Towards a European FDA?

The review of European pharmaceuticals authorization*

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Introduction

This paper provides a descriptive account of changes in European market entry regulations for pharmaceuticals that were passed in early 2004. However, our interest goes beyond description, as we are also interested in the dynamics of EU policy making and integration more generally. Since the 1960s, EU pharmaceuticals regulation has moved from legal harmonization, with the expectation of mutual recognition, to a complicated system that combines national regulatory procedures and mutual recognition requirements with direct EU-level regulation. Even though pharmaceuticals regulation has a direct effect on questions of public health, the European Union has successfully wrested considerable control from member states. Furthermore, the EU pharmaceuticals agency, EMEA (established in 1995 and renamed *EMA* in the latest legislative reform), has become an evaluatory body with considerable authority and impact on regulatory decisions at the European level, even though nominally it is not a US-style independent regulatory agency (IRA). (Majone 1997b, Kelemen 1997)

Did EU pharmaceuticals policy enter a trajectory towards European-level authority that by now has evolved into some king of self-sustained dynamic process? Or are we observing the output of policy coalitions involving social and institutional interests, whose Europeanizing decisions may be as easily revoked as they may be advanced? Considering that pharmaceuticals policy has been frequently viewed as a strong case for positive integration and European-level regulation, answers to those questions may help us understand the dynamics of EU politics in more general terms as well.

In this paper, we investigate revisions to the system of European medicines authorization that were passed in early 2004. The 1993 legislation establishing the Centralized Procedure of European pharmaceuticals authorization as well as the European Medicines Evaluation Agency (EMEA) (Regulation 2309/93/EEC) provided for a report by the Commission on the experiences with this Regulation six years after the new procedures had come into effect. Following evaluatory reports by different actors, the most extensive one on behalf of the Commission prepared by Consulting firms Anderson and Cameron/McKennan (European Commission 2000, October), the Commission launched a broad “review” process in 2001 to revise the existing system, which ended in 2004 with the passage of several pieces of legislation (Regulation (EC) 726/2004 and Directives 2004/27/EC and 2004/28/EC). We are interested in the extent to which the 2004 reforms have expanded the Europeanization of pharmaceuticals regulation in terms of the harmonization of standards, a further shift of regulatory decision-making authority to the

European level, and an increase in the “European character” of the regulatory bodies, especially EMEA (now: EMA) and its Scientific Committee, CPMP (now:CHMP). In addition, we try to identify the social, political, and institutional actors whose interests are reflected in the various policy changes, in order to get a sense of whether the changes might have been due to specific demands or whether they seem to exhibit a largely irreversible dynamic.

In order to make our analysis manageable, we had to select a limited number of reform issues for analysis. First, we focus only on provisions dealing with medicines for human use, even though parts of the legislation deal with veterinary medicines. Second, we only analyze issues concerning the marketing approval of medicines, thereby ignoring equally important and somehow parallel questions related to post-marketing pharmacovigilance or advertising of medicines. Third, we selected issues that were important, according to the perception of the different actors involved in the policy-making process. Fourth, we analyze only those issues that directly or indirectly deal with the harmonization of national regulatory behavior and/or the localization of power for operational regulatory decision making.

The background and empirical basis of our research has been a thorough historical analysis of European regulation in this policy field from its beginning in the 1960s and, especially, the political process and legislative output of the Legislative Review 2001-2004. Our analyses are based on legal documents, protocols or results of institutional negotiations and debates, on primary and secondary material reflecting the position of concerned and/or affected groups and on interviews with representatives of the most important actors in this process, be they institutional participants at the European or national levels or “outside” actors trying to influence the policy-making process.

Before we present our analysis, we will provide some thoughts on the extent to which our close analysis of institutional changes might contribute to an answer of our general question concerning a trajectory towards regulatory Europeanization. To this end we try to develop indicators which should be able to tell whether a policy measure contributes to the Europeanization path or not. We then provide a brief overview of the history of European pharmaceuticals authorization rules and procedures, followed by a description of the different issues of the Legislative Review that we chose to analyze. A detailed discussion of regulatory changes, the interest articulation concerning the various issues and their resolution in terms of

our theoretical question ensues. We conclude with a discussion of what we have learned from our investigation of this one policy field.

Europeanization and its dynamics: What we are looking for

The empirical investigation in this paper focuses on two related questions. First, we want to know whether the 2001-2004 revision of EU medicines authorization resulted in a higher degree of European-level control of authorization processes and decisions. Second, we ask whether any increase in European-level control is part of a trend, or at least likely to persist, or whether it is the outcome of a unique bargaining situation that may change and lead to a return to increased member state control in the future.

The first question, concerning the level of policymaking, leads us to several more specific questions whose answers all contribute to an understanding of what is commonly called *Europeanization*:

(a) The constitutional (treaty) basis of the decision making process determines the degree to which lawmaking is dominated by intergovernmental or supranational processes. Specifically with respect to the revision of EU pharmaceuticals legislation, the question was whether Article 95 TEU (codecision process and qualified majority rule in the Council) or Article 308 TEU (consultation procedure and unanimity rule in the Council) should apply. Intergovernmental processes retain member state authority and control of policy-setting, if not implementation, whereas supranational policy-setting processes endow European Union institutions with varying degrees of decision-making power.

(b) The control of European-level actors over *implementing* decisions is an important aspect of the Europeanization of policy, as it determines that community rules are in fact executed in a uniform manner (or at least in a manner controlled by a EU-level authority). In fact, member state control over implementing decisions has in the past restricted the effectiveness of EU attempts of creating a single market for medicines (Feick 2002a).

(c) Administrative control over implementing policies and European-level making policy making authority are related to each other in a complex manner that interacts with the supranational/intergovernmental character of agencies. First, the degree to which national implementing bodies retain an autonomous role in the implementation process

influences the European character of the overall policy-making process. Second, the independence of European-level agencies and the degree to which their composition is controlled by European-level actors influences the degree to which decisions-making is Europeanized. If EU agencies are independent and staffing decisions are made through supranational processes, member state influence on implementing decisions tends to be limited. On the other hand, EU agencies that are independent of the Commission may be more susceptible to member state influence if member states can influence the selection of staff. Still, even member state appointed staff may develop "cosmopolitan" orientations that transcend member state interests (Majone 2002). As a result, the specific manner in which administrative autonomy interacts with supranational control of policy implementation cannot be determined a priori, but it is important, and possible, to detect the relationship empirically.

(d) At the output-side of the policy process, the question is whether, and which, standards have been further harmonized at the European level. Whereas community procedures to authorize individual products affect Europeanization with regard to specific products, harmonized standards and decision criteria set general rules to be followed in the entire community, provided they are adequately, or equivalently, applied at the national level. The question in terms of Europeanization is how much discretionary space at the national implementation level can be eliminated through legal harmonization at the European level.

While it is comparatively easy to describe the degree of Europeanization of a policy, at least in an inexact manner, it is much more difficult to deduce likely future trends from such a description. However, it is possible to use existing theories of integration and institutionalization to make a theoretically informed guess about the dynamics of substantive and institutional changes and the persistence of specific changes. Integration theories identify factors that are hypothesized to lead to integration and institution-building; several of those factors suggest dynamic processes. Factors that competing theories posit as driving forces of historical trends are particularly strong indicators. As we are using theoretical concepts to make guesses about the dynamics of European policy making, our ability to test those theories is very limited. Predictions about the future can be tested only in the future, of course. However, as theories of integration posit that certain factors are usually present in European policy making, our empirical results will reflect on the validity of those theories.

