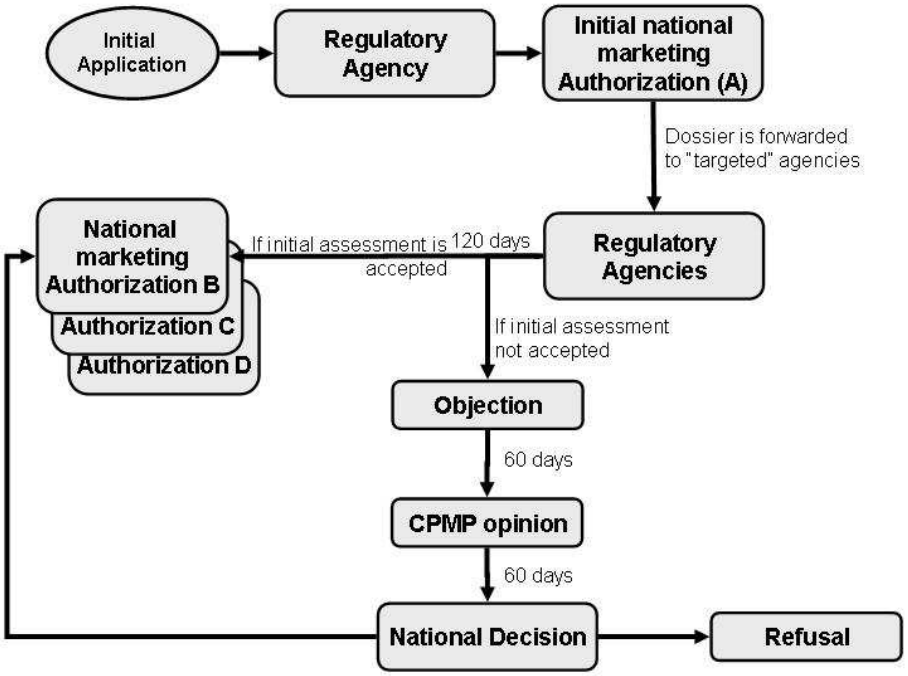
Source: EUR-lex

A.3: Key European pharmaceutical directives and regulations

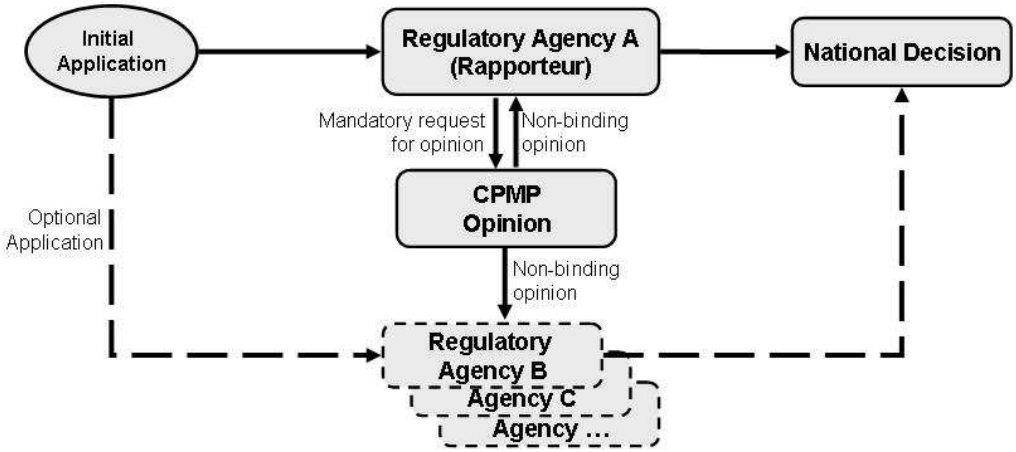
Directive	Release Date	Regulation	Release date
65/65/EEC	26 January 1965	EEC 2309/93	22 July 1993
75/318/EEC	20 May 1975	EC 540/95	10 March 1995
75/319/EEC	20 May 1975	EC 541/95	10 March 1995
75/320/EEC	20 May 1975	EC 542/95	10 March 1995
83/570/EEC	26 October 1983	EC 2000/141	16 December 1999
87/19/EEC	22 December 1986	EC 2004/27	31 March 2004
87/22/EEC	22 December 1986	EC 726/2004	31 March 2004
89/552/EEC	3 October 1989	EC 1084/2003	3 June 2003
89/341/EEC	3 May 1989	EC 1085/2003	3 June 2003
89/342/EEC	3 May 1989	EC 847/2000	27 April 2000
89/343/EEC	3 May 1989	EC 507/2006	29 March 2006
89/381/EEC	14 June 1989	EC 1901/2006	12 December 2006
89/105/EEC	21 December 1988	EC 1902/2006	20 December 2006
91/356/EEC	13 June 1991	EC 658/2007	14 June 2007
91/507/EEC	19 July 1991	EC 1394/2007	13 November 2007
92/25/EEC	31 March 1992	2049/2005/EC	15 December 2005
92/26/EEC	31 March 1992		
92/27/EEC	31 March 1992		
92/28/EEC	31 March 1992		
92/73/EEC	22 September 1992		
93/39/EEC	14 June 1993		
2001/20/EC	4 April 2001		
2001/83/EC	6 November 2001		
2003/63/EC	25 June 2003		
2003/94/EC	8 October 2003		
2005/28/EC	8 April 2005		
2008/29/EC	1 March 2008		
2009/120/EC	14 September 2009		
2009/53/EC	18 June 2009		

