

UiO : Centre for Entrepreneurship
University of Oslo

*The role of national medicines agencies
on the pharmaceutical innovative
production and scope: A comparative
case study of Norway and Sweden*

MSc in Innovation and Entrepreneurship

Sayeh Ahrabi

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS	i
TABLE OF CONTENTS	ii
ABSTRACT	1
LIST OF ABBREVIATIONS	2
1. INTRODUCTION.....	3
1.1 Research problem	5
1.2 Research question	7
2. THEORETICAL PERSPECTIVES	8
2.1 Institutional theory and resource based view	8
2.2 Development of propositions.....	9
2.2.1 Influence of the role of medicines agencies on SMEs' innovation.....	9
2.2.2 Influence of institutional forces on the role of national medicines agencies	11
2.2.3 Influence of strategic resources on the role of the national agencies	12
2.3 Summary of the theoretical framework	14
3. METHODOLOGY	15
3.1 Case study methodology.....	15
3.2 Dependent variables	15
3.2.1 Definition of SME.....	15
3.2.2 Innovative scope.....	15
3.2.3 Innovative productivity	16
3.3 Independent variable: Role of the national medicines agency	18
3.4 Institutional environment and strategic resources	19
3.5 Control variables.....	19
4. CASE STUDY	19
4.1 Innovative scope and productivity of SMEs in Norway and Sweden	19
4.1.1 Innovative scope of SMEs within drug discovery and development	19
4.1.2 Innovative productivity of SMEs within (bio) pharmaceutical segment	21
4.1.3 Summary of the results for innovative scope and productivity.....	23
4.2 Role of the national medicines agencies.....	24
4.2.1 Strategic goals and the predominant role of NOMA.....	24
4.2.2 Strategic goals and the predominant role of MPA	28
4.2.3 Conclusions on the roles of NOMA and MPA	30
4.3 Influence of the institutional environment on the roles of the national medicines agencies	31
4.3.1 European and national institutional environment in Sweden and Norway	31
4.3.2 Institutional environment that shaped NOMA's role.....	33
4.3.3 Institutional environment that shaped MPA's role	35
4.3.4 Conclusions on the influence of the institutional environment of NOMA and MPA on their roles	37
4.4 Availability and influence of strategic resources on the role of the national medicines agencies	37
4.4.1 Influence of the strategic resources at NOMA.....	38
4.4.2 Influence of the strategic resources at MPA	41
4.4.3 Conclusions on the influence of strategic resources	44
4.5 Other influential factors on the innovation scope and productivity	45
4.5.1 Government initiatives	45
4.5.2 Scientific environment, clusters and network	45
4.5.3 R&D expenditure and VC investments.....	47

4.5.4	Success stories and other cognitive variables	47
4.5.5	Conclusions on other influential factors on innovative productivity and scope	49
4	DISCUSSION	49
5.1	Summary of the main findings	49
5.2	Theoretical implications	50
5.3	Practical implications	53
5.4	Limitations of the study and future research	58
5	CONCLUSION	59
	APPENDIX	61
	REFERENCES	62

ABSTRACT

This thesis aims to investigate the role of national medicines agencies on the innovative scope and productivity of national pharmaceutical small and medium-sized enterprises (SMEs) through comparative case study of Norway and Sweden. Institutional theory and resource based view are used to investigate the influence of institutional forces and strategic resources on shaping the roles of the agencies. The findings indicate that both factors have influenced the roles of Swedish medical products agency (MPA) and Norwegian medicines agency (NOMA). MPA seems to have an innovation facilitation role whereas NOMA does not. However, the Norwegian SMEs within drug discovery and development seem to perform better regarding innovative scope. The innovative productivity among Norwegian biopharmaceutical SMEs also appears to be on the rise. It is suggested that control variables, such as governmental initiatives on funding and tax benefits, have stronger influence on innovative scope and productivity compared to the role of the national medicines agency. Norwegian SMEs regularly seek guidance at medicines agencies in other countries. It is discussed that NOMA can contribute to an even higher performance of Norwegian SMEs if the agency changes its role towards more innovation-orientation and acts as a supporting organization. The practical implications of this research for NOMA have been elaborated.

LIST OF ABBREVIATIONS

CHMP: Committee for Human Medicinal Products

CP: Centralised Procedure

DG: Director General

EEA: European Economic Area

EMA: European Medicines Agency

FDA: Food and Drug Administration

HoD: Helse- og omsorgsdepartementet (Ministry of Health and Care services)

IMI: Innovative Medicines Initiative

ITF: Innovation Task Force

LMI: Legemiddelindustrien (The Association of Pharmaceutical Industry in Norway)

MA: Marketing Authorization

MP: Medicinal Product

MPA: Swedish Medical Products Agency

NCE: New Chemical Entity

NHD: Nærings- og Handelsdepartementet (Ministry of Trade and Industry)

NOMA: Norwegian Medicines Agency

RBV: Resource based view

R&D: Research and Development

SAWP: Scientific Advice Working Party

SLK: Statens Legemiddelkontroll (Norwegian Medicines Control Authority; former organization prior to establishment of NOMA)

SME: Small and Medium-sized Enterprise

TLV: Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency)

VC: Venture capital

1. INTRODUCTION

The number of innovative medicines that reach the market has been more or less constant in the past 50 years despite the enormous increase in the research and development (R&D) expenditures in this research intensive industry (Munos 2009). Less than one percent of new drug candidates reach the market, and among those, only less than 20 percent generate profits (Pregelj et al. 2010). Furthermore, emerging technologies and complex global development programs and costs makes predictability a key issue in this industry (Ormarsdottir et al. 2008). This has attracted the attention of politicians and the regulatory authorities in the USA and Europe (Milne 2006) because there is still a rather large extent of unmet medical needs in the fields such as cancer, neuropsychiatric disorders (Kaitin and DiMasi 2011), infectious diseases (Norrby et al. 2005), paediatrics and rare diseases.

Pharmaceutical business including the development of medicinal products (MPs) is global in nature; i.e. the main rule is that new MPs are aimed to be launched worldwide. For MP developers in Europe, normally the first markets to address are Europe and the USA because of the large size and high income of the population. The central authorities in charge of drug approvals are the European Medicines Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the USA. In Europe there are also (one or several) national agencies in each of the European countries. The reason is that not all approvals or authorizations are centralized.

EMA's main responsibility is "the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use" ... "The Agency also plays a role in stimulating innovation and research in the pharmaceutical sector" (www.ema.europa.eu). In fact, one of the main reasons for establishment of EMA was to assist innovative biotechnology reach a wider market (Ormarsdottir et al. 2008).

Today, most new and innovative MPs are assessed and authorized through EMA and centralised procedure (CP). A CP approval means that the MP will be granted marketing authorization (MA) in all EU/EEA countries upon application from the company. EMA has at its disposal the pool of experts and scientists from all EU/EEA medicines agencies in order to assess applications for approval of new MPs. The evaluation of CP products is done by the scientific committees that are composed of members from each of the 27 EU countries plus Norway and Iceland. Experts from two of the above countries are appointed to independently assess each application and lead the scientific discussions in the relevant committees.

Before the establishment of EMA in 1995, pharmaceutical industry had to deal with regulators in all the European countries in which it aimed to place its MP on the market. This was ineffective and time-consuming. Centralized and decentralized procedures as well as several committees and working parties existed also before 1995, but their decisions were not legally binding. The shortcomings of European national regulatory frameworks were addressed through the establishment of EMA in that a coherent framework was founded to safeguard the public health in the European Union (Bauschke 2011). As explained above, national agencies in Europe turned into a network of regulatory experts to collaborate on approvals of new MPs. Accordingly, the success of the EU pharmaceutical regulations system and EMA lies in the fact that the member states have a real influence on the decision-making for regulatory policies (Krapohl 2004).

Pharmaceutical industry has long been known as profit-maximizing, especially Big Pharma. There are many examples of MP development based on minor modifications to already existing MPs, which do not result in significant therapeutic improvements. This is in contrast to the society's need for new therapies for life-threatening diseases such as infectious diseases caused by resistant microorganisms or cancer. Moreover, innovative pharmaceutical industry has traditionally been one of the most important industries in many European countries strongly contributing to the national economics. In the recent years, there has been a tendency that groundbreaking technologies are increasingly being developed by start-up firms (Danzon et al. 2005), so-called small and medium size enterprises (SMEs). Since SMEs commonly lack expertise and resources that Big Pharma has, they are more prone to making wrong regulatory decisions. As a rule SMEs require more scientific and regulatory guidance to succeed. All these facts have drawn the attention of the (European) authorities who have recognized the industry's need for advice and risk-sharing (Antonanzas et al. 2011).

In order to rapidly bring new therapies for major diseases to the market, European authorities have established a number of initiatives such as Innovative Medicines Initiative (IMI), Innovation Task Force (ITF), the SME office, giving Scientific Advice for the development of innovative medicines, arranging Briefing meetings for informal exchange of information and guidance. All this is to address the predictability issue in MP development. EMA is responsible for the majority of the above mentioned initiatives and uses the experts in the national agencies for all such scientific activities including advising the innovators. When the expertise of the national agencies is being used in the regulatory and scientific activities across Europe, one might expect that national institutions and policies exploit such resources

for the benefit of national industry. However, the role of national medicines agencies in facilitating pharmaceutical innovation in their own countries has not been addressed in the literature.

The only aspect of the national authorities' contribution to innovation addressed in the literature is pricing and reimbursement strategies, both of which are nationally regulated (Lopez-Casasnovas 2008; Van Wilder et al. 2010). Reimbursement is a key factor to the success of innovative MPs in Europe, where healthcare is publicly financed. If national authorities decide not to reimburse a MP, its use will be restricted to the patients willing to pay for the treatment. Such MP will not be widely used in that country and the applicant probably will not be willing to launch it there. Also, if the granted price by the authorities is too low, the applicant might not launch the MP in that specific country.

There is a plethora of literature focusing on regulation of medicines in the EU leading to more rapid approvals (Mossialos et al. 2004; Milne 2006). Although quite useful, none of the above activities have so far resulted in a significant improvement of the situation in terms of more innovative therapeutics in the market (Munos 2009). However, such initiatives are expected to give results in the long-term. In fact, 35 new drugs (with new molecular entities) were approved by the FDA in 2011, which was a 7-year-high result. The numbers between 2006 and 2010 varied between 18 and 26 (www.fda.gov).

Given the ever growing complexity of new MPs, there is little doubt that the state organizations and regulatory authorities play an important role on innovation (Ormarsdottir et al. 2008). Recent studies on innovation models suggest that research and innovation are not confined to the firm any more but take place in the interrelationship between the actors: academia, state and industry (Giesecke 2000). The concerns about patient safety must always stay as the number one responsibility of regulators. However, this must not hinder their involvement in bringing the new and life saving MPs to the market for the benefit of the patients.

1.1 Research problem

The biotech landscape in Norway has been flourishing recently. In the 10 year period of 1995-2005, the number of Norwegian innovative start-up pharmaceutical companies increased by 11.4% (LMI 2007). A search of NorBiobase (Innovation Norway's database on Norwegian biotech and medical technology companies) in 2012 with the keyword "Biomedical" resulted in 96 hits, the majority are SMEs. Such SMEs have limited resources, both human and capital,

and need support from the state and supporting organizations to survive and grow. Hence, the focus of the current study will be on pharmaceutical SMEs.

Since the drug scandals in 1960s, the most famous being the Thalidomide scandal (Bauschke 2011), the main task of the authorities regulating medicinal products was defined as ensuring that the new drugs that enter the market were safe. This has resulted in that pharmaceutical sector has become one of the most strictly regulated industries. The emphasis of the regulations has been placed on thorough assessment of the detailed documentation provided by the applicant, as well as inspection of the production facilities and laboratory control of finished products. In other words, “control” is the key word that summarizes how this sector has been and currently is regulated.

As mentioned earlier, with establishment of the EU network and EMA, the authorities have also become responsible for innovation facilitation and stimulation. The question is: In this truly centralized system regulating the medicinal products in Europe, what role can a national agency play to promote or facilitate the innovation for the national SMEs? Innovation is multifaceted and in this study the focus will be placed on innovative productivity and innovative scope (described in section 3) which are important aspects of MP development. From a regulatory perspective, pharmaceutical innovative scope is of utmost importance due to the society’s need of new and breakthrough treatments. Consequently, for the comparison of innovative scope at SMEs between the two countries, only pharmaceutical SMEs within drug discovery and development are analysed since they contribute most to new treatments.

Some national authorities such as Swedish Medical Products Agency (MPA) have long been active in giving guidance to pharmaceutical firms through all phases of drug development. This rather large organization (687 employees in the beginning of 2012) has a national scientific advice procedure which resembles the EMA’s procedure. In 2010 and 2011 they held 218 and 192 such meetings, respectively (MPA 2011). Other authorities such as Denmark’s regulatory authorities participate in a network of public-private researchers and stakeholders called Biopeople.

Norwegian Medicines Agency (NOMA) is not involved in any such activities. Norway, as opposed to both Sweden and Denmark, has never had a truly innovative national Big Pharma either, which may point to the lack of competencies and resources as one explanation to why NOMA has not been more active in the scientific arena. NOMA is a rather small agency with approximately 240 employees (229 in permanent positions) in 2012.

There seems to be a clear difference between the roles of MPA and NOMA as the regulatory agencies, although both have the aim of protecting public health. MPA has apparently selected an innovation facilitation strategy while NOMA seems to mostly focus on the traditional controlling aspect of the regulation. This research will try to shed a light on the effect of such different national regulatory strategies and roles on the scope of innovation and innovative productivity within the SME segment in these two countries.

The study will use institutional theory and resource based theory (also called resource based view or RBV) to address the following questions: Does the national institutional environment, reflected in the roles that the agencies have taken, influence the innovative productivity and scope at pharmaceutical SMEs? Is it the regulative, normative and cultural-cognitive aspects of the institution that dictates the role of the agencies, or is it the strategic resources and competencies that the agency is in the possession of, or is it both? Is there any interplay between the institution and the strategic resources?