The classic example of a dynamic theory of European integration is Haas's neofunctionalism (Haas 2004). His central concept of spill-over is based on a hypothesis about the orientation of social actors: As European integration progresses, societal actors such as interest associations direct their objectives and interests towards the European level of decision making. In the most extreme characterization, Haas suggests collusion between the European Commission and societal actors, effectively bypassing member state governments.

We do not need to review the debate over neofunctionalism and intergovernmentalism (see e.g. (Wolf 1999), but it is worth noting that even theories decisively critical of Haas's approach agree that the orientation of societal actors may change as a result of integration and induce further integration. Moravcsik, for example, submits that governmental positions, the foundation of intergovernmental bargaining processes, may become more pro-European due to an increasing European orientation of society, which in turn may be the result of increasing European interdependence – indirectly an effect of EU policy making (Moravcsik 1998). As a result, the question of societal support or opposition to specific Europeanizing measures is an important indicator of the dynamics of European policy making[1]. If we can identify a general societal orientation towards European-level decision making, it is more likely that Europeanization will proceed in the future. If, however, support for Europeanizing measures is clearly split, we should be skeptical with our expectations. Similarly, if the focus of societal debate is explicitly on the Europeanization of decision making, with a clear split between those in favor and those opposed to European-level decision making authority, we should be skeptical that claims of Europeanizing trends are true. On the other hand, if the main debate centers around substantive policy choices but not on the level of decision making, it is well possible that Europeanization will continue in the future.

More recently, theories based on the concept of path dependence have replaced neofunctionalism as the dynamic integration theory of choice. Path dependence theorists such as Pierson have viewed European integration as the unintended consequence of negotiated agreements among member states (Pierson 1996). Once European Union institutions and decision-making processes have been established, there are positive returns for further European integration, resulting from a variety of mechanisms: more relevant and influential

[1] It should be noted that the question of general societal support for Europeanization, we refer not only to so-called societal interests – interests of actors that are not part of the governmental process – but also to political and administrative actors, whose political orientation can be "Europeanized" as well, with important consequences (Majone 2002, Wessels 1997).

actors may have a stake in further European integration; integration may change the economic conditions and dynamics so that further integration is economically functional, or European institutions, such as the European Court of Justice, obtain power resources that help them pursue further Europeanization.

Path dependency considerations suggest a number of indicators of Europeanizing trends. First, the question of European-level versus state-level policy making/implementation will be contested only when a new institutional system is established (at a so-called critical juncture). After that, the level of policy-making/implementation authority should not be one of the main points of contestation. Second, we should be able to observe actors whose support for EU-level regulatory authority can plausibly be the result of the establishment of such authority, and their support of European decision making secures the continuing existence of the institutional system. Third, European institutions themselves may be able to secure the continuing existence of the Europeanized system of policy-making because they are able to fulfill functions which might be difficult to relocate (an increasing return or lock-in mechanism), and/or because they have gained a position which allows them to successfully pursue their organizational self-interest. These indicators are neither necessary nor exhaustive, but they are the most likely observables that lend support to a path dependency account of European medicines authorization, which in turn would suggest a trend towards Europeanization.

The status quo before the Review: A historical overview

The history of EU pharmaceuticals regulation has been discussed more thoroughly elsewhere (see e.g.;Hart and Reich 1990, Deboyser 1991, Hancher 1996, Abraham and Lewis 2000, Feick 2002b). Here we provide only a brief overview of the changes that European medicines authorization went through since the 1960s. In addition, this section serves as a summary of the policy status quo before the legislative revision that is the main focus of our study.

The regulation of pharmaceuticals is a complex domain comprising very different regulatory sub-fields (Feick 2000). Practically every detail of the product itself, substantial parts of research, development, production, commercialization and medical utilization are regulated in one way or another in developed societies. However, only a small part of this regulatory spectrum has found its way into EU-level legislation, partly due to the ambiguous status of medicines regulation in EU law. On the one hand, medicinal products are goods for which the EC/EU-Treaty goal of a common or single market applies; on the other hand, their supply and

consumption are important ingredients of social security and health care systems, for which the national prerogative of public health protection largely applies (see TEC, Art. 30, formerly Art. 36), even after the extension of the EU's responsibilities to health matters in the Maastricht Treaty (see Art. 129). The tool of negative integration (Scharpf 1999, 2001), so potent in the hands of the Commission and the ECJ in other product and service areas, has been of very limited use in the pharmaceuticals sector.[2] Consensus or – since the extension of qualified-majority voting in the Council – quasi-consensus are needed in order to advance European legislation in these matters, thus largely protecting the principle of national voluntarism (Streeck 1995, 1997) in this sector.

Despite these regulatory obstacles, market entry for pharmaceuticals can be regarded as an exceptional subfield in which European regulation has advanced, over a period of thirty years, from legal harmonization targeted at national legislation and implementation to the centralization of regulatory implementation at the European level – at least for parts of the medicines' market. Thus, market entry regulation for pharmaceuticals can be read, at least partly, as a success story of Europeanization and as a strong case for discussing the question whether an irreversible regulatory trend or path has been opened, and if so, which factors are supporting this path, and whether they might be of such a general nature that other sectors could also be subject to their influence. On the other hand, if there are important factors counteracting Europeanization in such a comparatively successful (in terms of Europeanization) regulatory field, we should be very cautious about the prospects of further Europeanization in pharmaceuticals and other policy areas.

Legal harmonization and the failure of mutual recognition

Europeanization of pharmaceuticals policy has been pursued by two different strategies, the harmonization of national legislation (Europeanization at the national level) and procedural integration (Europeanization at the European level). While the first strategy requires that national authorities recognize one another's regulatory decisions, as they are based on harmonized law and expected equivalent implementation of that law, the second strategy requires the transfer of implementation power from the national to the European level.

[2] In public health matters the general policy responsibilities of the EC-level have been somewhat enlarged through the Maastricht Treaty, but with still very little effect for pharmaceuticals regulation at large.

The first attempts to harmonies European pharmaceuticals authorization was partly the result of the thalidomide crisis of the late 1950s and early 1960s and the American experience of preventing such a crisis in the US (see (Kirk 1999); (Silverman and Lee 1974: 94-98)) .The directive of 1965, 65/65/EEC, prescribed formal national marketing approval procedures in all EEC member states but left the precise legal transformation and implementation to the discretion of national legislatures and governments (Blasius and Cranz 1998: 66-67). This approach has been incrementally extended over the years, specifying regulatory requirements for authorization applicants as well as for assessing and evaluating national authorities – two directives in 1975, 75/318/EEC and 75/319/EEC,, were the next steps, followed by Commission communications, notes to applicants, etc..

Legal harmonization went far beyond minimal standards but, nevertheless, failed to trigger mutual recognition. In the mid-seventies and again in the 1980s the Commission tried unsuccessfully to convince member states to accept automatic mutual recognition without further national assessments and evaluations (Bel 1975: 507-508). In its June 1985 White Paper, the Commission expressed the hope that the European Court of Justice's (ECJ) 1978 Cassis-Dijon ruling would force national governments to accept mutual recognition of national controls of pharmaceuticals (Commission of the European Communities 1985, June 14 June 14: no 65). This hope was short-lived: For policy fields of special complexity, such as pharmaceuticals control, the European Court of Justice was not willing to extent mutual recognition requirements. "[A]lthough the Court is prepared to narrow the scope for residual national measures under Article 36 …, it is unlikely to require automatic mutual recognition of product licenses given the present stage of harmonization of national licensing requirements" (Hancher 1991: 831). Incremental advances, such as further legal harmonization and the improvement of "coordination procedures," were seen as the more "realistic perspective" (Glaeske 1988: 40-41).