Source: Eudralex

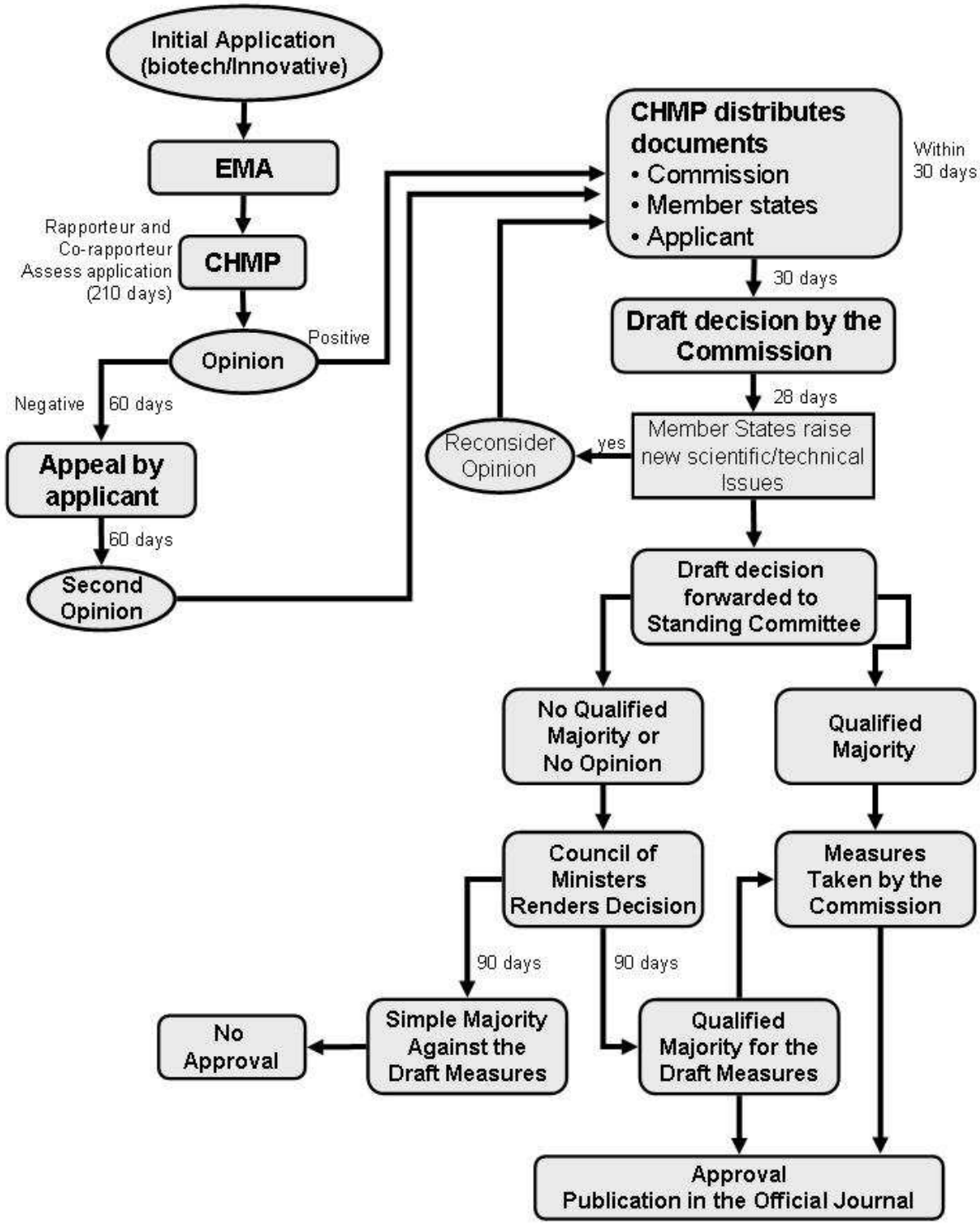
A.4: multi-state procedure