1.2 Research question

The main objective of the research is to better understand the role of national medicines agencies in promoting innovation within the national (bio) pharmaceutical SMEs, by studying the case of Norway and Sweden.

The main research question to be addressed is:

- a. What role do national medicines agencies play in promoting the innovative scope and productivity of the pharmaceutical innovation performed by SMEs in their own countries?
 - a. How can national medicines agencies facilitate and contribute to (bio) pharmaceutical innovation in terms of innovative productivity and scope?
 - b. How does the institutional environment of the national medicines agency influence its role?
 - c. What strategic resources at national medicines agencies are important in facilitating innovation?
 - d. What other factors in the national innovation environment contribute to the innovative productivity and scope of SMEs?

Chapter 2 will elaborate the theoretical framework of the study, followed by the description of the methodology in chapter 3. The case study method is used for this investigation. The

method is qualitative and is based on primary and secondary data. The case study results are presented in chapter 4 leading to the discussion of the findings and modification of the theoretical model and propositions in chapter 5. Practical implications of the outcome of the study will also be highlighted in chapter 5 as well as the limitations of the current study and suggestions for future research. Finally, chapter 6 outlines conclusions by addressing the answers to the research question(s).

2. THEORETICAL PERSPECTIVES

2.1 Institutional theory and resource based view

In this study we use institutional theory and resource based view (RBV) to understand the role of national medicines agencies in general and with respect to facilitation of innovative productivity and scope in SMEs.

According to neo-institutionalism, “Institutions are comprised of regulative, normative, and cultural-cognitive elements that, together with associated activities and resources, provide stability and meaning to social life” (Scott 2008, pp. 48). Institutions are beyond the organization’s boundaries. They reduce risk and decrease the level of uncertainty by defining rules and expectations (van Waarden 2001).

The regulative aspects of institutions normally take the form of regulations and politics, guiding the organizations by law enforcement and threat of legal sanctions (Hoffman 1999). The normative pillar includes both values and norms defining how things should be done through setting standards (Scott 2008). Hence this pillar defines not only the goals but also how to achieve them (Veciana and Urbano 2008). The cultural-cognitive pillar is subconscious. It includes symbols, (body) language, cultural rules and frameworks that guide one to understand the nature of reality, the basis of which becomes unquestioned (Hoffman 1999).

RBV has been developed to address one of the central questions in the field of strategic management: Why do some firms persistently outperform others? This theory suggests that the resource profile of a firm and how well this is recognized and applied by the firm are important factors leading to competitive advantage (Barney and Clark 2007). However, not all competitive advantages are permanent. To create sustained competitive advantage, the resources must be Valuable, Rare, Inimitable and exploited by the Organization, so-called

VRIO resources (Barney 1995). The resources that contribute to sustained competitive advantage of a firm are called strategic resources.

Institutional theory is based on the firms' tendencies toward conformity leading to homogeneity in their structures and activities. According to this theory successful firms are those who have conformed to social pressures. This is in contrast to the RBV that considers firm heterogeneity regarding resources and capabilities as the main reason for sustained competitive advantage and hence its success (Oliver 1997).

In the present study, institutional theory will be used at two levels: to explore the forces that the national medicines agencies apply to the innovative SMEs and to investigate how the entire institutional environment of MPA and NOMA has shaped their roles regarding innovation facilitation. RBV will be utilized to investigate if the available resources in terms of competencies and capabilities in these two national agencies can explain the difference in the roles these agencies have taken. RBV is also touched upon to elaborate the role of agencies in knowledge spillover.

2.2 Development of propositions

2.2.1 Influence of the role of medicines agencies on SMEs' innovation

The institutional environment, particularly regulative and normative institutional forces seem to play a major role in influencing all activities in the pharmaceutical industry including innovation.

All stages of product development, production, approval and post-approval changes are subject to regulations and inspections. Depending on the level of severity, any lack of conformity is followed up for corrective actions or will result in withdrawal of the product from the market. This represents the regulative institution.

Important normative forces of the institutional environment on the pharmaceutical industry are represented by the construction of standards and guidelines for product development. Although not legally binding, guidelines are sufficiently detailed to describe the expectations of regulators regarding different aspects of pharmaceutical regulations. National medicines agencies, including NOMA and MPA, actively participate in the development of those standards and guidelines. Due to complexity of the field, numerous guidelines have been developed. The challenge of pharmaceutical industry and the regulators lies in interpretation

of relevant guidelines in each single case. The task of the regulators regarding innovation facilitation is to help the developers interpret those guidelines correctly from early on.

Many authors have studied the influence of the institutional forces on innovative productivity and scope within pharmaceutical sector. FDA's initiatives to apply new scientific tools in order to facilitate drug development as well as the agency's initiative on a number of public-private projects to reduce the uncertainty have been reviewed (Woodcock and Woosley 2008). Another group recommended more regulatory involvement to promote therapeutic advances within pharmaceutical innovation and to oversee the safety aspects of new MPs that are developed by utilization of new scientific tools (Abraham and Davis 2007). The importance of "users" in pharmaceutical innovation has also been addressed (Smits and Boon 2008), pointing at the increasing knowledge among the patients and the costs-conscious buyers (insurance companies or the state) who demand higher added-value products.

In the present study we address the influence of the role of the national medicines agencies, particularly through regulative and normative pressure, on national pharmaceutical SMEs, and how this affects the innovative productivity and innovative scope of products developed by those SMEs.

From the RBV perspective, it can be argued that national medicines agencies might play an important role in innovation due to knowledge spillover. The concept of knowledge spillover through being a part of a network (Dyer and Hatch 2006) is considered to be one of the important factors to improve innovative productivity (Ahuja et al. 2008). Supporting organizations are shown to have a significant role in innovation through knowledge spillover (Xavier Molina-Morales and Teresa Martínez-Fernández 2011). Supporting organizations are defined as public or private organizations (academia, research institutes, etc.) that interact with different firms and try to solve various forms of challenges, hence linking the firms and clusters together via what is called a "hyper-network" (Biggiero 1999).

With respect to pharmaceutical innovation, both the innovative scope and the innovative productivity are highly important to the regulators; i.e. new treatments for serious diseases will reach the patients faster. At the same time new and breakthrough innovations are more risky and uncertain than incremental innovations, demanding higher extent of assistance from supporting organisations to develop effective strategies (van Waarden 2001). Consequently, when society needs entirely new treatments, public organizations including national medicines agencies have a responsibility to support that kind of innovation.

A SME's success depends on the regulatory and scientific advice it receives and it is not unusual that a SME seeks advice from several national medicines agencies in different countries in addition to EMA in order to check the grounds. Provision of guidance to SMEs requires high level of competence and experience from national medicines agencies. In today's complex European structure of regulation, a national agency is exposed to the national, the European and the international actors, both to the Big Pharma projects and the SME projects. The more the agency is involved in such projects, the better it will be prepared to be the link that connects the knowledge and challenges of those different actors. As a consequence, when a national medicines agency takes an innovation facilitation role, such as MPA does, it acts as a supporting organization. Therefore, it is expected that MPA exhibits stronger positive effect on the innovative productivity and scope of the national SMEs compared to NOMA.

Proposition 1: A national medicines agency's active role in innovation facilitation will result in higher levels of innovative productivity and scope among national pharmaceutical SMEs.

2.2.2 Influence of institutional forces on the role of national medicines agencies

National medicines agencies are a part of a complex drug regulatory institutional framework. As a result, their tasks and roles are also subject to institutional forces.

Studies relating to institutional pressures on government agencies are seldom since those agencies are considered to be actors and creators of institutionalization rather than being affected by these forces. One of the few studies (Frumkin and Galaskiewicz 2004) suggested that governmental organizations are more responsive to all three aspects of institutional forces compared to profit and non-profit organizations. There seems to be two important reasons for this. One is the inaccuracy of measuring the performance of governmental agencies, forcing them to rely on external references to seek legitimacy. The second reason is their financial dependency on the state treasury and on ministerial cabinets for deciding on their direction and scope of operation and the fact that they compete with other public sector organizations to get larger portion of the state's total budget (Matthews and Shulman 2005).

With regards to funding, NOMA is a typical public sector organization, whereas MPA is more like a non-profit organization since it is self-financed. Accordingly, it may be expected that NOMA's role is more influenced by the national institutional environment and policies.

As described earlier, in Europe, rules, regulations and norms regarding innovation and product development in the pharmaceutical industry are defined and decided on the European level. Both Dyrdal (Dyrdal 2004) and Vestlund (Vestlund 2009) who studied the adaptation of the national medicines agencies in Norway (and Sweden in case of Dyrdal) to the Europeanization emphasize the importance of both national institutions and affiliation to the EU on this process. How the EU regulations and norms are being translated in each country is a matter of national institutional forces and how well those are aligned with the EU institutional laws and norms; i.e. it is more likely that the national and EU forces match better when the country is a member of EU, such as the case of Sweden and MPA. Krapohl (Krapohl 2004) argues that problems arise when the interests of the national authorities contradict with the EU policies. In the case of pharmaceuticals, the national institutional environment is particularly influential in the nationally regulated aspects, e.g. price and reimbursement strategy in Norway.

In summary, it can be expected that the different roles of MPA and NOMA regarding innovation facilitation is because they experience different levels of pressure from the EU and the national institutional environment. There are two main reasons for that: a) Sweden is an EU member and Norway is not, and b) NOMA's budget is provided by the government whereas MPA is self-financed.

Proposition 2: Institutional forces at both the European and national level will influence the role of national medicines agencies with respect to innovation facilitation.

2.2.3 Influence of strategic resources on the role of the national agencies

RBV seems to be a suitable tool to study strategic resources of an organization. According to RBV, one of the most important managerial tasks is to understand the link between a firm's resources and its sustained competitive advantage. Sustained competitive advantage is very important for the success of firms in the private sector since optimal use of available resources will ultimately benefit the firm itself in terms of value creation. For the public sector, however, this has been argued to represent a paradox (Matthews and Shulman 2005). Public sector organizations are created to deliver service for the benefit of the society, e.g. create knowledge and services to develop an industry. The authors suggested that public sector can benefit from developing sustained competitive advantage only in cases where the organization is not exposed to extreme competition in terms of governmental financing. Another study

(Carmeli and Tishler 2004) showed that local government authorities in possession of strategic human capital which was highly educated and had organization-specific competencies and experience that was not easy to imitate exhibited a better financial performance than those authorities without such valuable resources.

RBV also emphasizes on the importance of the particular time and space in the history of an organization in building sustained competitive advantage through acquiring and exploiting its resources (Barney and Clark 2007).

As described in section 2.1, strategic resources according to RBV can be defined as the VRIO resources that provide the organization with sustained competitive advantage. In this study, strategic resources address both the available expertise in the national medicines agencies and the managerial capabilities to recognize and exploit the expertise in building competitive advantages. Did the people in the two organizations have influence on the ultimate role of the agency?

Upon establishment of EMA, MPA decided to be very active in the scientific evaluation of MPs and to become one of the preferred authorities in the EU in this respect. MPA also decided to get more involved in the entire development stages of the products and actively give advice to the firms. It is likely that the architects behind such ambitious goals regarding scientific activities were the management of MPA, who not only had the right people and competences in the organization, but also recognized their potential and took advantage of the time window of opportunity for building the sustained competitive advantage. Parallel to this, it is possible that NOMA did not have the same level of scientific competence at hand at that time, or leaders to recognize their potential, to be able to resist the traditional controlling role.

Proposition 3a: *The type and level of competence of the strategic human resources at the national medicines agency will influence the role of the agency with respect to innovation facilitation.*

Proposition 3b: *The ability of the management to recognize the organization's resources and capabilities and to take advantage of the time window of opportunity for building sustained competitive advantage at the national medicines agency will influence the role of the agency with respect to innovation facilitation.*

2.3 Summary of the theoretical framework

Based on the propositions, the framework of the study can be summarized as follows:

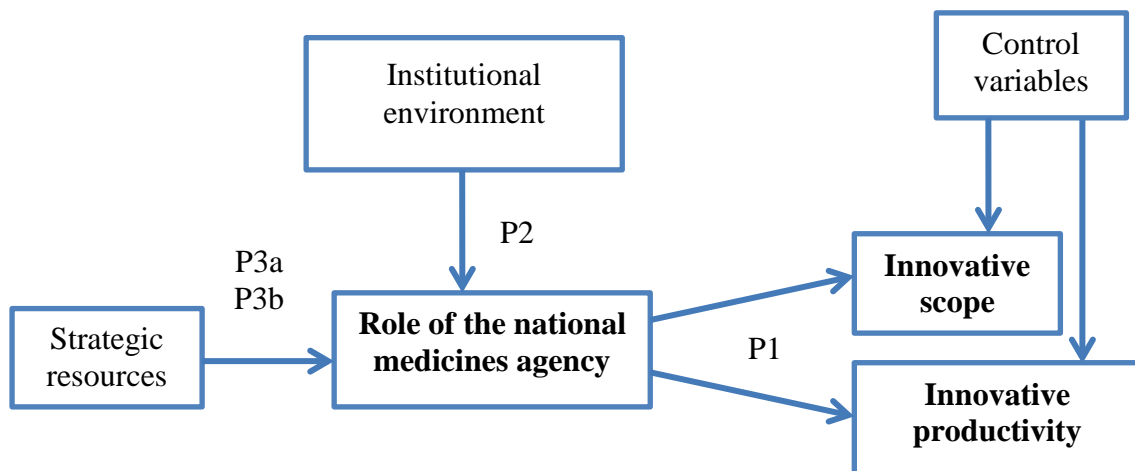
The dependent variables are the innovative scope and the innovative productivity for national SMEs in Norway and Sweden.

The independent variable is the role of the national medicines agencies in relation to the SMEs. It is proposed that the active role of an agency as innovation facilitator will have positive influence on the innovative productivity and scope in the national pharmaceutical SME segment.

The control variables are all national influential factors other than the pharmaceutical regulatory forces, which are thought to have a direct impact on the innovative scope and productivity of SMEs. Since the purpose of this study is to understand the role of the national medicines agency on innovative productivity and scope, factors which might have a direct impact on SMEs innovation activity are controlled for. These include funding (both government and private), tax regulations, patent laws, scientific environment, clusters and networks, R&D level and expenditure in the country, entrepreneurial spirit and capabilities, etc. Such factors do have a major impact on the success of a start-up firm and building up an industry.