Non-binding institutional and procedural supports

Besides further legal harmonization, the failure of mutual recognition led to the introduction of institutional supports that would encourage mutual recognition without actually requiring it. Between 1975 and 1983 several pseudo-European approval procedures were introduced on an optional basis, providing for enhanced communication and cooperation between national authorities without interfering in their final decisions – the so-called Community Procedure, introduced in 1975, was modified in 1983 and renamed Multi-State Procedure.) A scientific committee (the Committee for Proprietary Medicinal Products, CPMP) was created and located at

the Commission level in 1983; its members were representatives of national authorities, which could be consulted for assessments and evaluations.

The so-called Concertation Procedure of 1987 was another major evolutionary step, with three important innovations: (a) the procedurally consequential separation of medicinal products into less or more innovative ones, the *Concertation Procedure* being reserved for the latter group (and required for the most innovative ones); (b) the obligation to consult the CPMP before a decision was taken at the national level, and (partly as a result of this) (c) an increase in importance of the CPMP body. Nevertheless, the final approval decision was with the national authorities.

While the Community/Multi-State Procedure failed to achieve the goal of mutual recognition, the Concertation Procedure was comparatively more successful (European Commission 2000; Vos 1999; Sauer 1990) . There are two reasons for this: First, the restriction of the Concertation procedure to the more (and in particular the most) innovative products made it easier for national authorities to achieve common assessments and evaluations, as such products did not yet have national regulatory records. Second, the procedural requirement that the CPMP issue its opinion before national authorities could decide on theirs increased the chances that national decisions conformed to the CPMP model. However, while the Concertation Procedure resulted more often in similar national assessments, there were still national differences and efficiency losses as national authorities insisted on the conduct of national assessments in addition to the European assessment (see (Vos 1999: 206-211); (Macarthur 1993: 25-28); (European Commission 2000)).

The 1990s: Procedural Europeanization

In the early 1990s, the European Union introduced fundamental institutional changes by establishing two new authorization procedures that would, to a large extent, replace the existing procedures and create the three-layered system of pharmaceuticals authorization that still exists today (see Table 1). A 1993 Regulation[3] introduced the so-called Centralized Procedure (CP, in effect since January 1995), to be mandatory for biotechnology-based pharmaceuticals and optional for other innovative medicines. Hence, the CP replaced the older Concertation procedure. Similarly to the Concertation Procedure, the CP was based on CPMP assessments, but the final regulatory decision was now made by the Commission, subject to the regulatory comitology procedure, and not by the member state authorities. Member state authorities, however, were included in the decision-making process through their representation in CPMP and their important

[3] Council Regulation (EEC) No. 2309/93, OJ L 214, 24.8.1993.

participation in providing the basic assessments for CPMP through a rapporteur/co-rapporteur system.

The second new authorization procedure was introduced by a 1993 Directive[4] and was applicable to all medicines introduced in more than one member state for which the Centralized Procedure was not obligatory. Called the Mutual Recognition Procedure (MRP), it built on the Multi-State Procedure, which it replaced. It introduced two main innovations: First, it restricted the grounds on which member states could reject another member state's assessment (only potential risk to public health were acceptable grounds, though not sufficiently operationalised) and, second, it provided for mandatory EU-level arbitration if a member state rejected another member state's assessment. But, in this procedure, the final marketing approval rests with the national authorities.

Whereas the Centralized Procedure has been commonly viewed as a success, both in terms of European integration and regulatory efficiency, the Mutual Recognition Procedure has failed to guaranty quasi-automatic mutual recognition. Although the MRP tried to add teeth to mutual recognition by requiring binding EU-level arbitration, companies often used the exit-option of avoiding EU-level involvement by withdrawing the marketing application from the objecting member state(s). These experiences correspond to Majone's conclusion that European "centralization of regulatory authority is the only way of ... preventing the local regulation ... from becoming a trade barrier," (Majone 1996:279-280) – and of overruling distrust among national regulators (Majone 1998).

The institutional changes of the 1990s included the establishment of a European agency, the European Agency for the Evaluation of Medicinal Products (EMEA), in which CPMP and other scientific committees (for example for veterinary medicines) have been located. It coordinates the assessment and evaluation of applications under the Centralized Procedure – in the Mutual Recognition Procedure it oversees binding arbitration – and formulates an opinion that forms the basis of a final regulatory decision by the Commission after going through a regulatory comitology procedure (Art. 10, Art. 72 and 73 of Council Regulation (EEC) No 2309/93; see also Feick 2002b).The emergence of European-level agencies, with a few exceptions mainly in 1990s ((Everson 1995; Kreher 1996; Everson 1999), can be seen as an attempt to de-politicize and to professionalize regulatory decision-making (see e.g. (Majone 1997a; Thatcher 2002; Krapohl

[4] Directive 93/39/EEC. A companion Directive, 93/40/EEC, introduced a similar procedure for veterinary medicines. The procedures went into effect in 1995. In 1998, the Mutual Recognition Procedure became mandatory for all medicines not subject to the CP and introduced in more than one member state.

2004). The Europeanization of implementation has also been introduced as a means of rationalizing regulatory decision-making in order to reduce the regulatory costs for industry ((Deboyser 1991 Feick 2005, January)). In general, the new EU agencies have considerably less authority than US-type independent regulatory agencies, as their functions are mainly confined to information gathering, monitoring and supporting decision-making at Commission or Council level. Nevertheless, the impact of EMEA/CPMP goes much beyond providing the Commission with expert information, as its professional opinion constitutes a blueprint for the Commission's final regulatory decision. [5]

Although the attention of this study focuses on the new European procedures, the purely national procedures are by no means a residual category but represent still the largest part of applications. Furthermore, in the Mutual Recognition Procedure approvals are still granted by national authorities, but there are clear procedural obligations for concerned national authorities to cooperate even though a formalized coordination infrastructure at the European level has not been installed. Still, the MRP contains a Europeanized phase that allows for binding arbitration at the European level in cases of disagreement among national authorities. As mentioned above, applying companies had an exit option by withdrawing their application from dissenting countries. The fundamental institutional innovation of 1993/1995 has been the introduction of the Centralized Procedure. For the obligatory medicinal products it deprives pharmaceutical companies of the chance to strategically select their target countries and, as a procedure - obligatorily taken (Part A) or voluntarily chosen (Part B) – removes regulatory autonomy from the national authorities. Regulatory decisions are taken by European institutions and are valid for the entire EU. But as a kind of necessary compensation, without which the legislation would have had no chance to pass in 1993, national regulatory authorities are closely integrated into the assessment, evaluation and decision-making process which, nevertheless, is a European one.

This regulatory situation characterized the status quo after 1995, with the MRP in full operation since 1998. The 1993 Regulation stipulated that an evaluation of the authorization system should be undertaken by the Commission in 2001 in order to introduce proposals for legislative improvements. This evaluation process became known as the Legislative Review and eventually developed into a full-fledged revision of the authorization system, gaining additional urgency by

[5] The Commission decision is subject to a regulatory comitology procedure, but so far all final decisions have been according to the Commission drafts, and the comitology committee has never referred a Commission decision to the Council of Ministers.

the fact that 10 new member states were to join the EU in Mai 2004, whose regulatory integration would pose problems without preceding reforms. In the end, the legislative revision, encompassing new issues as varied as prescription drug advertising and data protection, took about three years and was eventually concluded by the end of March 31, 2004 – just one month before the new member states joined the EU.