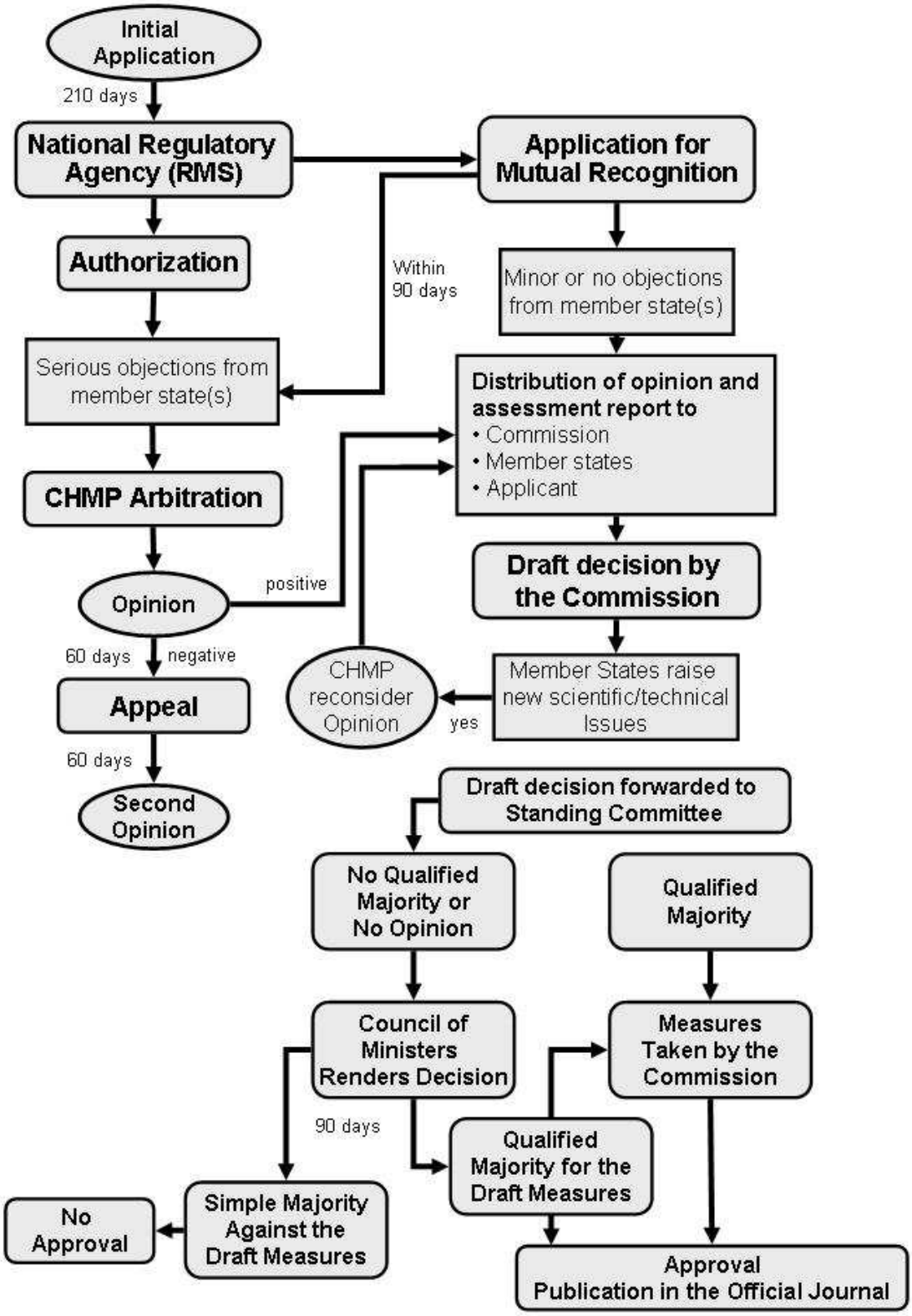
A.5: concertation procedure



A.6: Centralized procedure (initial concept)