The theoretical framework is presented in Figure 1.

Figure 1- Schematic representation of the theoretical framework



3. METHODOLOGY

3.1 Case study methodology

The study is explorative and follows an inductive approach. It is qualitative in nature and comprises embedded case studies comparing the case of Norway to the case of Sweden. The term embedded means that both the regulatory part and the innovative industry part are analysed. The analysis includes both primary and secondary data as explained below. It is believed that using multiple source of evidence, also called data triangulation, will minimize any error. Yin's method for the case study research is applied (Yin 2009). The cases are an example of polar types (Eisenhardt and Graebner 2007); i.e. two extreme cases of Norway and Sweden regarding the role of the national medicines agencies in facilitating innovation.

3.2 Dependent variables

3.2.1 Definition of SME

The definition of SME according to EMA/EU Commission recommendations 2003/361/EC is summarized below (ema.europa.eu /SME office):

Table 1- Definition of SME according to EMA

Enterprise category	Headcount: Annual work unit	Annual turnover	OR	Annual balance sheet total
Medium-sized	< 250	≤ € 50 mill	OR	≤ € 43 mill
Small	< 50	≤ € 10 mill	OR	≤ € 10 mill
Micro	< 10	≤ € 2 mill	OR	≤ € 2 mill

In the present study we defined SMEs only by the number of employees / headcounts according to the above table.

3.2.2 Innovative scope

Innovative scope refers to radical (or breakthrough) innovation as opposed to incremental innovation (Sorescu et al. 2003). Radical/breakthrough innovation in this study means an innovation which is major in scope and creates an entirely new product (Koberg et al. 2003). In comparison, an incremental innovation has lower impact (Koberg et al. 2003); it is rather an improvement to the existing technology (Garcia and Calantone 2002).

An inherent characteristic of a radical innovation is the high level of risk and uncertainty (Baba and Walsh 2010), which necessitates firm strategies and supportive institutions that can reduce the risk. The risk is high both in the development stage and in the market introduction

stage; i.e. will this innovation ever end up in the market and even if it does, to what extent will it be adopted? (Sorescu et al. 2003).

In terms of innovative scope of MPs, a radical innovation may be attributed to a product with a whole new mechanism of action, a NCE/new biological product or a new treatment for a neglected disease (orphan drugs). One way to operationalize this is to use FDA's definition of which products are given priority review by this authority (Wildson and Nitsche 2004). FDA gives priority to review/assess applications based on significant improvements, defined as "drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists" (www.fda.gov). Priority review is done faster than standard review (six months as opposed to ten months). Annual FDA reports of the drug approvals are public and indicate the new MPs with priority review. This list, however, seldom reveals the name of the SME that started developing the product since at the stage of approval the MP is normally out licensed to other larger firms.

Norbiobase, Scandinavian life science database and Vinnova's 2011 list of life science companies in Sweden were used to extract all the SMEs in Norway and Sweden which are involved in drug discovery and development; i.e. new chemical entities (NCE) or new biological products. The mentioned databases as well as the SMEs' websites were used to identify those with a pipeline of products in the preclinical/clinical phases or lead identification/optimization (the research activities to select and optimize a drug candidate for development), as well as the number of the products in that pipeline. See appendix A for the list of the SMEs included in this analysis.

When the SME had products on the market, it was checked if the product was a NCE / new biologic product and if so, was it approved under the Orphan drug regulation or had received a priority review from the FDA. Both the FDA annual lists for the past 5 years and the SMEs' websites were used to extract this information. The combination of a new NCE / biological product and orphan/priority review status was defined as breakthrough or radical innovation.

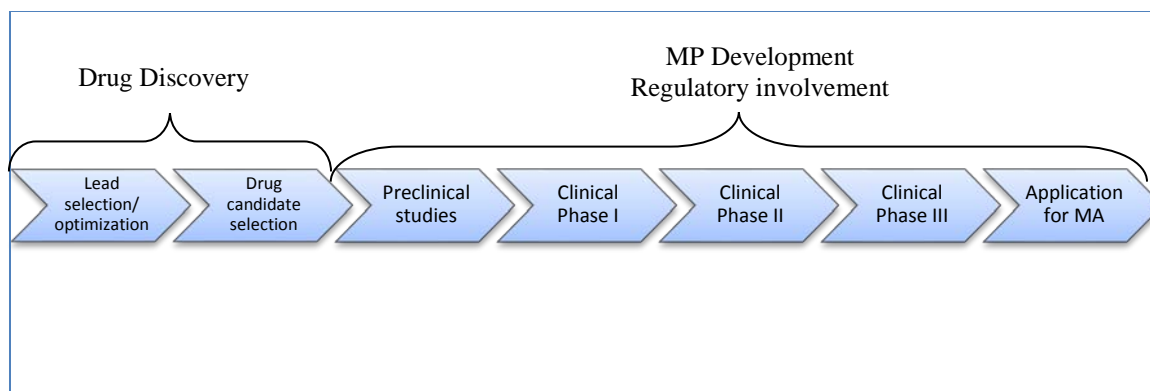
3.2.3 Innovative productivity

Innovative productivity or innovative output is the result of innovative input or research (Ahuja et al. 2008). Light (Light 2009) has defined the pharmaceutical productivity as the number of new compounds that successfully complete the clinical trials. Usually it is not possible to define beforehand which line of input/research will be productive. However, the

larger number of “input” projects directly improves the chances for the larger number of “output” or results.

Pharmaceutical drug development is a complex and lengthy process. All new chemical entities and new biological products have to show their quality, safety and efficacy through preclinical phase and 3 clinical phases before approval and launch (Figure 2).

Figure 2- Scheme of pre-approval R&D process in pharmaceutical industry



The purpose for each of the development phases is clearly defined: preclinical studies are aimed to make sure the drug is safe enough to be tested in humans, clinical phase I (Ph I) is primarily focused on ensuring non-toxicity in humans, clinical phase II (Ph II) is the proof of concept and establishment of optimal dose, clinical phase III (Ph III) is large studies aimed at establishment of benefit-risk ratio (does the effect of the product outweigh the side-effects?) through testing the product on large number of patients as well as comparison to other products on the market. There is a high attrition rate between the phases, meaning that a drug candidate’s chances for success (receiving MA) increases significantly as it proceeds from one phase to the next.

The level of pharmaceutical innovative productivity in both countries was defined as the number of ongoing projects in different clinical phases compared to each other. For this purpose, the publications from the Norwegian Bioindustry association (Biotekforum) (Biotekforum 2011) and SwedenBIO (Swedenbio 2011) were used. Biotekforum conducts annual survey among Norwegian pharmaceutical firms to map their clinical development pipeline that is based on Norwegian R&D. SwedenBIO also conduct annual surveys aimed at mapping the clinical development pipeline of Swedish biotech firms that perform research in Sweden, and includes those based on Swedish research. Biotekforum report uses the Swedish report to compare the Norwegian situation to the progress in Swedish bioindustry (2007-2011

for Norway and 2006-2011 for Sweden). In this thesis, these comparative results are reported directly as a strong indication for innovative productivity of the SMEs in the two countries.

70% of the Norwegian firms responded to the survey in 2011 (42 were asked), 19 of them had a pipeline based on Norwegian research, but only 14 had a clinical pipeline. Only the results for these firms are presented. Among the Swedish firms that responded the 2011 survey (88% of the 85 companies), 35 had a clinical pipeline and 11 had only late preclinical pipeline. Only the results for the firms with clinical pipeline will be presented in this thesis. Projects from AstraZeneca are not included here since it is not a SME.

3.3 Independent variable: Role of the national medicines agency

Primary data was acquired through interviews of selected employees in the agencies, the SMEs, and the trade associations in both countries. The interviews were performed using one standard set of questions. The follow-up questions in the course of the interview were adjusted to the informant's level of information in the area. All interviews were performed in person, taped after permission from the informants and later transcribed. In Norway the interviews were done in Norwegian, and in Sweden in English. Table 2 gives an overview of the interview set up.

Table 2- Overview of the interview set-up

Country	Organization	Total number of informants	Key informants*	Total number of interviews
Norway				
	NOMA	4**	2	4**
	HoD	1	1	1
	SME 1	1	1	1
	SME 2	1	1	1
	LMI	1	1	1
	Sum	8	6	8
Sweden				
	MPA	1	1	1
	SME 1	3	2	1
	SME 2	1	1	1
	SwedenBio	2	2	1
	Sum	7	6	4

* Strategic / senior position or long term employee

** Including one pilot interview

3.4 Institutional environment and strategic resources

Both the primary data from the interviews and a range of secondary data (historical facts, strategy documents, annual reports, scientific papers and government reports) were used. The timeframe of this retrospective analysis was defined to start around the establishment of EMA in 1995- with the implementation of the new approval system for MPs- until today.

3.5 Control variables

Both the primary data from the standard interviews and a range of secondary data were used (OECD reports, government reports, etc.). In addition a limited interview of a Norwegian senior advisor in a European venture capital (VC) investment organization within healthcare was performed only to discuss the differences in the innovative environment of Norway and Sweden.

4. CASE STUDY

The findings are based on the primary and secondary data and are presented with a structure that reflects the research question and the theoretical model. Each of the following sections describe the findings related to one of the variables in the theoretical model; i.e. section 4.1 shows the results for the innovative scope and innovative productivity of the SMEs (dependent variables), section 4.2 describes the findings for the role of the two national medicines agencies NOMA and MPA (independent variable), section 4.3 investigates the influence of the institutional environment on the role of the agencies, section 4.4 presents the influence of strategic resources on the role of the agencies, and section 4.5 describes other influential factors affecting the innovative scope and productivity of SMEs. Each of the sections describes the findings in Norway and in Sweden and is concluded with the summary of the findings.

4.1 Innovative scope and productivity of SMEs in Norway and Sweden

4.1.1 Innovative scope of SMEs within drug discovery and development

The results indicate 3 important differences between the two countries:

1. Although the total number of the SMEs within drug discovery and development in Norway is 1/3rd of that of Sweden, the relative number of medium-sized firms is significantly higher in Norway (20% in Norway and <1% in Sweden)
2. Despite the fact that the number of products under development in the portfolio of the mentioned SMEs in Norway is almost 1/3rd of that of Sweden, several products are launched by the Norwegian SMEs.
3. Comparison of the launched products in Norway and Sweden reveals that surprisingly, Norwegian SMEs have produced more NCE/new biological products, one of which has received priority review from FDA.

Table 3 illustrates the innovative scope of SMEs in Norway and Sweden within drug discovery and development.

Table 3- Innovative scope of SMEs within drug discovery and development

	Total No SMEs¹⁾	Micro / Small / Medium size	EMA SME status²⁾	No. Prod. Under dev.	No. Prod. Launched³⁾	NCE / New Biological prod.⁴⁾	Orphan / Priority⁵⁾
Norway	22	14 / 4 / 4	7	49	7	6 *	1**
Sweden	62	38 / 19 / 5	20	145	4	1	-

¹⁾ See appendix A for the list

²⁾ According to EMAs SME register for Norwegian and Swedish companies.

³⁾ Only from the websites of the companies. Marketed products which are entirely out-licensed are hence not included

⁴⁾ NCE = New chemical entity means that the active substance is completely new

⁵⁾ From the FDA annual lists (when the SME was the sponsor or applicant) and information on the websites of the SMEs

*Including 3 fish vaccine products which are by definition not entirely new biological products

** Photocure's Hexvix received a priority review in 2010 and is launched.

Both total number of the SMEs and their size (micro/small/medium, judged by the number of employees only) are presented in the first two columns.

The third parameter shows how many of those SMEs have SME status at EMA, which grants substantial fee discounts to SMEs. This reveals the firms who have realized their need to seek regulatory and scientific advice. It may indicate the level of knowledge at the SME about what is offered regarding regulatory assistance. It may also reveal that those SMEs have

reached a certain point in the product development that necessitates seeking regulatory assistance, e.g. formal preclinical or Ph I clinical studies. The results is in line with the total number of SMEs (Norway is 1/3rd of Sweden) indicating that there should not be a big difference between the two countries.

The fourth parameter is the number of products under development, which also is in line with the number of SMEs in the two countries (Norway 1/3rd of Sweden).

The fifth parameter shows the number of products that are launched, which is surprisingly almost the double in Norway; i.e. 7 in Norway and 4 in Sweden. The sixth parameter shows that 6 of the 7 launched products in Norway is a new chemical entity (NCE) or a new biological product. Even if we exclude the three fish vaccines which are considered not to be entirely new, Norway still has 3 original products compared to Sweden who has only 1.

As defined in the methodology, in this paper a breakthrough product is defined as one which has received a priority review in the FDA or an orphan drug designation in EU or USA. One of the products developed by Norwegian SMEs had received priority review by FDA. None of the products developed by Swedish SMEs had any of these two criteria.

4.1.2 Innovative productivity of SMEs within (bio) pharmaceutical segment

Figure 3 compares the clinical development status for Norwegian and Swedish projects that are based on the research in each of the two countries. The trend is that, since 2008, there has been an increase in the number of projects in all phases of clinical development among the Norwegian SMEs. In Sweden, however, it seems like the number of projects in the clinical phases are levelling off or decreasing.

Figure 3A compares the projects in Ph I clinical studies in Norway and Sweden. The number of projects in Norway has increased from 6 in 2008 to 17 in 2011, while in Sweden it has decreased from 25 to 18 in the same period. This might indicate that in Norway there has been a larger portfolio in the preclinical phase that has successfully entered clinical studies. It may also indicate that the financial situation and access to financing has been better in Norway since it is far more expensive to perform clinical studies than preclinical ones. The recent financial crisis has affected Sweden in a greater extent than it has affected Norway. Another explanation might be that in Norway most of the clinical studies are done in the field of oncology/cancer. This is the only therapeutic area where Ph I studies are done on patients and not on healthy volunteers. It is a very attractive situation for the investors since in the same

study, not only the safety profile of the product is verified (which is the main goal of Ph I studies), but also some proof of concept on the effect of the product is collected.