Table 1: European authorization system since 1995/1998

Procedure	Legal Basis	Scope
Centralized Procedure: single Community authorization	Regulation EEC No. 2309/93	Mandatory for biotechnical medicines (Part A of Regulation Annex) and optional for innovative medicines (Part B of Regulation Annex).
Mutual-Recognition Procedure: "harmonized" national authorizations	Directive 93/39/EEC; Harmonized law	Mandatory for all medicines introduced in more than one MS and for which the CP is not mandatory.
National procedure: national authorization	Harmonized MS law.	Mandatory for all medicines not authorized by the CP and introduced only in one MS.

The "Review" of European medicines authorization and legislative reform

The Commission launched the so-called *Review* of European medicines authorization in 1999, by awarding a contract for a report on the existing authorization system to the consulting firms CMS Cameron McKenna and Andersen Consulting (CMS Cameron McKenna and Andersen Consulting 2000). The consultants based their report on questionnaires distributed to marketing authorization holders and consultation with companies, regulatory authorities, governmental

ministries, and patient and professional associations[6]. Although the authors of the report noted that it was difficult to find a general consensus among consultees about questions of detail, they offered a number of general conclusions:

(1) The Centralized Procedure received a generally positive evaluation, and several companies and member state authorities supported an extension of the procedure to additional products (12). However, there were complaints by companies about the efficiency of the decision making process after the CPMP/EMEA has submitted its draft decision to the Commission for a final decision. In addition, there were concerns that enlargement required a review of CPMP procedures and institutional structure (15).

(2) The Decentralized Procedure was in for greater criticism: the report concluded that "[t]here is no true mutual recognition" as member states repeated assessment and authorization processes that they were supposed to recognize. The report specifically pointed to the "risk to public health" argument, whose unclear delineation allowed member states to raise points that were only remotely related to public health. Companies furthermore complained about the fact that arbitration procedures prevented the introduction of medicines in states in which they had been approved before the arbitration process had concluded.

(3) The report highlighted that innovative companies and several national authorities perceived a need to harmonize protection periods for research data, and to extend those periods for research on new indications, in order to improve access to medicines and innovation in the pharmaceutical industry (19).

(4) In view of the 2004 EU enlargement, the report argued that the internal structure of the CPMP had to be reformed. In particular, the report argues that, "at the very least," the size of national representation in the Committee had to be reduced (38). Also, several regulators were in favor of basing membership on expertise rather than national quotas (38).

[6] According to the report, the following actors were included in the consultation: national authorities (including those in EU accession countries), the head and "key personnel" of EMEA, the chairmen of the EMEA scientific committees, including CPMP, and the Mutual Recognition Facilitation Groups, marketing authorization holders who had used the CP and MRP, pharmaceutical industry associations, national ministries for health, social services, finances, and agriculture (also in accession countries), national professional associations representing physicians, dentists, pharmacists and veterinarians, patient associations, and national consumer associations.

It is interesting to note that the report does not make any recommendations on a number of issues that became highly contentious in the legislative process, for example the limited permission of advertising for prescription drugs.

After further consultation in the Joint Human and Veterinary Pharmaceutical Committees, a public hearing, and the circulation of discussion documents, the Commission adopted its proposals for a new regulation and two new directives (one for veterinarian medicines) on July 18, 2001. The proposals suggested an extension of the CP's scope: mandatory for all medicines with new active substances and optional for therapeutic innovations and generics of centrally approved medicines; also, they proposed abbreviated deadlines for member states to comment on proposed authorizations in the CP. The Commission also proposed to reduce the size of the CPMP (and the CVMP, its veterinary counterpart) to one delegate per member state (down from two) and added five additional members that were to be chosen for scientific expertise; EMEA's management board would have been changed from a body mainly representing the member states to a body with equal representation for Council, Commission, and EP, and additional representations of patients and industry. In addition, the Commission proposals defined a harmonized 10-year period of data protection, with a one-year extension for new therapeutic indications. With respect to the DP/MRP, the Commission proposals made mutual recognition mandatory for all medicines to be authorized in more than one member state; they reduced the time for member states to forward existing marketing approvals to other MS and to grant the final marketing authorization; mutual recognition could be denied only for "serious potential risk to public health," which tightened the existing language a little bit. The informal Mutual Recognition Facilitation Group was proposed to be formalized as a Coordination Group, to provide consultation in cases of conflict between member states over mutual recognition. Although the Commission proposal did not make arbitration mandatory, it proposed to shorten the time line within which arbitration takes place.

Between February and October 2002, the proposals were debated in various EP committees; the main debate on the legislation occurred in the Committee for Environment, Public Health and Food Safety (ENVI)[7]; the proposals attracted more than 600 amendments in the committee. The Parliament's first reading took place on October 23, 2002, increasing the number of amendments to around 1000. The Council did not decide on a common position until September 2003 – the main part of the common position had been agreed upon in the Council's Working Party and in

[7] Rapporteurs were Rosemarie Müller (PES, Germany) for the Regulation and Françoise Grossetête (EEP-ED, France) for the Directives.

Coreper, but two important issues needed involvement of the Council of Ministers in June 2003 –, creating time pressure to pass the legislation relatively quickly before the accession of ten additional members of the European Union. Using informal consultation between the EP, the Council (Working Party) and the Commission before the second reading of the Parliament, the laws could be passed by March 31, 2004.

Space does not allow for a detailed analysis of the decision making process in this study. Instead, we focus on the policy outcomes and the political cleavages involved. Since the legislative proposals on EU medicines authorization were so complex (the number of parliamentary amendments serves as a good indicator), we also had to focus on specific issues and ignore others. First of all, the legislation dealt with the authorization of both human and veterinary medicines; we deal exclusively with provisions concerning human medicines. Furthermore, we focus on issues that we consider (a) particularly important and (b) indicators for the degree of Europeanization of pharmaceuticals authorization. This means that we ignore some issues that turned out to be important from the perspective of several actors involved. For example, following industry interests the Commission proposed to permit direct patient information by the industry about certain groups of prescription drugs; this issue raised a storm of lobbying activities by public health and other non-industry groups who were strictly opposed to any such proposal, which they, like most member states, interpreted as a permit to advertise prescription drugs directly to patients. Since this issue does not provide much insight into the question of Europeanization, we do not analyze it here.

Table 2 introduces the issues under consideration and specifies how they relate to questions of European-level v. member state control of policy making and implementation. The constitutional basis for the regulation was not a controversial issue before the legislation reached the Council. Under Article 95 TEC, the original basis proposed by the Commission, the legislation was decided under codecision and with qualified majority rule in the Council. Several member states, however, viewed Article 308 TEC as the appropriate basis. Under this proposal, the Parliament would have been less influential (consultation), and the Council decision would have to be made unanimously, increasing the veto power of individual member states.

The scope of the Centralized Procedure is importantly related to the degree of European control over pharmaceuticals authorization as it is the only “real” European procedure and has been the most successful European authorization procedure so far. A related issue is the possible

introduction of tighter deadlines within the CP, which would make the procedure more attractive for medicines that do not fall under its mandatory scope but for which the CP is optional.