A.7: Decentralized/Mutual Recognition Procedure



A.8 List of National Agencies

Country	Abbreviation	Name	Location	Webpage
Austria	AGES-PharmMed LCM	Austrian Agency for Health and Food Safety	Vienna	www.ages.at
Belgium	FAMHP	Agence Fédérale des Médicaments et des Produits de Santé	Brussels	www.fagg-afmps.be/
Bulgaria	BDA	Bulgarian Drug Agency / Institute for Control of Veterinary Medicinal Preparations	Sofia	www.bda.bg
Cyprus	n.a.	Ministry of Health - Pharmaceutical Services	Nicosia	www.moh.gov.cy
Czech Republic	SUKL	State Institute for Drug Control	Prague	http://www.sukl.cz/
Denmark	DKMA	Danish Medicines Agency	Kopenhagen	www.dkma.dk
Estonia	SAM	State Agency of Medicines	Tartu	www.sam.ee
Finland	FIMEA	Finnish medicines Agency		www.fimea.fi
France	(Afssaps)	Agence française de sécurité sanitaire des produits de santé	Paris	www.afssaps.sante.fr
Germany	BfArM	Bundesinstituts für Arzneimittel und Medizinprodukte	Bonn	www.bfarm.de
Greece	EOF	National Organization for Medicines	Athens	www.eof.gr
Hungary	OGYI	National Institute of Pharmacy	Budapest	www.ogyi.hu
Ireland	IMB	Irish Medicines Board	Dublin	www.imb.ie
Italy	AIFA	Agenzia Italiana del Farmaco	Rome	www.agenziafarmaco.it
Latvia	ZVA	State Agency of medicines	Riga	www.zva.gov.lv
Lithuania	n.a.	State Medicines Control Agency	Vilnius	www.vvkt.lt
Luxembourg	n.a.	Direction de la Santé Villa Louvigny Division de la Pharmacie et des Medicaments	Luxembourg	www.ms.etat.lu
Netherlands	CBG-MEB	College ter Beoordeling van Geneesmiddelen	Den Haag	www.cbg-meb.nl
Poland	n.a.	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	Warsaw	www.urpl.gov.pl
Portugal	INFARMED	Instituto Nacional da Farmácia e do Medicamento	Lisbon	www.infarmed.pt
Romania	ANM	National Medicines Agency	Bucharest	www.anm.ro
Slovakia	SUKL	State Institute for Drug Control	Bratislava	www.sukl.sk
Slovenia	JAZMP	Agencija za zdravila in medicinske pripmocke	Ljubljana	www.jazmp.si
Spain	AGEMED	Agencia Española de Medicamentos y Productos Sanitarios	Madrid	www.agemed.es
Sweden	MPA	Medical Products Agency	Uppsala	www.lakemedelsverket.se
United Kingdom	MHRA	Medicines and Healthcare products Regulatory Agency	London	www.mhra.gov.uk

Source: agencies' websites

A.9: Withdrawn products approved through the CP (1995-2010)