**Figure 3- Ongoing clinical studies by SMEs in Norway and Sweden.
A: Ph I, B: Ph II, C: Ph III**

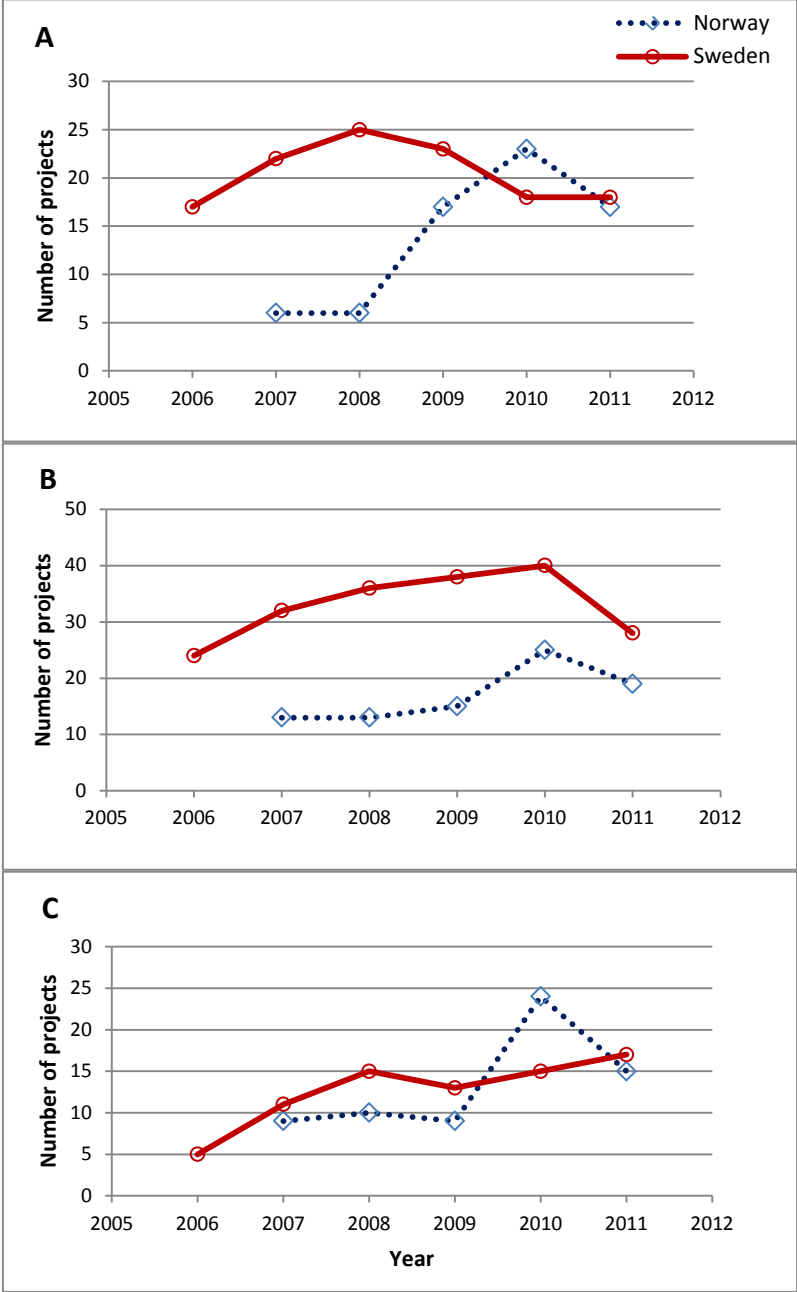


Figure 3B compares the projects in Ph II in the two countries. The figure illustrates that between 2007 and 2010, there has been almost double as many Ph II studies in Sweden compared to Norway and with the exception of 2011, the number of these projects has been increasing. The majority of the Swedish projects are in Ph II.

Figure 3C shows the ongoing projects in Ph III. Swedish projects in Ph III show a steady increase over the time, whereas in Norway there has only been an increase since 2009 following 3 years of stagnation. According to the report (Biotekforum 2011), the “jump” in 2010 to 24 projects might have been due to over-reporting. Ph III studies are so large and expensive that normally the SMEs are not able to perform it alone and most of them join some type of alliance to be able to do this. If financing is the reason that Swedish SMEs move back regarding Ph I and II studies, this last graph might indicate that Ph III studies are less sensitive to financial crises than the two initial phases. One reason might be that due to the history of Big Pharma in Sweden, it is easier to find partners for expensive Ph III studies.

4.1.3 Summary of the results for innovative scope and productivity

The results seem to reveal an overall superior position of the Norwegian pharmaceutical SMEs regarding both innovative scope and productivity compared to the Swedish pharmaceutical SMEs.

The innovative scope among Norwegian SMEs within drug discovery and development shows a trend towards breakthrough innovations, while a similar trend was not observed among Swedish SMEs. Norwegian SMEs have launched 6 original MPs, one of which received “priority review” status at FDA. Whereas in Sweden there is only one original MP launched by SMEs but it neither received “priority review” nor orphan status.

The innovative productivity of Norwegian biopharmaceutical SMEs, judged by the number of ongoing projects in clinical trials, reveals an overall increase in the recent years. In the same period the innovative productivity of Swedish biopharmaceutical SMEs shows decrease or stagnation for Ph I and II studies, but Ph III studies have a trend of slight but steady increase. The number of Ph II projects is significantly higher in Sweden than it is in Norway.

Financial problems are normally the major reason for stagnation or decrease of the number of the clinical studies.

Focus of Norwegian SMEs on the therapeutic area of oncology, also discussed in section 4.5, might be one explanation for the unexpected performance of Norwegian SMEs with regard to innovative scope and productivity.

4.2 Role of the national medicines agencies

4.2.1 Strategic goals and the predominant role of NOMA

The main strategic goal of NOMA is in accordance with the political goals set by HoD, stated in the yearly budget allocation statement (Tildelingsbrev) and NOMA's strategy document 2010-2015. These are as follows:

“NOMA shall contribute to ensure the fulfilment of the political goals regarding MPs and the reimbursement policies; i.e. Patients should have access to safe and effective MPs regardless of their ability to pay for the treatment, MPs should be used therapeutically and economically correct, MPs should have lowest possible price.”

It is striking that NOMA has the health economic aspects of the MPs in focus in all three strategic goals of the organization.

NOMA's goals may be broken into three main categories: 1) Making sure that patients have access to necessary MPs which are safe and effective, 2) keeping the State's costs on MPs under control, and 3) providing “producer-independent information” regarding MPs to the patients and the health professionals.

The above strategic goals have strongly defined the role of NOMA in general and in relation to innovation facilitation.

Table 4 summarizes the findings from the interviews regarding these 3 main categories.

Regarding the first main goal, there is controversy as to how successful NOMA has been. NOMA statistics show that only 40% of MPs that have MA in Norway are on the Norwegian market (search in the NOMA's internal database “Athene”). Most of these MPs are generics. According to a NOMA informant the small size of the Norwegian market, the strict pricing strategy, and the structure of the pharmacy chains in Norway who have their own preferred MPs can in sum explain this phenomenon. On the other hand, necessary innovative and generics MPs are continuously introduced to the Norwegian market despite the lower prices to an extent that few Norwegian patients suffer from lack of available and effective treatment. The HoD informant highlighted this fact as a sign of success for the pricing and reimbursement system. Norwegian market is seldom the first market for introduction of innovative MPs. According to the industry counterpart this is the direct result of the strict pricing and reimbursement strategy in Norway since the first country settles such vital factors for the success of a MP.

There is strong evidence that NOMA has had a remarkable success in achieving the goal to control the state's costs on MPs, judged by the fact that Norway has one of the lowest MP prices in Europe (Håkonsen et al. 2009a), and a strict reimbursement strategy. NOMA's success to achieve this goal was supported by all Norwegian informants except one who did not have any knowledge on this.

Table 4- Summary and highlights of interviews regarding how successful NOMA has been to achieve its main strategic goals

Main political goals	NOMA/HoD informants	SME/LMI informants
1. Ensure that patients have access to safe and effective MPs	<ul style="list-style-type: none"> - Other countries look to NOMA's success that the MPs stay on the Norwegian market despite lower price - Limited and passive contribution to bringing new MPs to the market through assessment and approval of applications for MA. - Only 40% of MPs with a MA in Norway are on the Norwegian market, one of the reasons being tough price control 	No one wants to introduce their innovative MP in Norway as the first market due to the strict pricing policy. As a result, Norwegian patients will have to wait for the latest available treatment, including the breakthrough MPs.
2. Ensure that the state's costs on MPs is under control	Very successful	Very successful
3. Provide producer-independent information to the patients and health professionals	<ul style="list-style-type: none"> - The generics substitution has been a success, but is it due to the law enforcement or the information? - Active campaigns when the scepticism to the generics rise in the society have been successful - NOMA has achieved great success with the information regarding the reimbursement strategy and the generics substitution. 	<ul style="list-style-type: none"> - Not successful - Invisible in the media and society - Focusing on keeping the negative news/aspects of the MPs under control rather than pushing the positive aspects forward

The success of the third goal regarding provision of producer-independent information to the patients and the health professionals also seems to be controversial. Most of these activities are aimed at generics substitution, which is enforced by the law and has been very successful. According to this law, when a MP goes off-patent, it is mandatory for the prescribers to prescribe the cheapest available generics if the MP is to be reimbursed. Despite several campaigns to convince the users that the approved generics are as good as the original MP, there is still evidence that not all patients or prescribers are convinced (Håkonsen et al. 2009b; Dalen et al. 2011). The information department at NOMA runs regular campaigns to inform better on this issue. When it comes to information regarding innovative MPs, NOMA seems to be rather invisible in the society and the media. Two of the informants from the industry

counterpart stated that NOMA's focus regarding information is directed at controlling the negative aspects and news rather than communicating the positive news.

There is little doubt that NOMA's focus has been to control the industry. Both the NOMA employees and the industry counterparts expressed unanimously that the role of NOMA is to keep the MP prices low, have a strict reimbursement strategy, and to ensure that the industry complies with the current European legislations and rules through control and inspection.

An indication that NOMA might have a responsibility regarding innovation was highlighted by the HoD informant to lie in the first part of the first goal; i.e. *“patients should have access to safe and effective MPs regardless of their ability to pay for the treatment”*.

There is no evidence that NOMA at any time has had an active role regarding innovation facilitation. The NOMA informants thought of their role in innovation facilitation as non-existing. A key NOMA informant stated:

“To promote innovation is an unknown concept here. Maybe to facilitate or rather to be helpful is closer [to the reality]. Even that is not the direct intention, so the concept is underdeveloped. But the scientific assessors think that it is exciting to work with new and innovative products...Even the clinical trials unit thinks as an authority, they are gate-keepers...clinical trials must not harm the patients.”

Another NOMA informant had the following comment:

“In my experience, as long as I have been working at NOMA [since 1998] our role has been defined: How can we survive in this system without using many resources on it [scientific work] so that we can rather use our resources on the producer-independent information and the pharmaco-economics? We decided not to take an active role [in the EU collaboration] but to [largely] adopt the decisions. When you take such a role you implicitly choose to set aside any innovation facilitation role. You just cannot be active, simulating and helping innovation when you want to let the world take the responsibility!”

Nevertheless, although NOMA has not been actively “marketing” that the organization is willing to provide scientific and regulatory advice, there has been held numerous discussion meetings on the initiative from the industry. NOMA's employees have also been available for informal discussions by phone. The informant from the Norwegian SME 1 actively contacted NOMA's scientific and regulatory employees when there was a need for discussions and

advice. This informant thought of NOMA's experts as knowledgeable and competent and wondered why NOMA is not trying to make this competency more visible through better "marketing" (actively informing the actors on the areas of competence). During a recent meeting with some NOMA employees, the informant from Norwegian SME 2 had been positively surprised to hear that they recognized their task to give guidance to SMEs. Both Norwegian SMEs had been seeking scientific advice at several medicines agencies in other European countries, including MPA.

NOMA has historically been short of necessary resources to handle the increasing number of applications. This has led to queues and long overdue deadlines, which are in principle legally binding. The necessary resources to resolve this situation have been provided, but it has taken years to remove the bottlenecks. Additionally, NOMA requires longer assessment time for clinical trial approvals than other European countries do. This has contributed to the reputation that NOMA is constantly short of resources or lacks enough experience and competence to rapidly assess the documentation (SME 2 informant).

NOMA also has little activity regarding initiative to arrange information/educational meetings. Apart from SMEs, the academic research groups are in great need of such support.

The absence of an active role regarding innovation facilitation at NOMA was indirectly confirmed by one NOMA informant and the HoD informant who stated that Norwegian regulations might contribute to breakthrough innovations by exercising strict price and reimbursement strategy; i.e. only real therapeutic improvements compared to existing MPs on the market are rewarded by a good price and inclusion in the reimbursement list. However, they did not address how the small Norwegian market can have such an impact on a firm's strategy.

Balancing the role of advice giver and discussion partner for the development of products on one hand and approving the same products on the other end was mentioned as potentially problematic by NOMA informants. This concern may be attributed to NOMA's lack of sufficient experience in providing advice or in general scientific contact with the SMEs, since the MPA informant did not express similar concerns (see 4.2.2). The approval system is strictly regulated with hundreds of guidelines and regulations and there is little left to subjective evaluations. The LMI informant expressed concerns about such reasoning being used as an excuse not to give advice especially to SMEs.

It is worth noting that all Norwegian informants, both from the industry side and NOMA/HoD side, suggested that supporting innovation should be included as one of the main points in NOMA's strategy. Several informants pointed out that NOMA has now the competence and is mature enough to undertake such a task. This is also in the line with the current governmental activities regarding innovation (see section 4.5).