Regarding the Mutual Recognition/Decentralized Procedures[8], there were several issues that most likely influence the viability and acceptance of the procedures. The first issue deals with the sequencing of the decisions of the Reference Member State (RMS), which prepares the reference assessment, and the Concerned Member State (CMS), which has to decide whether to recognize the RMS's assessment. Whereas under the old MRP, the RMS decided before the CMS(s), proposals for simultaneous decision making were introduced, in order to improve the communication between the two states. A related issue dealt with the question whether arbitration should remain optional, with companies being able to withdraw their application from CMS(s) that raised objections to mutual recognition. One proposal was to combine mandatory arbitration with a provisional authorization of contested medicines in states in which the authorities were willing to grant an authorization.

Decisions related to the composition of the EMEA management board and Scientific Committees (in our case: CPMP) were to determine the degree to which those bodies developed a European identity. In general, the conflicts surrounding these issues dealt with the question whether those bodies should be representative of the various member state authorities, or whether they should be decidedly European bodies, with members chosen for their expertise and not necessarily appointed by national authorities. A stronger European identity of EMEA/CPMP would decrease national influence and increase supranational control over implementing bodies.

Two further issues that we investigate deal with the harmonization of standards. First, the definition of "serious public health concern" is essential to the functioning of the MRP/DP, as it is the reason for which CMS can deny mutual recognition of regulatory assessments. A uniform European definition of this term therefore might prevent frivolous use of this term. Second, the harmonization of data protection is important with respect of the protection of innovating companies, on the one hand, and for the establishment of a European market for generics, on the other. This issue gained particular importance with the prospect of the 2004 EU expansion, as

[8] The *Mutual Recognition Procedure* is applied when a product has already been approved in one or more Member States and approval is sought in one or more additional Member States. In the equivalent *Decentralised Procedure* the product has not yet received authorisation in any Member State. Both sub-procedures belong to the same category because the decision-making processes are fundamentally identical.

several of the accession states had comparatively short or no periods of scientific data protection, adding to the differences already existing among the member states.

Policy outcomes, cleavages, and tentative conclusions

In this section, we discuss the policy outcomes of the legislative process, again focusing on the issues introduced in the previous chapter. In addition, we summarize the political cleavages associated with an issue and use these observations to draw first, tentative conclusions about the degree of Europeanization and the possible future of the EU system of medicines authorization. Table 3 provides an overview of our conclusions.

The Treaty basis: Co-Decision and Qualified Majority or Consultation and Unanimity?

The Commission proposed Art. 95 TEC as legal basis for the legislative decision making process, which required the parliamentary co-decision described in Art. 251 TEC; not surprisingly, the European Parliament endorsed this position. Despite strong opposition from some member states (particularly Germany, followed by the UK, Denmark, and a few other member states), the Commission prevailed, for several reasons. First, it benefited from the first-mover advantage. The only way for the Council to oppose Article 95 would have been to formulate a common position (Art. 251 (2) TEC) which would then go back to the EP for further debate and eventual negotiation with the Council. Since there was neither consensus, nor even a qualified majority in the Council (Working Party) for an insistence on Art. 308, there was no chance to overrule the Commission (and the EP). Thus, given the high hurdles to change the Commission's proposal, the Commission as first mover, or agenda-setter, was in a strong position from the very beginning, the opponents in a weak one. Second, time pressure before the scheduled enlargement hampered the opposing member states. The necessity to reform at least some institutional (EMEA/CPMP) and substantive (especially data protection) matters before enlargement outweighed more philosophical differences over the treaty basis to be used. Germany and the UK, the two main opponents to Article 95, are among the largest producers of innovative medicines, after all, and therefore had a clear interest in a functioning European system before accession states increased the ranks of countries with less-innovative pharmaceutical industries or none at all.

The success of the Commission's proposal for the legal basis of the reform strengthened Europeanization in two respects:

(a) The **decision rule in the Council**. Unanimity was not required in the Council; single MSs lost their veto power. Thus, a higher threshold was established for the Council to refute Commission proposals. As a result of this and other institutional prerequisites, the Commission, a supranational institution, gained stronger agenda-setting powers.

(b) **Participatory rights / actor inclusion**. The co-decision procedure gave the EP, the other more supranationally oriented institution, an important role in the legislative process, further strengthening the European perspective.

Legal harmonization

The past implementation of the MRP/DP had been hampered by the existence of diverging national standards such as those regarding the definition of public health risk, nationally varying Summaries of Product Characteristics (SmPCs), or the related content of package leaflets[9]. Hence, questions of legal harmonization obtained an importance that went beyond the search for uniform standards; they were of fundamental relevance for the improvement of the decentralized European authorization system.

Data protection

The debates on data protection pitted member states with no or little data protection, together with the generics industry, against member states with strong innovative pharmaceutical industries, who were interested in monopoly returns on their research investment that were not diluted by generics competition. In addition, member states had an interest in containing health care costs by promoting the consumption of generics, creating a dilemma for those member states with a strong innovative industry. The interests in the Council Working Party were rather diverse, and in the end the Council of Ministers had to decide this issue. At times the array of different proposals by the different institutional actors made for different protection periods (depending on the approval procedure utilized and the type of medicinal product processed) became very confusing. Practically at the last moment, before the second reading of the directive in the EP, Council, EP, and Commission reached a compromise on the so-called 8+2+1 formula: Ten years of data protection plus one additional year for additional indications. After 8 years, generics producers were permitted to prepare approval applications based on

[9] We did not find any evidence that divergent national periods of data protection (application data utilized by the originator) were hampering the MRP; however, it is clear that these national differences imposed restrictions on the single market in medicines, as they led to divergent markets in generics.

existing scientific data, even though they were not allowed to market their products before the ten- (or even-) year period had passed (so-called BOLAR provision). The compromise satisfied the innovative industry, which had been confronted with much less protection in some countries, but also gave something to the generic companies – and to those caring for cost-containment in the national health care systems.

The harmonization of data protection is a remarkable outcome as it constitutes a clear success in terms of Europeanization of rules. There are several reasons for this, mainly related to the heterogeneity of actor interests: First, we can identify a coalition of member states with strong innovative industries, the innovative industry, and the Commission, in favor of comparatively long protection periods. The main opposition to a high level of data protection was voiced in Parliament, by the generics industry, and by some member states, including the accession states, with no or a little innovative industry and an interest in the containment of health care costs through. But even member states with an innovative industry had to consider the interests of its generics producers and health care institutions. In the end the Parliament was instrumental in proposing the compromise solution. Second, the harmonization of data protection has a comparatively strong functional justification; as mentioned before, unequal periods of data protection constituted an impediment for the single market in generics. As a result, even though it would have preferred a lower level of data protection, the generics producers could not be completely against the harmonization as such.

Potential risk to public health

Although this was an important topic – the unclear definition of public health risk arguably contributed to the problems encountered with the MRP, and the problem was mentioned by the Cameron McKenna/Andersen report – the outcome is somewhat ambiguous, and the question created very little controversy. A precise definition was not included in the legislative package and will have to be specified in a Commission guideline (Art. 29, 2. of Directive 2004/27/EC; a proposal was published in February of 2005). It is unclear, whether the definition proposed by the Commission, and its implementation, will in fact strengthen mutual recognition, or whether individual member states will find additional ways to deny it. A similar question is raised by the definition of generic medicines claiming to be “essentially similar” to already authorized products. The effect of such definitions will partly depend on their interplay with institutional factors, such as mandatory arbitration and provisional authorization during arbitration, and their

interpretation by the ECJ (see, for example, the January 20, 2005, ruling in SmithKline Beecham v. Lægemiddelstyrelsen, in which the Court made use of a comparatively broad definition of essential similarity).