Name	approved	withdrawn	voluntary	commercial reasons	prior suspension
Acomplia	19.06.2006	05.12.2008	Yes	n.r.	13.11.2008
Allex	15.01.2001	10.03.2004	Yes	Yes	
Bextra	27.03.2003	27.03.2008	Yes	n.r.	October 2005
Cea-SCAN	04.10.1996	27.09.2005	Yes	Yes	
Clopidogrel BMS	16.07.2008	12.11.2009	Yes	Yes	
Cotronak	07.05.1999	10.03.2004	Yes	n.r.	
Daquiran	27.10.1997	02.02.2006	Yes	Yes	
Destara	25.06.2006	22.11.2005	n.r.	n.r.	
Duloxetine Boehringer	08.10.2008	26.05.2010	Yes	Yes	
Dynepo	18.03.2002	17.03.2009	Yes	Yes	
EchoGen	17.07.1998	22.01.2001	Yes	n.r.	
Ecokinase	29.08.1996	30.07.1999	Yes	n.r.	
Evotopin	15.04.1997	28.01.2000	Yes	n.r.	
Exubera	24.01.2006	26.09.2008	Yes	Yes	
Forcaltonin	11.01.1999	29.10.2008	Yes	Yes	17.12.2003
Fortovase	20.08.1998	27.06.2006	Yes	Yes	
Hepacare	04.08.2000	23.10.2002	Yes	Yes	
HumaSPECT	25.09.1998	24.09.2003	Yes	n.r.	
Indimacis 125	04.10.1996	30.09.1999	Yes	n.r.	
Infanrix HepB	30.07.1997	25.04.2005	Yes	Yes	
Infergen	01.02.1999	05.05.2006	Yes	Yes	
Irbesartan BMS	19.01.2007	11.11.2009	Yes	Yes	
Irbesartan Hydrochlorothiazide BMS	19.01.2007	11.11.2009	Yes	Yes	
Ixense	28.05.2001	28.09.2004	Yes	Yes	
Leeviax	09.07.2001	18.12.2007	Yes	Yes	
Monotard	07.10.2002	14.11.2006	Yes	Yes	
Nespo	08.06.2001	05.12.2008	Yes	Yes	
Neupopeg	22.08.2002	05.12.2008	Yes	n.r.	
Nyracta	11.07.2000	08.12.2004	Yes	n.r.	
Olansek	07.10.1996	17.03.2003	Yes	Yes	
Opulis	15.01.2001	10.03.2004	Yes	Yes	
Orlaam	01.07.1997	19.04.2001		n.r.	28.03.2001
Parareg	22.10.2004	05.12.2008	Yes	Yes	
Patrex	15.09.1998	15.09.2003	Yes	Yes	
Paxene	19.07.1999	26.11.2009	Yes	Yes	
Posaconazole SP	25.10.2005	20.11.2008	n.r.	n.r.	
Primavax	05.02.1998	27.07.2000	n.r.	n.r.	
Procomvax	07.05.1999	14.05.2009	n.r.	n.r.	
Protopy	28.02.2002	22.08.2008	Yes	Yes	
Pylori-Chek	15.06.1998	05.07.2000	Yes	Yes	

Name	approved	withdrawn	voluntary	commercial reasons	prior suspension
Quintanrix	17.02.2005	28.08.2008	Yes	Yes	
Quixidar	21.03.2002	11.03.2008	Yes	Yes	
Raptiva	20.09.2004	09.06.2009	Yes*	n.r.	19.02.2009
Rayzon	22.03.2002	24.06.2005	Yes*	n.r.	
RotaShield	07.05.1999	24.01.2001	Yes	n.r.	
Taluvian	28.05.2001	13.07.2004	yes	yes	
Tecnemab K1	05.09.1996	09.02.2000	yes	n.r.	
Tekturna	22.08.2007	02.09.2009	yes	yes	
Tenecteplase	23.02.2001	09.08.2008	yes	yes	
Theryttrex	07.01.2003	02.02.2006	yes	yes	
Tikosyn	29.11.1999	02.03.2004	yes	Yes	
Trazec nateglinide	03.04.2001	20.11.2008	yes	yes	
Triacelluvax	11.01.1999	28.02.2002	yes	Yes	
Trovan/Turvel	03.07.1998	20.03.2001	Yes	n.r.	10.08.1999 (renwewed september 2000)
Trovan IV	03.07.1998	20.03.2001	Yes	n.r.	10.08.1999 (renwewed september 2000)
Trudexa	01.09.2003	09.07.2009	Yes	Yes	
Turvel	08.07.1998	20.03.2001	Yes	n.r.	10.08.1999 (renwewed september 2000)
Turvel IV	03.07.1998	20.03.2001	Yes	n.r.	10.08.1999 (renwewed september 2000)
Ultratard	07.10.2002	14.11.2006	Yes	Yes	
Uprima	28.05.2001	28.05.2006	Yes	Yes	
Valdyn	27.03.2003	24.06.2005	Yes	Yes	
Velosulin	07.10.2002	30.01.2009	Yes	Yes	
Venvia	11.07.2000	08.12.2004	Yes	Yes	
Viraferon	09.03.2000	13.10.2008	Yes	Yes	
Vitrasert Implant	18.03.1997	02.04.2002	n.r.	n.r.	
Vitravene	29.07.1999	30.07.2002	Yes	Yes	
Xapit	22.03.2002	02.03.2004	Yes	Yes	
Zartra	18.09.1998	11.06.2002	Yes	Yes	
Zenapax	26.02.1999	10.06.2008	Yes	Yes	
Zimulti	19.06.2006	05.12.2008	Yes	n.r.	23.10.2008

Source: EMA

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