4.2.2 Strategic goals and the predominant role of MPA

The strategic goals (or main tasks) of MPA as defined in the annual report of 2011 is "to advance the health of Swedish people and animals. Both the patients and the health professionals should have access to safe and effective MPs with good quality. MPs shall be used in an efficient and cost-effective manner... MPA has a normative and regulative authority role regarding development of new products. Regarding product development MPA gives scientific advice, assesses the documentation for clinical trials and applications for MA..."

This was confirmed by the MPA informant who stated it in another words:

"Overall goal is to contribute to ensure that there are MPs on the market which have an acceptable benefit-risk balance, that the information about the product is adequate and useful, and that appropriate post marketing follow up is undertaken."

The goal described above can be broken down to the following: 1) ensure that MPs reach the market, 2) ensure that the benefit-risk balance of the MPs on the market is evaluated and is acceptable, 3) ensure that the necessary information about the MPs is available, and 4) ensure the appropriate post marketing follow up of the MPs. Both the innovation/industrial aspect of the MP development as well as the patient's wellness and safety are highlighted in the goals.

There is strong evidence that MPA has been successful to work towards their goals through assessment of a large number of MPs and through active involvement in the scientific advice activities, both at the European and the national level to make sure that they have enough knowledge about the products under development. Already in 2001 MPA was one of the most frequently used authorities in Europe, and in 2005 they were very close to be one of the leaders in the EU collaboration (see section 4.3). MPA is also very active with providing information and news, both to the public and to the health professionals through the electronic service called "Information from MPA" and their phone information service.

MPA does take an active role regarding both patient safety and innovation facilitation. Both MPA and the Swedish SMEs/SwedenBIO expressed that the MPA's main role is to ensure patient's safety through all the phases of drug development, approval and post marketing. They do this through active involvement by giving scientific and regulatory advice to the pharmaceutical industry, helping them to do the right things first time. MPA was regarded as a very competent authority by the majority of the informants from both countries.

With regards to MPA's active role and direct responsibility in innovation facilitation, the MPA employee commented:

“Our role is to give scientific advice to guide to as optimal development as possible to avoid wasting resources and time on the development or even losing good drug candidates. We see this as our contribution to enable that in the other end we get adequately studied products.”

The MPA informant did not appear to be concerned about having “two hats” or a double role; i.e. one that helps the industry to develop MPs, the other evaluates the same MP. The impression is that MPA's extensive experience in such activities gave them confidence that there is no double role when it comes to the scientific aspects. What they do is to translate the guidelines to the product specific enquiries from the industry, especially SMEs, and make it clearer for them what studies they need to perform.

MPA's organization culture of openness and interaction, strongly fostered by the management, was unanimously indicated as a key success factor by the informants from both Swedish and Norwegian SMEs and trade associations. Transparency of the assessments and decision making and focus on customer relations were highlighted by the Swedish SMEs and SwedenBIO, who also stated that this organization culture has gradually evolved probably since MPA became an independent organization in 1990.

The Swedish innovative pharmaceutical industry seems to take it for granted that their national agency is interested in them and their needs. The special need of the SMEs to have access to a service-minded authority that can give guidance on a short notice was acknowledged both by the MPA and the SwedenBIO/Swedish SME informants. The informant from the Swedish SME 2 stated:

“Small companies have 2-3 people who are not experts in any field. We have consultants, of course. They can say I am not sure but I will call MPA and get back to

you. There is a web of interactions. You need to pose intelligent questions to get proper answers... One clinical study is a huge undertaking for a small company in terms of money and efforts. [It is] very important to get the advice to do it properly for the benefit of everyone.”

Both of the Norwegian SME informants had experience with MPA regarding scientific advice and were in general satisfied with the outcome. However, the informant from Norwegian SME 1 stated that despite MPA’s active marketing of this service to be expedite, they actually under-delivered regarding the timelines and were not prepared for all the pre-submitted questions, but for the most critical ones.

SwedenBIO informants said that they have had several meetings with the current DG of the MPA with the suggestion to establish a unit at MPA to handle the needs of the SMEs. The response has been quite promising, they said.

4.2.3 Conclusions on the roles of NOMA and MPA

The overall impression from the interviews is that NOMA’s dominating role is one of “controlling the pharmaceutical industry”, whereas the dominating role of MPA is one of “actively facilitating/ supporting innovation in the pharmaceutical industry”.

NOMA’s predominant role is to ensure that the industrial actors conform to the regulations mostly through control and also to a less extent through information and guidance. The few non-routine activities at NOMA in favour of innovation and guidance to the innovative companies have a passive character where the intention on the NOMA’s side is seldom contribution to innovation. The organization is characterized as somehow closed and seems to lack initiative with regards to innovation. This should not be surprising since the concept of promoting innovation is not defined as one of the tasks of NOMA in its steering documents.

MPA’s role is to ensure that patients have access to MPs with acceptable risk-benefit and quality. They do this mainly by active involvement in product development from early stages so that the industrial actors do the right things first time, and through assessment of documentation for numerous new MPs. To contribute to and oversee the development of MPs is defined as one of the tasks of MPA in the steering documents. The organization is characterized by transparency regarding decision making and openness to customers.

The annual reports and the strategy documents of both agencies confirm the above observations (explained more in section 4.3). This difference in roles and attitudes regarding innovation is also in agreement with the author's initial reason to study these two agencies as contrasting or polar cases.

4.3 Influence of the institutional environment on the roles of the national medicines agencies

4.3.1 European and national institutional environment in Sweden and Norway

EU and national institutional forces have influenced the roles of the agencies along two different axes. Naturally, the EU has the predominant influence on MPA since Sweden joined the EU, while NOMA seems to experience the national forces to a larger extent.

Table 5 summarizes the historical events that shaped the structure, roles and activities of MPA and NOMA (Dyrdal 2004, Annual reports and public information). There are four important differences in the institutional environment of the MPA and NOMA:

1. Sweden joined the EU, Norway did not.
2. Sweden has a history of strong innovative pharmaceutical industry such as AstraZeneca and Pharmacia. Pharmaceutical Industry was once the third most important source of income for the Swedish state. Norway only had a medium size innovative company, Nycomed Imaging, within niche product portfolio (imaging diagnostics techniques). Norwegian economy never relied on the pharmaceutical industry.
3. In contrast to NOMA, MPA never had the responsibility for price and reimbursement of MPs. In Sweden, another organization (TLV) has the task to determine whether a MP shall be subsidized by the state.
4. MPA is an independent and self-financed organization, NOMA is not (see section 4.4)

EU has traditionally had a market orientation, focusing on free movement of the goods and development of predictable conditions for the pharmaceutical R&D in order to ensure innovation (Vestlund 2009). On the other hand, in Sweden and Norway the consumer and health-oriented philosophy has historically been steering the control of pharmaceuticals (Dyrdal 2004). There are and have been variations between the two countries, which are elaborated below in organization-specific sections.

Table 5- Historical events that shaped the structure, roles and activities of MPA and NOMA

Chronology of events	Norwegian medicines authority	Swedish medicines authority
1990 The traditional Nordic collaboration within drug assessment and evaluation is still ongoing	SLK is a unit in National Board of Health (Helsetilsynet). Spesialitetsnemnda (Specialties Board) still has the decision making authority. Since 1941, "Behovsparagrafen" (the Need clause) has been in force.	MPA established as an independent and self-financed organization with fee-based income. The goal is to improve the organization into a more effective one and to prepare for the future EU collaboration system. MPA does not evaluate Price and reimbursement.
1993- EU finally decided on the structure of the "New system" for MP approvals		MPA has already adapted to the EU's New system.
1994	Norway joined EEA. "Need clause" was abolished. SLK established as an independent organization. The goal was to become more effective and market-oriented	Sweden receives observer status in EU due to EU membership and gains access to the committees and documents. Swedish government gives MPA the task to use the preparatory period to develop a competitive European authority
1995- The EMA is established	Norway is excluded from the drug evaluation activities in EU and the assessment documents are not available to EEA members. With Denmark, Sweden and Finland in the EU, Norway and Iceland are on their own.	
1994-1999 Explosion of the public pharmaceutical costs	In 1997 Strømutvalget and Grundutvalget deliver their reports on pricing and reimbursement strategies. Pharmaco-economic unit established at SLK. Negotiations on extension of EEA agreement to include the New system for MPs.	In 1997 media criticized MPA for the close relations with the industry. MPA invited them to inspect the organization and its procedures. In 1998 MPA is one of the best providers of product information on the national level
1998- The extended EEA agreement is approved	Observer status for Norway in the EU system	
2000- Extended EEA agreement is in force	SLK is fully operative in activities except the decision making processes where it is observer without a voting right. SLK international vision stated in the annual report: - Norway to become one of the preferred assessors within its fields of expertise - Norway to be world leader within fish diseases	"Contribution to cost effective use of MPs" is stated as one of the tasks of MPA
2001	NOMA is established through integration of the reimbursement and the inspection/licensing functions. Generic substitution becomes mandatory	MPA is one of the most frequently used authorities in the EU system. The responsibility for medical devices is transferred to MPA
2002 - Drug reforms in Sweden, TLV is established	Same international vision as in 2001	
2003	NOMA international vision was entirely removed from the annual report	
2005	The new national policy for pharmaceuticals (Legemiddelmeldingen) is presented. Strongly influences NOMAs future strategy	The initial goal that MPA should be one of the leading authorities in the EU looks realistic
2007	Norway has one of the lowest MP prices among 10 Northern European countries	
2009	Reorganization- The new Information department is established	MPA is one of the most preferred authorities in the EU due to "Regulatory excellence".
2010		National strategy for pharmaceuticals 2010. MPA receives the national task to contribute to better MP use and to collaborate with the actors in this area. New vision is established.

The Norwegian pharmaceutical regulatory system has been summarized as autonomic and closed with a small volume of national pharmaceutical industry, cultivating only the patient's interests. In comparison, the Swedish system appears as a more open system with a well developed relationship between the authorities and the large national pharmaceutical industry (Dyrdal 2004).

4.3.2 Institutional environment that shaped NOMA's role

The consumer/health-oriented philosophy in Norway resulted in introducing "the need clause" (Behovsparagrafen) in 1941, which largely limited marketing of generics to a controllable level (maximum 5 for each indication) (Dyrdal 2004). This clause, required medical need for a MP to get registered and was removed in 1994 due to the EEA agreement. However, a review of 1999 annual report from SLK (Norwegian Medicines Control Agency, the predecessor organization to NOMA) shows that "To regulate the market entrance and oversee public's need for good and effective MPs" is stated as the first of the two principal goals of the organization. This may indicate that the tradition of regulation through limitation of market access was now being translated into new forms.

The national medicines agencies practice and implement the national pharmaceuticals strategy/policy established by the politicians. Although EU/EEA agreements demand that the centrally approved MPs receive MA in all the member countries, there are no common regulations on national health care policies including pricing or reimbursement strategies. Here is where the different countries can control the introduction of the new MPs to the market. This window of opportunity has been extensively used by the Norwegian authorities in order to control the health-related costs. Maybe not surprisingly (and most probably unconsciously) this has been done through regulations that have resulted in limited market access of MPs. As mentioned previously, 60% of the MPs that are approved in the European system, mostly generics, never enter the market in Norway. This is by choice of the MA holder and there are several reasons to it, one of them being strict price and reimbursement strategy in Norway.

Norway was one of the first countries in the world to establish priority setting /health economic strategies (Calltorp 1999), the so-called "Lønning I" in 1985. Already in 1991 the doctor's duty to prescribe the cheapest copy product had been introduced. The background was the general rise in the sales of the pharmaceutical, growing at a yearly rate of 5.2%

between 1980 and 1995. This was mostly attributed to higher price for the newer MPs. Norwegian state covered 2/3rd of the costs, which was becoming formidable. The yearly increase in the reimbursement budget was at 8%. However, NOMA's annual reports in the 90s repeatedly pinpoint that the cost of pharmaceuticals in Norway was lower than other Nordic countries. It is likely that lack of Norwegian state's dependency on income from a strong and influential Big Pharma made it quite easy for the authorities to select cost control on pharmaceuticals as their most important strategy to control the costs of public health.

In the late 1995/ early 1996 two different groups were appointed by HoD (highly encouraged by the Ministry of Finance) to assess the framework for: 1) price and turnover for pharmaceuticals (Strømutvalget) and 2) reimbursement of pharmaceutical costs (Grundutvalget). Both reports were finalized in January 1997 and have influenced the later political direction not only regarding maximum price and reimbursement strategies, but also the availability of the producer-independent information to prescribers and setting limitations on the contact between the pharmaceutical industry and the prescribers.

In 2005 the Norwegian national strategy for pharmaceuticals (Legemiddelmeldingen) was finalized. The document indicated that the superior political goal for the pharmaceuticals is their correct use, main focus being on the costs (discussed in section 4.2). Chapter 7 of this document describes the government's ambitions regarding research on pharmaceuticals. In short, "The public organizations should focus their efforts on knowledge that is of interest to the patients and the society, the research type which the industry does not perform today" (St.meld.nr.18, 2004-2005, pp. 9). This is an indication that probably the health authorities in Norway do not have any specific ambitions regarding innovation facilitation for SMEs. This is in contrast to the increasing level of other government initiatives and attempts to facilitate biomedical innovation in Norway, some of which are mentioned in section 4.5. The national strategy for innovation "An innovative and sustainable Norway" was published by NHD in 2008 (St.meld.nr.7, 2008-2009). One of the main points was that the government will facilitate the innovation in SMEs (Ibid, pp. 6). Those intentions have been reinforced through the recently published whitepaper "Tools for Growth", where the formation of different seed-funds for, among others, health related industry has been addressed (St.meld.nr.22, 2011-2012). According to the LMI informant, LMI has been actively seeking collaboration with NHD regarding innovation in pharmaceutical industry since HoD does not show interest in industrial development. A statement from the HoD informant was in the line with this observation:

“With NHD’s objectives it is great that Norwegian pharmaceutical industry is flourishing. According to HOD’s objectives, we should give priority to cost effective MPs for serious conditions. Where the innovation is done geographically does not influence this”

There is evidence of NOMA’s resistance to the traditional view and the institutional unilateral focus on controlling the industry. Annual reports reveal that in the transition period of inclusion in the new EU system and the establishment of NOMA (1999-2002) the agency had some ambitions regarding the level of its assessment competence in the MP approval process (Table 5). NOMA even aimed at becoming the world leader in the area of fish diseases. Apparently, no additional resources were allocated from HoD to realize these scientific ambitions, since all the ambitious goals were removed from the annual reports since 2003. A key NOMA informant said:

“When we try to explain [to HoD] that Norway is much larger than many other countries, Cyprus, Malta, etc., and cannot be free-rider, or that it is advantageous for us to have the areas of expertise because then we also learn about the therapeutic area for the benefit of the reimbursement strategy, it is very difficult to get any response.”