Institutional and procedural changes in the context of the European approval procedures

Some of the regulatory outcomes were purely symbolic - they changed the names attached to organizations and procedures. EMEA became EMA, CPMP became CHPM, and the Mutual Recognition Facilitation Group became the Coordination Group. Not surprisingly, our focus is on the more substantive institutional and procedural changes, even though the symbolic changes may reflect some of those substantive changes.

The Scope of the Centralized Procedure

The question to which extent the Central Procedure should be applied, and even be mandatory, to additional categories of medicines was one of the most controversial issues of the legislative reform that at Council level had to be decided by the Council of Ministers. On the one side, the EP, supported mainly by France, was in favor of an extension of the CP's scope, as proposed by the Commission (the EP even went further than the Commission). On the other side, the majority of member states were opposed to a weakening of national or nationally-based (MRP/DP) procedures – some even proposing the free choice between CP and MRP/DP.[10] Since a restriction of the CP's mandatory scope was not realistic, the political aim of the nationally oriented governments was to prevent a substantial extension of the scope. The EP's proposal to require the CP for all new active substances would have been such a substantial extension; as a compromise (and partial success for the "nationalists"), the scope was enlarged only in regard to new active substances for four medical indications.

The significance of the scope extension, in terms of Europeanization of authorization procedures, is under dispute. The nationally oriented governments maintain that the extension did not result in a significant shift to the European level, as medicines for the specified

[10] In fact, large parts of industry supported such a completely free choice between procedures, as this would have given applicants or pharmaceutical entrepreneurs more "flexibility," a value in itself for industry. The reason why industry supported the Commissions proposal of scope-extension was that it expected something in exchange from the Commission: the right of direct-to-patient "information" (which failed) and more, as well as harmonized, data protection.

indications had already predominantly been authorized through the CP. On the other hand, several Europe-oriented actors point to the fact that the final compromise stipulates that the scope will be extended again in four years' time, then including also new active substances for "the treatment of auto-immune diseases and other immune dysfunctions and viral diseases." (Directive 2004/27/EC, (8)). This would, in their view, finally include practically almost all new active substances which had not been included obligatorily, so far.

In the short term the supporters of Europeanization may seem to have lost their case, but in the longer term they may have won it. This evaluation is shared by supporters of continuing national authority[11]. While the defenders of national autonomy try to resist Europeanization in the name of national public health protection and political responsibility for it, they easily admit that the general thrust is towards increased Europeanization. Their main goal is to slow down this process ("step by step"-approach) and to assure an institutional configuration that would leave the national level participation rights in the assessment and authorization processes ("network-approach" versus institutional centralization/European FDA). Some representatives of national authorities freely admit that they might not be able to prevent a European FDA – but they may delay it for another 20 or 30 years.

Centralized Procedure: Evaluation and approval deadlines

The question here was whether deadlines should be shortened to increase regulatory efficiency to the advantage of pharmaceutical companies. The proposal of the Commission mainly reduced the evaluation times of the rapporteurs and co-rapporteurs, who prepare the CPMP draft assessments together with their respective member state authorities. Shorter deadlines would have substantially reduced the assessment and evaluation work of national regulatory authorities in preparation of CPMP decisions. Other proposals suggested shorter decision processes at EMEA level after the Scientific Committee's (CPMP) assessment, and then later at the Commission stage. While there was a general sense that regulatory efficiency should be raised, most national governments strongly opposed a reduction of assessment and evaluation periods at the national level. The Council, finally, succeeded in restoring the original deadlines for assessments and evaluations at the MS level, while obliging the Commission to accelerate its purely administrative procedures.

[11] This point was shared in interviews with representatives of several national authorizing bodies.

The conflict over evaluation and approval deadlines reveals interesting lines of conflict. On the one hand, there is a conflict between speed and efficiency of procedures and the level of public health protection. Several member state authorities, public health groups, industry critics, and some MEPs opposed the acceleration of assessment and evaluation processes, as they may lead to less thorough assessments; on the other hand, potential applicants for authorizations were interested in a speedy process, which was usually justified by increased-access arguments. On the other hand, there was a conflict between member states and Commission: While the Commission tried to speed up the process by forcing member states to accept shorter deadlines, the member states restored those deadlines and forced the Commission to accept shorter deadlines for its own decisions.

While it is obvious that this was a defeat of the Commission against national governments and authorities, it is not so clear whether the substantive outcome fostered or inhibited Europeanization. Certainly, national authorities have defended their regulatory space. On the other hand, by strengthening of the assessment and evaluation components of European authorization procedures, which are mainly performed at the national level, the member states may also have strengthened the credibility of European authorization processes.

MRP/DP: Obligatory binding arbitration

The most important issue in the reform of the MRP/DP has been the question whether binding arbitration should be obligatory if a Concerned Member State (CMS) raises objections to a Reference Member State's (RMS) assessment and authorization decision. Although previous legislation had provided for binding arbitration, applicants could avoid the lengthy process by withdrawing their application in the dissenting member state. The legislative reforms have closed this loophole with a combination of provisions: First, disagreements concerning assessments will "immediately" be reported to EMEA "with a view to application of the procedure under articles 30 …" (Art. 29, 4. of Directive 2004/27/EC) which signifies the obligation to enter binding arbitration. Second, and very important, withdrawal of an application does not prevent the arbitration procedure. Third, member states who accept the RMS's decision may provisionally authorize the medicinal product for marketing, pending the arbitration outcome. (Art. 29, 6. of Directive 2004/27/EC) The third point made binding arbitration more palatable for industry and national authorities, the latter having preferred the status quo.

As it stands, the new provision seems to strengthen the European level compared to the member states. However, the impact of the new provisions is uncertain until it is implemented. For example, it is not clear what happens if mutual arbitration results in a denial of authorization, even though some MS provisionally authorized the product. Theoretically, the product would lose its authorization also in those states that had originally permitted it. Would this be enforceable? Would applicants be able to pursue liability claims against the Commission or member states for allowing them to market their products, only to withdraw the approval after arbitration? Or was the rule written under the assumption that, practically, arbitration would always result in a decision in favor of the RMS's and the mutually recognizing CMS's position? (The problem may sound more dramatic than it actually is: Often, the subject of arbitration is not the general approval decision, but rather details of the approval as contained in the Summaries of Product Characteristics (SmPC).)

MRP/DP: Change in procedural sequence

This seems to be a minor change but one with possibly important future effects. While in the past the MRP foresaw that in the first phase the RMS had to issue its regulatory decision before the CMSs started their consideration – whether to accept the authorization or raise serious concerns on public health grounds – the new legal text introduces a different sequencing of the regulatory decision process: The RMS will inform the CMSs of its evaluatory position before arriving at a final regulatory decision, thus providing room for discussion with CMSs and allowing for mutual adjustments among RMS and CMSs. This increases the likelihood that the RMS's final conclusions will be mutually recognized.

Together with the introduction of obligatory binding arbitration, the change of procedural sequence can be regarded as strengthening the European aspect of a procedure that is still nationally based. The threat of binding arbitration may induce member states to use the opportunity of closer cooperation and voluntary mutual adjustment provided by the new sequence of decision making.