On the cognitive aspects, one can certainly point at the general scepticism towards the profit-maximizing pharmaceutical industry in the Norwegian society. The underlying egalitarian mindset has deep roots in the Norwegian culture and is expressed as the scepticism towards any attempts to making profit.

4.3.3 Institutional environment that shaped MPA’s role

As opposed to the NOMA’s situation, the institutional environment of the MPA seems to be less complex and rather straight forward due to Sweden’s EU membership, which dominated any national institutional forces. According to Dyrdal (Dyrdal 2004) because of the more holistic national pharmaceutical strategy in Sweden, which balances between the industrial structure and the patient’s safety, the response to the increase in the state’s expenditure on pharmaceuticals came rather late; i.e. in 1998 it came on the political agenda resulting in the 2002 drug reforms. Although MPA has earlier been involved in evaluation of the MPs for the reimbursement, the agency never had the responsibility for this task. In 2002, TLV was

established with similar tasks as the department of pharmaco-economics at NOMA. In the same year generic substitution became mandatory in Sweden (Godman et al. 2009).

MPA has clearly selected to influence EU's scientific decision making through strong and active involvement in the development of regulations regarding MPs. The importance of the high quality of the national pharmaceutical industry in taking this active role cannot be overemphasized.

Already in 1993-1994, MPA started to get more involved in dialog meetings with the industry in order to facilitate pharmaceutical development. This was considered not only to help the pharmaceutical firms but also to increase the competence of the assessors and prepare them for the assessment work in the European community (MPA 1993-1994). In 1997, MPA was subject to criticism from the media due to close contact with the industry in aftermaths of safety problems with some MPs. MPA, however, declared that they have a clear policy in all these cases and invited the media to inspect the organization and its routines (MPA 1997). There is no sign of such inspection in the annual reports of 1998 or later.

In 2005 MPA was inspected by Swedish state authorities, which concluded that MPA's goal to be one of the leading countries in the EU is not far to be achieved (MPA 2005).

Recently MPA has been criticized to be less visible in the national arena than in the EU. For this reason, the efforts of the current DG are mainly focused towards the national actors (MPA and SwedenBIO informants). In 2009, MPA decided that their vision of becoming the centre of regulatory excellence was achieved. In accordance with increasing national focus, MPA selected a new vision: A leading force in the collaboration for better health (En ledande kraft i samverkan för bättre hälsa). In 2010, MPA received the national task and the resources to form a centre for better use of pharmaceuticals and in 2011 the responsibility to coordinate the activities related to the national strategy for pharmaceuticals.

Nevertheless, such recent national focus at MPA has not resulted in less activity of the agency at the EU level. It seems like the long and rich experience of intensive EU collaboration has equipped MPA with necessary skills and competence to also handle the national tasks.

In 2010, the revised Swedish national strategy for pharmaceuticals was published with the title "Correct use of pharmaceuticals for the benefit of patients and the society" (Rätt läkemedels-användning till nytta för patient och samhälle). The five pillars of the strategy are world class medical results and patient safety, equal health, cost-effective use of MPs,

attractiveness for innovation of products and services, minimum of environmental hazards. This illustrates that even when the costs become serious issues, the innovation is not being neglected by the health authorities in Sweden.

4.3.4 Conclusions on the influence of the institutional environment of NOMA and MPA on their roles

The major institutional forces influencing the roles of both agencies are at two levels: EU and national. Both agencies have been strongly influenced by the EU regulations. In Sweden, these forces have been mostly in the same direction as the national forces; i.e. innovation and industry orientation. MPA has protected the national tradition of focus on the patient safety through active participation in the approval procedures for new MPs and preparation of regulatory guidelines. The result has been the predominant innovation facilitation role.

In Norway, the national institutional forces appear to be more at conflict with the EU framework with regard to innovation facilitation. Norwegian health authorities seem to continue the tradition of control of market access for MPs (the heritage from “the need clause”) in new forms; i.e. through strict price and reimbursement strategies. It seems likely that an important factor for the absence of the authorities’ real interest and an active role regarding innovation facilitation is due to historical lack of an innovative national Big Pharma in Norway. All the above mentioned factors in addition to the general scepticism of the Norwegian society towards the profit maximizing pharmaceutical industry have been imposing a predominantly controlling role to NOMA.

4.4 Availability and influence of strategic resources on the role of the national medicines agencies

National medicines agencies are typical examples of knowledge-intensive organizations that depend solely on the knowledge and competence of their employees to fulfil their tasks. The results from the interviews indicated that being in possession of employees with diverse background and high level of relevant education and industrial experience is considered as strength for the medicines agencies that serve the pharmaceutical industry as a customer. Industrial background of the employees increases the level of awareness about the challenges that the pharmaceutical firms, especially the innovative ones, face. All informants from the industry side in both countries as well as several of the informants from the agencies

mentioned the importance of exchanging employees between the regulatory authorities and the industry.

The availability and the background of the strategic human resources in NOMA and MPA seem to be one of the reasons for the differences in their roles. All the informants in both countries regarded the existence of strategic resources as vital to the role.

The results also showed that it is not considered to be particularly prestigious to work at any of the two national agencies with the possible exception of senior positions. However, increasingly more experienced and competent people seek jobs at both agencies due to the cut downs in the industry. Having access to knowledgeable clinicians/MDs is a great strength regarding evaluation of risk-benefit of the MPs and especially in scientific advice situations. MDs are considered to be difficult to recruit in both agencies, MDs with industrial background were considered almost impossible to recruit even in Sweden with the large industry sector.

When discussing the strategic resources in the two agencies, one important factor should be taken into consideration: MPA was established as a self-financed organization whose income was fee-based (there are fees for various types of assessments, scientific advice activities, annual fees to keep the MP's on the market, etc.). They have had the freedom to develop the organization more or less as they wished as long as they kept their budget. This is in contrast to NOMA, which is also in practice completely fee-financed, but the "income" is directly transferred to the state treasury and it is the parliament that allocates the yearly budget for NOMA along with the tasks to be fulfilled.

Sections 4.4.1 and 4.4.2 describe the development and growth of the two organizations in general, with emphasis on the development of competences in relevant units that are or can be involved in innovation facilitation in addition to the units that have enjoyed the greatest political attention.

4.4.1 Influence of the strategic resources at NOMA

Before the establishment of NOMA in 2000, SLK had 98 employees in 1999, which has more than doubled in 2012.

The DG in the critical period of establishment of the new EU system and EMA (until 1996) was of the opinion that with the extension of the EEA agreement and inclusion of SLK in the

European collaboration system, SLK will be able to reduce the number of its (scientific) employees, since Norway could trust other countries to do the assessments (NOMA informants). According to one NOMA informant, some people at HoD still remember this and might be waiting for this time to come.

Between 1996 and 1999 there was lack of any strategic plan for adjustments to the extended EEA/EFTA agreement and preparations for the establishment of NOMA. For more details see section 4.3.

Table 6- Overview of NOMA’s organization growth with emphasis on selected units

Employees	1998	2000	2001	2006	2012
Total No. (full-time equivalent work years)¹⁾	98 (March 1 st 1999)	117	139	173 [^]	229 [^]
Master degree or higher²⁾ (% of permanent positions)	-	-	-	106 (61%)	134 (58.5%)
MD/PhD/Pharmacist	-	-	-	-	5 /39 /59
Scientific assessment of applications³⁾ (% permanent positions)	-	-	-	39* (22%)	51** (22%)
Pharmaco-economics	5***	-	9***	23#	23 [^]
Information	-	-	-	7#	21 [^]

¹⁾ According to the government documents (St. prop.) for the corresponding years

²⁾ According to the State’s database (SAP)

³⁾ Sources are the NOMA resource mapping document in 2006, a draft report for the department for MP approvals before the 2009 reorganization

[^] Number of Permanent positions

*In department for MP approvals plus 5 employees dealing with assessment of vaccines, and 3 employees who assessed the pharmacovigilance and 4 who assessed clinical trials applications.

** Estimation of total number of people working in all units corresponding to the same units reported in the 2006 organization

*** Reported in the annual reports for SLK/NOMA

Full-time equivalent work years according to the NOMA resource mapping document in 2006

The development of NOMA as an organization has been in accordance with the political goals and vision. Table 6 summarizes the growth of the organization in terms of the number of employees and specific competencies/units. Currently, 60% of the employees at NOMA have Master degree or higher. 25% of the employees are pharmacists with Master degree; several of them have PhD and are also included in that statistics.

The department of pharmaco-economics had a steep growth from 9 to 23 employees (+220%) between 2001 and 2006, which indicates the political focus on this function. Several of the employees have industrial background, and historically, many of the employees in this department have ended up in the pharmaceutical industry. According to the NOMA and HoD informants there is a direct contact and close collaboration, through both formal and informal meetings, between the Pharmaco-economics department at NOMA and the Pharmaceutical section at HoD, which is the unit that endorses NOMA's budget and annual plans. The current head of the Pharmaceutical section at HoD was employed as the head of the pharmaco-economics department at SLK/NOMA between 1998 and 2004. After moving to HoD, he took over the responsibility for the compilation of the 2005 national strategy for pharmaceuticals (see section 4.3).

The department of medical information was established in 2008 (previous to this it was the information section) and has as its main task to provide "producer-independent product information" in accordance with the NOMA's political goals. This also aims at reducing the costs of the MPs through provision of information basically in the direction of "cheaper medicines are as good as more expensive ones" (NOMA informant). Today this department has 21 employees, a 300% increase since 2006. According to the NOMA informants there is a close collaboration also between this department and the Pharmaceuticals section at HoD.

Following extension of the EEA agreement the assessment units needed to be strengthened with several committee members and assessors. NOMA strengthened the assessment function by 11 new employees in 2000. Today approximately 50 employees, including the committee members, work in the assessment units. The relative increase in the number of employees in these units has been 26% in the past 6 years despite the increasing number of scientific committees and more complex regulations and guidelines during this period.

Currently there are only 5 MDs working at the agency, 2 of them work in the assessment department as committee members. Nevertheless, 31 out of the 39 employees with PhD work in the assessment units (17% of the employees at NOMA have a PhD). This indicates the high level of scientific competence in these units. The number of PhDs at NOMA has been increased in the recent years, mostly due to the general increase in the number of PhDs in Norway and lack of other relevant jobs. Only a few employees in the assessment units have industrial experience.

The informants from the assessment department did not experience any direct contact with the Pharmaceuticals sections at HoD, apart from the formal and seldom reporting meetings (once or twice yearly) where the entire top management of NOMA attend. According to a key NOMA informant this is a sign of independency of the agency regarding decision-making; i.e. NOMA's scientific decisions cannot be politically or otherwise influenced by the ministry. NOMA informants from assessment units, however, argued that a closer contact with HoD might increase the ministry's understanding of their situation, tasks and obligations.

The observations regarding what units at NOMA have open and direct contact with HoD also reflect the political priorities, well documented in NOMA's steering documents (Section 4.3).

NOMA has always had employees with industrial experience. However, due to the historical lack of national innovative Big Pharma, most of them had background from daughter companies of international innovative giants where the research and innovation activities at large took place in other countries. According to one NOMA informant this might be one important reason for lack of attention towards strengthening of the organization to contribute to national innovative activities.

Despite NOMA's contribution to many of EMA's committees and working parties, the agency does not contribute to the scientific advice working party (SAWP). This is the group that receives and assesses the questions from the developers and provides them with advice on how to design their studies and is considered to be one of the most important initiatives in respect to innovation facilitation. According to one NOMA informant the reason that NOMA did not attend in SAWP to start with was attributed to both the continuous lack of sufficient resources (in the assessment units) and to the level of competence of the available resources at that time. This informant stated that NOMA is currently in quite a different situation with regard to competence and degree of maturity within assessment functions, and now would be the right time to undertake this kind of responsibility. The interviews at NOMA revealed that the recent awareness on NOMA's responsibility towards pharmaceutical innovation has been initiated by one of the newly employed top management members with a background from a large innovative pharmaceutical company.

4.4.2 Influence of the strategic resources at MPA

A review of MPA annual reports from 1992 onwards showed that the ambition of the agency and its mandate from political side has been to develop the organization to become a competitive European authority already in 1992 (LVs uppdrag är att utveckla organisationen

till en konkurrenskraftig europeisk myndighet). One of the main reasons for MPA to select this ambitious goal was to be able to control the MPs that enter the market to protect Swedish patients (MPA informant).

The changes in MPA's organization happened in parallel with establishment of EMA and Sweden becoming an EU member. At the time MPA was in possession of a DG who, according to the MPA informant, was a visionary clinician and the first Swedish member in the European Committee for Human Medicinal products (CHMP). It seems like the DG as well as several strong and ambitious senior scientific employees at the MPA were responsible for the selected vision of that time to become one of the leaders in the EU collaboration on drug approvals. All Swedish informants confirmed that such a vision could not have started from the political level; i.e. it was the key people and the management at MPA who recognized the potential of their available resources and competencies, decided that this organization can have a role in the EU, and influenced the politicians in this direction.

Table 7 illustrates the number of employees and some selected employee categories extracted from the MPA's annual reports. The organization has grown more than 300% since 1992.

The relative number of employees in the core business has been kept at 53-60%. The remaining employees are the leaders and the supporting functions (administrative officers/ secretaries/ assistants). The total number and percentage of MDs increased to 27 in 1998 following the EU membership of Sweden and the establishment of EMA. Unfortunately, the later reports do not include such details. According to a NOMA informant, many of the MDs at MPA were part time, since MPA management wanted them to keep their competence through clinical practice. The total number of PhDs has increased significantly, although its percentage of the total number of employees is decreasing.

According to the MPA informant, there are currently 200 people involved in the assessments and scientific advice activities. This does not include the pharmacovigilance unit who deals with follow up of side effects after marketing (signal detections and inspections).

Table 7- Overview of MPA's organization growth

Year	Total number of employees	Total number (%) within core competence ¹⁾	Number (%) pharmacist ²⁾	Number (%) MD ³⁾	Number (%) of other natural science major	Number (%) PhDs
1992-93	187	-	-	-	-	25 (13%)
1993-94	199	-	103 (52%)	17 (8.5%)*	-	40 (20%)
1994-95	204	-	101 (50%)	20 (10%)*	-	40 (20%)
1998	246	141 (57%)	70 (28%)**	27 (11%)**	24 (9.8%)**	80 (32.5%)
2001	308	172 (56%)	-	-	-	80 (26%)
2004	418	222 (53%)	-	-	-	100 (25%)
2009	590	351 (60%)	-	-	-	-
2011	687	-	-	-	-	146 (21%)

¹⁾ In Swedish: kärnkompetens

²⁾ Largest group

³⁾ Second largest group

* Includes also veterinarians

** In the core business

Due to the existence of leading innovative pharmaceutical firms in Sweden, MPA had better access to resources with industrial experience in R&D and innovation compared to NOMA. One of the informants from the Swedish SME 1 said:

“There have been lots of people from Academia in the MPA, or coming from the industry to the agency and vice versa. So I think there has been exchange of competences and experiences... There is a lot expertise in early phase research and they are even specialists in some areas.”

When MPA became an independent agency, it was a requirement that it should be self-financed. This is considered one of the main reasons that the management decided to develop the scientific assessment as the major pillar of the organization (MPA 1992-1993; Dyrdal 2004). This has brought some concerns regarding the degree of neutrality and independence of the agency from the industry. The MPA informant stated:

“The critics of some at the European level are that regulatory agencies are too close to the industry, since industry pays for the assessments, and the agencies depend on their fees. To us that does not influence our decisions. The assessors are not thinking about the fees”

4.4.3 Conclusions on the influence of strategic resources

MPA has always been a larger organization than NOMA, also when the population difference is corrected for. Since MPA has focused much more on the scientific competencies, it has attracted several MDs than NOMA has done. The relative number of PhDs at MPA has also been much higher than that of NOMA in the earlier years, and it has become more even just in the recent years. The exchange of employees and resources between NOMA: HoD: industry in the field of pharmaco-economics may remind of the exchange of people and experience between academia: industry: MPA in the scientific assessment related fields, illustrating where the priorities on building competencies and exchanging the experience have been placed in the two countries.

The political climate in Sweden at the time the country became EU member coincided with the existence of visionary DG and senior employees at MPA, all of them having scientific background, who decided to set ambitious goals for the organization in line with the political goals of the country. This was made possible also due to MPA being an independent self-financed organization based on the fees. Those ambitious goals not only formed the role of MPA in innovation facilitation, but also contributed to attraction of highly qualified employees with strong scientific background and industrial experience to further strengthen the role.

At NOMA, similar phenomenon is observed in the area of pharmaco-economics. The fact that the head of pharmaco-economics department at NOMA moved to HoD and has since been the head of pharmaceuticals section at HoD has settled the course for strengthening the field of pharmaco-economics. In addition, the information department with the main tasks in the same direction has been growing fast.

In the period of establishment of the new system of drug approvals, the DG of SLK did not seem to have a vision of taking the opportunity for growth, but actually thought that the scientific organization can be reduced. By the time the current DG (a former scientist/academic and assessor) started in her position, the main goals of the new organization were more or less established. Additionally, the competence of the assessors at that time was considered to be lower than necessary for getting involved in scientific advice activities.

In summary, there appears to be a strong connection between the type of background/expertise of the strategic key employees and their level of ambitions at the time of change in

both organizations. Those strategic persons seem to have strongly influenced the roles of both agencies also in the aftermath. Building strategic competences in different areas has attracted different types of competences to the two agencies which in turn has reinforced the defined strategic competence area.

NOMA does not seem to have a real choice of prioritizing its resources since its budget is connected to specified tasks and is allocated by the parliament/ministry of finance based on recommendations from HoD.

4.5 Other influential factors on the innovation scope and productivity

A plethora of literature has addressed the factors that impact innovation. Not only the determinants of innovative scope (Koberg et al. 2003) and innovative output (Ahuja et al. 2008) have been addressed, but also the effect of networking on innovation has been analysed (Pittaway et al. 2004). In general, the nature and structure of industry and the firms, network of the organizations, and the institutional factors such as national systems for innovation have been drawn upon as important elements of innovation.

There are numerous factors that may influence the innovative scope and productivity in pharmaceutical SMEs in Sweden and Norway, the most important ones are summarized in Table 8. These factors can be classified in different categories:

4.5.1 Government initiatives

In both countries there is some political attention towards innovation within (bio) pharmaceuticals and health sector. It seems, however, that Norway is a bit ahead concerning the infrastructure. This is particularly observed in the government funds and tax benefits. Also the bankruptcy regulation is in favour of Norway, which might partly explain why Norwegians are willing to take higher risks (cognitive variables in Table 8).

4.5.2 Scientific environment, clusters and network

In Norway, the number one field for clinical trials of products based on Norwegian research is cancer, followed by infections (50% less) which increased dramatically only in 2010 (Biotekforum 2011). Swedish pharmaceutical SME segment looks more diverse regarding therapeutic areas (Swedenbio 2011). Also in Sweden the number one therapeutic area for clinical studies is cancer, tightly followed by CNS (Central Nervous System). On the third level one finds infections, cardiovascular diseases, immunology and dermatology. Also there

Table 8- Influential factors in the national innovation environment in Norway and Sweden

The variables	Norway	Sweden
Scientific environment	Norwegian Radium Hospital in Oslo is the scientific centre with expertise within the field of cancer. Several successful SMEs stem from academic research in this hospital	Karolinska institute is the main scientific centre
Clusters/networks in pharmaceutical sector	Two national centres of expertise: Oslo Cancer Cluster (OCC) and Nansen Neuroscience Network (NNN)	Medicon valley (predominantly Danish firms), Stockholm/Uppsala, Umeå, Gothenburg
Trade associations	LMI is focused on innovative pharmaceutical industry. Recently LMI strategy changed to supporting the innovative SMEs by focus on political lobbying	SwedenBio established in 2002 to work for the benefit of entire life science industry in Sweden. Very active in political lobbying for the benefit of SMEs
Avg. R&D expenditure per biotech firm*	0.9 millions PPP \$	4.1 millions PPP \$
Biotech R&D expenditure by firm size **	< 50 employees: 60 % (102 firms) 50-249 employees: 35% (48 firms) > 250 employees: 40% (23 firms)	< 50 employees: 10% (45 firms) 50-249 employees: 30% (36 firms) > 250 employees: 60% (32 firms)
% Biotech to total R&D expenditures **	7.5%	5.4%
VC investments in life science as the percentage of GDP in 2007 **	0.008 Well below OECD average	0.089 Highest in OECD
Government funds	The Norwegian Research Council (NRC) and Innovation Norway.	Vinnova (Swedish innovation agency) established in January 2001. Many different actors, also regional. SwedenBIO works for centralizing this. Little work done beyond seed funds
Government initiatives	National strategy for Biotechnology, establishment of SIVA (incubator), Industrial PhD (50% financed by the government)	SciLifeLab established in 2010 (promoting university research), Innovationsbron established in 2004 (early phase investment, state-industry fund ownership)
Public innovation facilitation initiatives	The inventor and the University share the rights to the patent. Inven2 (TTO at the University of Oslo and Oslo University Hospital) evaluates and commercializes the inventions from these institutions	- The inventor owns the rights to the patent - Karolinska Development functions as the TTO, Karolinska Innovations encourages innovation among the students and academics and seeks to attract external collaborators.
Bankruptcy regulation and access to finance #	Most favourable among the Nordic countries	Weak on bankruptcy regulation, improving access to finance
Tax laws	SkatteFUNN since 2002: 20% reduction on the costs of preapproved projects concerning R&D activities	25% tax break for scientists that move to Sweden. A system similar to the Norwegian SkatteFUNN is on the way
Success stories among pharma SMEs	Pronova, Photocure, Algeta, Clavis Pharma, PCI Biotech, Lytix Biopharma, Pharmaq Norway has been very little affected by the recent financial crisis	Duocort (new formulation of an existing drug) which was sold to foreigners and disappeared. During 2010-2011 several firms have gone bankrupt probably due to the financial crisis ***
Cognitive variables***	- High risk takers (historically). - Individualists. - No problem if the firm or the product is sold to the foreigners as long as the money stays in the pharmaceutical business	- Believe in incremental innovations. - Good at creating systems and following them - Paradigm shift from Big Pharma to SMEs: How can we build a new Astra Zeneca if the innovative firms and ideas move abroad?

Nordic entrepreneurship monitor report 2010

* OECD science, technology and industry scoreboard 2011

** OECD 2009 (Beuzekom and Arundel 2009)

***Based on the interviews

are a large number of clinical studies in a group called “Other” including pain, osteoporosis and unknown. Additionally, there are several clusters in Sweden than in Norway. To summarize, Swedish clinical research is less focused and more diverse compared to the Norwegian clinical research. This might be one reason for the better success among Norwegian SMEs.

4.5.3 R&D expenditure and VC investments

The average R&D expenditure per biotech firm and VC investments within life science are extremely high in Sweden. Norway, however, seems to invest a larger portion of the total R&D investments in biotech. Nevertheless, these factors don't seem to explain the better performance of Norway regarding pharmaceutical SME's innovative productivity and scope.

4.5.4 Success stories and other cognitive variables

The number of successful pharmaceutical SMEs in Norway is striking. It is worth noting that the majority of them either develop products within cancer therapy, or within fish/marine segment. Both are considered to be strong areas of expertise in Norway due to the historically strong research at Norwegian Radium Hospital in Oslo, and the traditional fish industry and marine technology.

In Sweden, the pharmaceutical industry has been undergoing a significant transition since late 90s. Pharmacia was sold to Pfizer in 2002 and its different units were gradually sold and moved out of Sweden. AstraZeneca was formed from the Swedish Astra and the British Zeneca in 1999. Globally, it was the fifth largest pharmaceutical company in 2009, with R&D headquarters in Sweden. In the recent years the company has been shutting down different units in Sweden and in 2012 the company announced that they also move out the R&D headquarters. Thus, there is a fear that AstraZeneca will soon suffer the same destiny as Pharmacia and disappear from Sweden. It can be stated that the pharmaceutical environment in Sweden is experiencing a paradigm shift.

There appears to be a general concern about the great effort it will take for the nation to build another AstraZeneca. This was repeatedly mentioned by the Swedish informants on the industry side and is undoubtedly due to the history of the pharmaceutical industry in the two countries; i.e. in Sweden people cannot picture their country without a strong pharmaceutical engine whereas in Norway people are used to having none. The society's focus on the unbearable task of building another pharmaceutical giant might contribute to discouraging the SMEs who need to focus on small steps at a time.

All Swedish informants also were worried about the fact that the few national successful ideas/SMEs had been sold to foreign countries and vanished from Sweden. In Norway, only the informant from HoD expressed a similar concern. The informant from SwedenBIO expressed it in these words:

“In general half of the investments [in the SMEs] are from government funding and many of these companies are sold to the US. So I am interested to hear what the minister of finance says about this! Swedish tax money disappears like this.”

A Norwegian senior advisor at a venture capital investment organization within healthcare expressed his experience regarding licensing out the promising candidates or selling the entire firm to other countries with the following examples:

“In Norway, when Nycomed-Amersham was sold to GE Healthcare for 10 billion NOK, Oslo Stock Exchange lost 10 billion of its value. However, not many years later, we have managed to create the same value by Algeta, 5 billion NOK, Clavis Pharma, 2 billion NOK, Pronova, 2 billion NOK, plus all the other smaller ones at the sum of 1.5 billion NOK... I was surprised when similar phenomenon did not happen in Sweden when Pharmacia and Astra [units] were gone. There were plenty of competent former employees. I was expecting that with such locomotives a new generation of SMEs will flourish which in sum will become as big as those giants... [In Norway] GE Healthcare invested 4 billion NOK in the Lindesnes plant since they took over and they are not moving the manufacturing out... Here is where our ambitions should be...”

Another cognitive difference between the two countries was how much they believed in radical or breakthrough innovation. As the informant from Swedish SME 2 put it:

“In my world most [progress] comes in small steps. It is very seldom something ground-breaking pops up... Innovation normally goes in small steps.”

And the informant from SwedenBIO stated:

“There is very high risk in putting money in totally new ideas. Here in Sweden we need to think gradual, I think”.

The NOMA and HoD informants were mostly in favour of supporting new breakthrough innovation. For the MPA informant, it did not matter who asked for the advice and what type of project they had.

4.5.5 Conclusions on other influential factors on innovative productivity and scope

Factors that might explain the relative superiority of Norwegian innovative productivity and scope within the pharmaceutical SME segment are better infrastructure in government initiatives including tax and bankruptcy laws, more focused and less diverse therapeutic areas benefiting from concentrated cluster and other networks, and cognitive factors such as success stories among Norwegian SMEs and high risk taking attitude of Norwegians.

Sweden has superiority regarding R&D expenditures and VC investments, both are known as essential inputs to innovation. However, the “output” has been low. This is known as the “Swedish paradox” and has been studied by several authors (Andersson et al. 2002; Ejermo and Kander 2006).

A group in the Edinburgh University have analysed Swedish life science innovation strategy (Rosiello and Mastroeni 2010). They reported that in Sweden both government and private investors have become sceptical to investment in early stage SMEs within drug discovery and development (therapeutics) since such products are far away from market. In addition, the weak entrepreneurial culture and skills in Sweden were connected to the country’s industrial history by these authors. Although similar studies have not been performed to compare the situation in Norway and Sweden, the first two points (scepticism to invest in the drug discovery and development segment in Sweden as well as the lack of entrepreneurial culture due to the industrial history) can somehow explain the observed differences between Norwegian and Swedish SMEs’ innovative scope and productivity.