MRP/DP: Deadlines for evaluations and regulatory decision-making

Comparable to the deadline provision in the CP, the Commission proposed a reduction of the time Concerned Member States should have for commenting on the RMS's assessment and evaluation, and for arriving at their own position, be it mutual recognition or raising public health

concerns. In the past, the CMSs often replicated the evaluation assessment procedures already conducted by the RMS's regulatory authority, which led to delays in the approval process. Tighter deadlines could have helped avoid this problem. As in the CP many national governments opposed the reduction of the time resources available to their regulatory authorities with the argument that it was, in the end, national governments and authorities that were accountable for national authorizations.

Institutional-organizational modifications: EMEA and MRFG

EMEA / CPMP

The questions surrounding the organizational reform of EMEA (now: EMA) and CPMP (now: CHMP) have been very conflictual, with the main lines of conflict drawn between Commission/European Parliament and most member states. Societal interests were almost not concerned about the issue; the few statements that one finds tended to support the Commission/Parliament stance. The Commission's proposals concerning the composition and selection of the EMEA Management Board and the CPMP not only tried to take enlargement into account, by reducing the number of representatives of each member states, they also tried to reduce the influence of national governments on the selection of members. The Parliament went even further, proposing that EMEA should attain the same structure as the newly created European Food Safety Agency (EFSA), which would have reduced national influence even more. The final compromise solution largely maintained national government representation and role in the selection of members. One concession to the Commission was that the CPMP could co-opt five additional members on the basis of expertise, to complement areas of possibly missing expertise among the 25 representatives chosen by their respective national authorities. In addition, supranational expertise was strengthened by further developing the system of Working Groups and Scientific Panels at EMEA level. The proposal by the Commission and the EP, to include patient/consumer representatives on EMEA's supervisory Management Board, was undisputed, but not the proposal of the Commission to include industry representation. The latter was supported only by France, which employed the same arrangement in its regulatory Agency.

On the whole, the member states have been able to maintain their institutional position and influence within the organizational structure of the European authorization system. However, there have also been incremental changes towards a stronger emphasis on expertise, in

contrast to member state representation, in the EMEA. Even though these changes are comparatively small, some members of national authorities see them as symbolic of the erosion of their own monopoly on scientific expertise. Adding to this is the strengthening of scientific panels and working groups at EMEA-level, mainly with the task of complementing and helping the CPMP (CHMP).

MRFG – Coordination Group

The Mutual Recognition Facilitation Group had been an informal group established and maintained by the heads of national authorities in order to facilitate the introduction and performance of the MRP/DP. This Group has been officially recognized by the new legislation, which renames it “Coordination Group” and provides it with a secretariat at EMA. This institutional change was uncontroversial and can be regarded as supporting the Europeanizing elements of the MRP/DP.

Discussion and Conclusion

With this paper, we want to learn more about the direction that European pharmaceuticals policy has taken and might take in the future: Did the recent legislative reforms increase the importance and impact of the European level, both in terms of regulatory decisions taken at the European and the national levels and in terms of the character of the European institutions involved? And if so, is the increased European importance likely to last? Is it part of a trend?

Regarding the first question, we can diagnose an incremental increase in Europeanization, but it was a very limited increase even though some changes might produce important effects in the future (e.g. obligatory binding arbitration in the MRP/DP). Member states were rather successful in preventing too much transfer of authority to the supranational level: They largely maintained control over the appointment of EMEA and CPMP members; consented – for the time being - only to a limited extension of the CP’s scope; and resisted an acceleration of the national components (assessments and evaluations) of European authorization procedures. On the other hand, member states had to make concessions: Codecision and qualified majority rule seem to be firmly established for pharmaceuticals approval and pharmacovigilance regulation; and the changes in the Mutual Recognition Procedure/ Decentralized Procedure, with obligatory binding arbitration and the option of provisional authorizations, may in fact force them to recognize authorization decisions of other member states. And in the case of the CP’s scope,

member states agreed to further extensions within four years. In addition, European agencies such as EMEA, being part of and coordinating networks of national regulatory authorities, may lead to the development of “cosmopolitan” bureaucrats with a European orientation, thus Europeanizing the behavioral orientation of national agencies in the long run (Majone 2002; Wessels 1997; interviews with national regulators).

As to the future development of European pharmaceuticals authorization, our results or guesses can only be tentative. We found no issues in which decision making followed a clear functional dynamic; on the other hand, virtually all issues were characterized by conflicts between different actors, often pitting European-level institutions against member states. The harmonization of regulatory data protection was the only issue that may have been partially influenced by functional requirements, as different periods of data protection caused an impediment to the single market in generics. But even in regard to this issue, we could identify clear conflicts between different industry and member state interests that drove the final outcome.

Depending on the issue, political cleavages either separated member states from European institutions (particularly in issues regarding regulatory authorities), or they separated different member states, with societal interests, Commission and Parliament on different sides (for example, data protection or the acceleration of assessment and evaluation). As a result, the specific constellation of interests seems to depend on the specific issue. But as long as the constellation of the different interests involved remains fairly stable and is reflected in the diverse and complex procedural configuration, we should expect the European authorization system to remain be fairly stable as well.

On the other hand, if there should be a change in the relative strength of different social, economic, and political interests, for example a stronger role of public health services and social insurances, it is thinkable that national authorities and the national level, in general, may retain or regain more influence in the future.. But is such a reversal really conceivable? There are a number of reasons, most of which have been mentioned or touched upon above, why such a “regression” seems unlikely:

1. First of all, the whole configuration of marketing approval regulation for pharmaceuticals seems to represent a rather robust equilibrium, balancing a complex regulatory task environment and a heterogeneous interest structure that comprise practically all relevant actors, stakeholders and affected groups, with an equally complex regulatory and

procedural configuration. This system might represent an “institutional isomorphism” (DiMaggio and Powell 1983) which may provide the ground for further refinement and evolution in the direction of further Europeanization – of course always respecting the balance between the different, (especially economic and institutional) interests.

2. Related to point 1: National regulatory authorities, although losing autonomy, are included in the European procedures as indispensable participants, thus protecting their interest in organizational survival. This means that the interests of the potentially most critical adversaries of further Europeanization are quite well protected – at least for the foreseeable future.

3. Even among national regulatory authorities there are those who prefer further procedural Europeanization due to their limited own regulatory capacities.

4. Pharmaceutical marketing approval is now partly imbedded into international structures which even go beyond the European level and in which the EU regulatory authority already plays an important part on behalf of the European Community and, thus, all the national regulatory authorities. This is the context of the International Conference on Harmonization, in which the US, Japan and the EU take part, and where standards concerning the quality, safety and efficacy data for applications and assessments have been defined and integrated in a Common Technical Document. (see Vogel 1998, Sickmüller 1996) It is hard to perceive that the rather strong and institutionalized position of the EU regulatory authority in this international environment (see Art. 57, 1. (j) of Regulation (EC) No 726/2004) should be dismantled.

5. Looking for potential actors opposing further Europeanization, other than national regulatory authorities, one might cite representatives of national health care systems, certain consumer protection groups or specific pharmaceutical and medical critics. There are demands to consider the interests of national health care systems more thoroughly, to add additional criteria for marketing approval, to increase safety requirements and restrict relations between regulators and industry. Most of these criticisms apply to the national as well as to the European procedures. Regarding additional approval criteria such as comparative effectiveness controls, cost-effectiveness considerations etc., these demands are also not heard and not met at national levels, as far as marketing authorization is concerned. And where these additional criteria are observed, they are

introduced in procedures that are not part of the marketing approval process. Concerning the stricter safety requirements and greater distance between regulators and applicants, the problem is practically the same at the national level. In general, the European Centralized Procedure and the EMA have the advantage of being more open and transparent than most national regulatory agencies and procedures – which is acknowledged by the critics. In fact, for them the European institution and procedures might be the better target for improvement than the national agencies and procedures, and in the European Parliament they even seem to have an increasingly strong policy-coalition partner – the EP has successfully introduced many transparency requirements in the legislative review

As mentioned before, these conclusions are at best tentative and further analysis is required, including the analysis of additional issues which have been discussed in the reform process, and also those that have been non-issues. But even if one would subscribe to a trend towards further Europeanization, the institutional configuration of such a future Europeanized structure is not pre-determined. Even among regulatory authorities in the same member state different institutional preferences can be found. There are those who would prefer the further development of the existing “network” structure in which autonomously evaluating national regulatory authorities are part of a larger system coordinated by a European authority. And then there are others who, under the banner of “centers of excellence”, would prefer a more centralized structure, a kind of European FDA in which these specialized centers would be components of a more integrated and homogenous organizational structure. (see interviews with German, French, and British regulators).

Table 2: Issues discussed in the paper

Issues	Relationship to Europeanization
institutional meta-level	
Constitutional basis: -Art. 95 TEC (codecision of EP; qualified majority in Council)or - Art. 308 (consultation of EP; unanimity in Council)?	*Art. 95 provides individual member states with fewer opportunities to block provisions they do not agree with.* *Higher level of EU-institution involvement.*
institutional and procedural issues	
Scope of the Centralized Procedure: All medicines? All medicines with new active substances? Only biotech medicines?	*Larger scope increases the reach of the Centralized Procedure that is more successfully Europeanized and reduces the impact of single national authorities.*
Shorter deadlines in the Centralized Procedure	*Improves the efficiency of the CP, making it more attractive.*
Mutual Recognition/ Decentralized Procedure: - Sequencing of DP: RMS and CMS decide simultaneously; - obligatory binding arbitration; - option of provisional authorization; - shorter deadlines for MS.	 *- May be a crucial mechanisms to make the DP a viable European authorization procedure in view of homogeneous regulatory decisions and the creation of a single market.;* *- regulatory efficiency considerations, but indirectly also incentive for CMSs to adopt the RMS's assessment*
EMEA management board composition and selection	*Change towards equal representation of Council, Commission, and EP would strengthen the EU-institutions versus MSs.*
CHMP (formerly CPMP) composition and selection	*The main question was whether this Scientific Committee should represent national regulatory authorities or be composed mainly of "independent" experts and whether they should be selected by national authorities or EU-bodies.*
MRP/DP Institutionalization of position and role of the MRFG (Mutual Recognition Facilitation Group)	*Legal institutionalization would increase the chances to arrive at mutual recognition and, thus, strengthen the Europeanization aspect of the procedure.*
legal harmonisation issues	
Application data protection: How many years? With or without Bolar provision?	*Harmonization of standards and facilitating a single market for generics..*

Issues	Relationship to Europeanization
Operational definition of serious public health concerns	*A clear definition may reduce the opportunity for MSs to deny mutual recognition, thus strengthening the Europeanization aspect of the procedure.*

Table 3: Outcomes of the legislative process

Issues	Policy outcome	Main cleavage
Constitutional basis: Art. 95 TEC (codecision, qualified majority) or Art. 308 TEC (consultation, unanimity)?	Art. 95 TEC	Commission and several MSs (F, FIN, B, NL, IRL) for Art. 95 // D, DK, UK (and tendentially E, P, I, GR) for Art. 308
Scope of the Centralized Procedure: All medicines? All medicines with new active substances? Only biotech medicines?	Extension of CP to new active substances for four groups of indications: diabetes, aids, cancer, neurodegenerative disorders; After 20 May 2008 extension to auto-immune diseases, immune dysfunctions and viral diseases; additionally option to modify this list by qualified majority (Council) on Commission proposal.	Industry and a majority of MSs for free choice of procedures by applicant ("flexibility"). // Commission proposes extension of scope to new active substances, supported by the EP (first reading) and some members of the regulatory community.// Some public health/patient/consumer organizations demand the CP for all medicines to be marketed in more than one MS.
Data protection: How many years? With or without Bolar provision?	10 years of data protection, with possible 1-year extension for new indications. 2-year Bolar provision allowing generics producers to start work on their application after.8 years. (8+2+1)	Innovative industry for extended data protection. // Commission for harmonized 10-year period. // Public health/patient/consumer groups, generics producers, Council majority, and EP majority are for shorter data protection.// EP introduces Bolar provision.
Definition of serious public health concern	No definition in the regulation; Task of the Commission to define guidelines defining the meaning of "potential serious risk to public health."	Although described as important by some regulatory officials almost treated as a non-issue. Industry demands a clear, restrictive definition. // Commission and MSs endorse later adoption of a precise definition by the Commission. //Only some MSs suggest an expanded definition in the Working Party).
Deadlines in the Centralized Procedure	Commission has 15 (previously 30) days to act on EMA/CHMP position to formulate draft decision draft; MSs have 22 (previously 28) days to comment on the draft decision. (Deadlines related .to "bureaucratic" procedures.) No cuts for assessments by rapporteurs, co-rapporteurs.	Industry, EP, and Commission for shorter deadlines. // Some MS (DK, D, NL, A, I) resist proposed deadline cuts for the assessments my national regulatory authorities // Public health groups and industry critics defend longer deadlines for assessments.

Issues	Policy outcome	Main cleavage
Deadlines in the DP/MRProcedure	Attempts to introduce shorter deadlines for assessments by MS regulatory authorities fail.	Commission, EP, and industry support shorter deadlines for preparation of assessment reports and/or CMS replies. // Several MS (D, UK, A, NL, and others) back the old deadlines.
Sequencing of DP	Concerned MSs response takes place before the Reference MS makes its final decision, allowing for negotiation among both sides.	Issue was not controversial.
Obligatory binding arbitration in MRP/DP	Binding arbitration now required whenever national regulatory authorities fail to find consensus in assessments and evaluations.	Not a highly contested issue although it reduces national authorities autonomy and creates uncertainty concerning the arbitration outcome and the fate of already approved and marketed medicinal products (option of provisional authorisation).
EMEA management board composition and selection	One representative of each MS, plus two Commission and two EP representatives, two representatives of patient organizations and one representative each of doctors' and veterinarians' organizations. The patient, doctor, and veterinarian reps are nominated by the Commission and appointed by the Council, in consultation with the EP.	Commission proposed equal representation of Commission, EP, and Council, with additional patient and industry representatives appointed by the Commission. EP proposed the EFSA model, which the Commission also endorsed (support only from France as MS). // Council opposed loss of MS influence in Management Board and the inclusion of stakeholders (industry).
CHMP (formerly CPMP) composition and selection	Each MS appoints one CMPH member. CMPH may co-opt five additional scientific experts, nominated by the MS or EMA.	EP and Commission (supported by France) for selection by EMA director upon nomination by MS. Support from industry. // Most MS (particularly D, DK, UK, NL) vigorously defended their traditional position in selecting their representatives .
MRP/DP Institutionalization of position and role of the MRFG (Mutual Recognition Facilitation Group)	Institutionalization of a Coordination Group (one representative per MS) with administrative support from EMA and an active role in the MRP/DP whenever disagreements arise over assessments and evaluations; but no arbitration competencies (Art 27,29 of Directive 2004/27/EC(Art. 27 Directive)	Uncontroversial issue of strengthening assessment and evaluatory deliberations with the view of fostering mutual recognition.

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