4 DISCUSSION

5.1 Summary of the main findings

The findings indicate that Norwegian SMEs within drug discovery and development seem to perform better than Swedish SMEs regarding innovative scope. The innovative productivity among Norwegian SMEs within biopharmaceuticals seems also to be on the rise during the past years, whereas Swedish biopharmaceutical SMEs do not show the same trend in all clinical phases. Since NOMA does not actively support or facilitate innovation whereas MPA has an active role in supporting pharmaceutical innovation, it seems plausible that in the cases of these two countries, the influence of control variables (such as government funds, tax and bankruptcy regulations, etc.) on innovative scope and productivity are much stronger than the

active involvement of the national medicines agencies. Norwegian SMEs seem to seek scientific advice from national agencies in other European countries, including MPA, and regard such guidance as vital for the progress of their programs. In summary, our findings did neither support nor rejected the positive influence of an innovation orientated national medicines agency on the national SMEs innovative performance.

The roles of NOMA and MPA are strongly influenced by institutional environment, both at the EU and the national level. In Sweden the EU and national forces seem to be aligned more or less along the same axis and direction in that both work in favour of promoting innovation in pharmaceutical industry. In Norway, however, the national forces appear to strongly moderate the influence of the EU institutional framework regarding innovation facilitation in pharmaceutical industry. There is no indication that NOMA has as one of its strategic goals or main tasks to facilitate innovation, although all informants thought that it should have had. NOMA's general role seems to be the traditional control of the pharmaceutical industry.

There is evidence that strategic resources and competences, including the vision of the management and their ability to take advantage of the right timing, at the time of establishment of EMA and/or official entrance to the EU/EEA collaboration in both countries have been important factors in shaping the direction and roles of the national medicines agencies. The findings also indicate that this may have resulted in that the two agencies have built their sustainable competitive advantages in completely different fields; i.e. MPA has selected the scientific activities, one aspect of it being guidance and support of innovative SMEs, whereas NOMA has selected pharmaco-economics to control the costs of (innovative) pharmaceuticals.

5.2 Theoretical implications

The aim of this study was to investigate the role of national medicines agency on promoting innovative scope and productivity of the national pharmaceutical SMEs. The results suggest that the initial assumption that MPA has predominantly an innovation facilitation role whereas NOMA has a controlling role seems to be correct.

It was proposed (P1) that an active role of the agency in innovation facilitation will positively influence both the innovative scope and productivity. The findings, though, do not support this proposal in that the Swedish pharmaceutical SMEs seem to be less innovative in terms of

scope and productivity than the Norwegian ones. This result was unexpected given the historical success of the pharmaceutical industry in Sweden and the active innovation facilitation role of MPA. We have discussed that this is due to the stronger influence of the control variables in the model, which seem to be different in the two countries. In Norway there seems to be a better infrastructure in government initiatives including tax and bankruptcy laws, more focused and less diverse therapeutic areas benefiting from concentrated cluster and other networks, and cognitive factors such as success stories among Norwegian SMEs and high risk taking attitude of Norwegians. “National systems of innovation” may be used as a collective term for this kind of national environmental variables encompassing government (economic) policies, industrial relations, cultural aspects, etc. (Freeman 1995; Lundvall et al. 2002). The literature on national systems of innovation within the field of biotechnology and pharmaceuticals is rich (Laursen 1996; Casper and Matraves 2003; Kaiser and Prange 2004). There is little doubt that such factors will have a tremendous influence on innovative productivity and scope of national pharmaceutical start-up firms. In fact, national medicines agencies may become a part of the national systems of innovation due to the knowledge spillover effect described earlier. In a future research it would be interesting to investigate the different roles of national medicines agencies in countries where most of such factors in their national systems of pharmaceutical innovation are similar. Since this is not the case for Norway and Sweden, it is not easy to conclude on this one factor alone. In addition, Norwegian SMEs actively seek advice and guidance from other countries’ national medicines agencies. This confirms that national medicines agencies do have an important role in positively influencing the innovative scope and productivity of national and foreign SMEs. This means that the first proposal (P1) is neither supported nor rejected by the findings.

The perceived roles of NOMA and MPA by the national industrial actors have contributed to different attitudes towards these two national agencies. In Sweden, MPA seems to be perceived as a discussion partner with a low threshold to contact, and an authority who is interested in the success of the SMEs. In Norway, the predominant controlling role of NOMA and the organization’s passive role in innovation facilitation has resulted in that the Norwegian SMEs turn to other countries’ national medicines agencies, including MPA, when they need guidance. Apart from being impractical as well as time and resource consuming for SMEs, this also means that NOMA does not have much influence, and quite limited knowledge, on the pharmaceutical innovative activities at the national level. This also means that NOMA is most probably not acting as a supporting organization in terms of knowledge

spillover for the national SMEs or academic research centres, and is losing the chance to strengthen its competence and actively contribute to the national scientific and innovative arena. As explained throughout this thesis, national medicines agencies are in possession of knowledge that can facilitate pharmaceutical innovation through guidance of the actors how to do the right things first time to avoid wasting time and resources. In Norway, where innovation in the health sector has become one of the national priorities, it is quite unfortunate that the innovative organizations and SMEs cannot take advantage of NOMA's knowledge in the best possible way.

The present study also aimed at investigating the influence of institutions and the strategic resources on shaping the role of the two national medicines agencies.

The findings seem to confirm that institutional environment at both EU and national level has had significant influence on the role of the national medicines agencies in innovation facilitation (proposition 2). As discussed in depth in section 4.3, in Sweden the EU forces seem to be mostly in the same direction as the national forces; i.e. innovation and industry orientation. In Norway, the national environment appears to be more in conflict with EU's innovation and industry orientation.

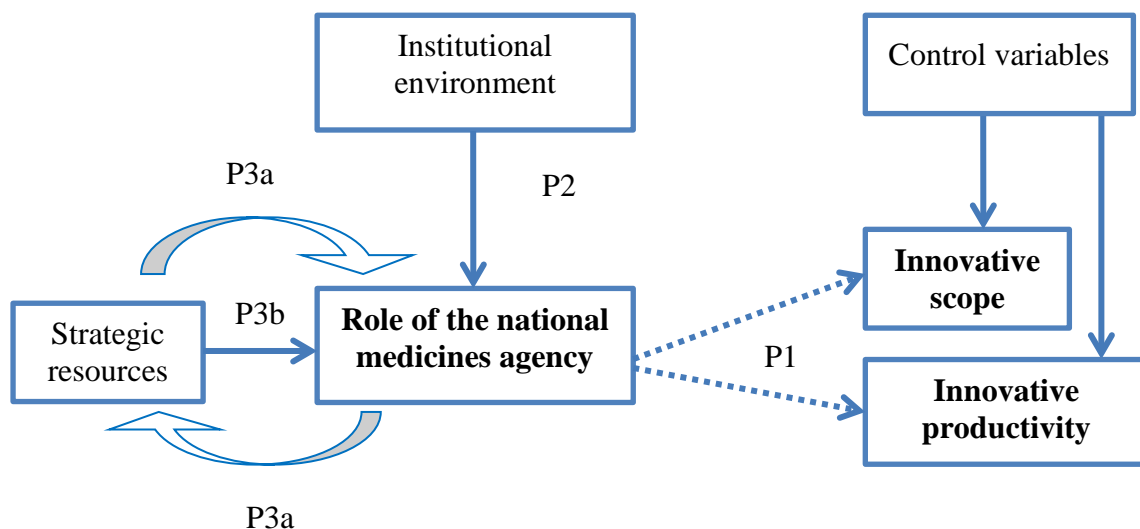
The impact of the strategic resources (management, timing, competences) in selecting the role by the national agencies also seemed to be supported by the observations (propositions 3a). However, there appears to be evidence that the relationship between the strategic resources and the role of the agency is a type of circular/cumulative causation. In the business literature "Circular causation is a common situation in complex systems (with several interconnected causes and effects) where an action is controlled or affected by its own outcome or result" (BusinessDictionary.com). In other words, existence of certain type of competence reinforces itself; i.e. when an organisation decides to strengthen an existing area of competence it will in turn attract people having high levels of that specific type of competence. There is evidence in the literature that cumulative causation is one of the crucial characteristics of the RBV (Foss 1998). Proposition 3a is therefore suggested to be revised to reflect this finding.

Revised proposition 3a: *The type and level of competencies of strategic human resources at the national medicines agency will influence the role of the agency with respect to innovation facilitation. The role of the agency has in turn a positive influence on further building up the strategic competencies.*

Proposition 3b seems to be fully supported by the observations. The management's recognition of the level of existing competencies and their decision on what competences to strengthen in the time window following a significant institutional change has been crucial to the different roles of the national medicines agencies. MPA decided to build up the scientific competence, mostly thanks to the visionary GD who had a scientific background and was a member of CHMP. At NOMA, on the other hand, the GD at the time of the establishment of EMA had the vision to reduce NOMA's scientific activities. In addition, the former head of pharmaco-economic department at NOMA moved to the ministry (HoD) as the head of the unit which endorses NOMA's budgets and annual plans. It should probably not be surprising that NOMA rather built up the competence within pharmaco-economics.

The outcomes of the study do not completely match with the proposed theoretical framework. Thus the modifications to the framework, presented in Figure 4, seem to be necessary.

Figure 4- Modified theoretical framework



5.3 Practical implications

One of the findings of this thesis is the indirect influence of a high-income-generating innovative national pharmaceutical industry in shaping the role of the national medicines agency with respect to innovation facilitation. It appears that when such industry is large enough to play an important role in the national economy, their needs will be recognized by

the government. As such, it can be suggested that existence of a blooming innovative industry would strongly contribute to shaping the role of the national medicines agency towards innovation facilitation through the influence on national institutional environment. As one key NOMA informant stated:

“I am really not sure if it is a national medicines agency’s facilitating role and attitude that contributes to more innovation, or is it a dynamic innovative pharmaceutical industry that forces the agency to take such a role? It is the hen and the egg dilemma...”

The interviews revealed that not all Norwegian pharmaceutical SMEs have ideas on how to use their own national medicines agency since they seek advice in other European countries. This is in contrast to the Swedish SMEs who took it for granted that they can use MPA as a discussion counterpart, both formally and informally. Both Norwegian SME informants and the LMI informant mentioned that having access to an innovation oriented and more visible national agency was highly beneficial. NOMA has yet to position itself with this regard and become more visible to the industrial customers.

As explained above, lack of national innovative and income generating Big Pharma in Norway has most probably contributed to the controlling role of NOMA. Nevertheless, waves of change with regard to national institutional forces seem to be on the rise, which might have an influence on the role of NOMA in the future:

- The historically unmatched increasing number of innovative (bio) pharmaceutical SMEs, forcing the politicians to recognize their potential of bringing income after the age of oil.
- The global consciousness on knowledge-based economy has also influenced the society and the politicians in Norway, resulting in substantial initiatives and whitepapers on innovation. Several of those are addressed in the case study section of this thesis.
- A 2010 study performed by European commission showed that Norwegians are among the most optimistic of Europeans regarding the potentials of biotechnology. This is a real change from the nation’s negative attitude in 1990s.
- There are signs that Norwegian authorities are about to reconsider their focus on strict control. One of the key NOMA informants stated:

“The European system is built on trust... I think that our society as a whole is undergoing a transition between control and [acknowledgement of] the actor’s responsibility”

- There is a concern about the decrease in the number of clinical studies in Norway (and other Nordic countries) and there have been (government) initiatives to improve the situation. NOMA can actively contribute to lower the regulatory barriers for the academia and SMEs.
- All Norwegian informants, including those from NOMA and HoD, indicated that facilitating pharmaceutical innovation should be included in NOMA’s strategy as one of the main points. Several of them suggested that NOMA should more actively share its scientific expertise both in the international and the national arena through active guidance and advice.
- Norway has achieved cost containment on pharmaceuticals. As one key informant at NOMA stated, now it should be time for strengthening the scientific assessment area and focus on scientific advice for the benefit of national industry.
- Several members of NOMA’s top management and many other employees in different units of NOMA are in favour of innovation facilitation (author’s own experience), mostly thanks to the one top manager who recently brought this vision to the organization.

What does all this mean for NOMA? Is this another time-window of opportunity? Shouldn’t HoD and NOMA be interested in taking a role in the national efforts regarding innovation facilitation and actively contribute? How can NOMA actively take part in building up a knowledge-based pharmaceutical industry in Norway?

One purpose of this study is to provide practical implications for NOMA in order to be able to meet the needs of its industrial customers. Several recommendations grounded on the interviews regarding the SME’s needs as well as the informants’ experiences follows:

- 1. National SMEs as well as academic research centres need active information, guidance and advice in order to do the right things the first time and, if necessary, to change the course early on. Otherwise they will waste valuable time and resources which is vital for their existence.**

The need of both SMEs and academic research centres for NOMA’s guidance is first and foremost related to scientific and regulatory guidance and how to obtain the necessary

permissions for manufacturing and import of the product for clinical studies. However, too much focus on starting the clinical studies in order to attract more financing may result in that SMEs lose their perspective on what they are developing and who will be interested to pay for it (LMI informant). Recently, all national authorities are becoming increasingly demanding regarding the health-economic requirements meaning that new MPs should bring real therapeutic benefit in order to get a high maximum price and be reimbursed. Therefore there is also a need to guide the developers on what type of products are needed and what studies to run in order to demonstrate the superiority of their product compared to the existing treatments. According to the LMI informant, it is increasingly popular for the European authorities to give this type of advice already in early phases of development. MPA invites TLV for such joint meetings at the request of the firms.

Having both scientific and the pharmaco-economic units in the same organization, NOMA can clearly benefit from mutual competence building between the assessment and the pharmaco-economic units. Through offering such joint meetings to SMEs, NOMA will be able to significantly contribute both to their innovative scope and innovative productivity.

2. Would Norwegian pharmaceutical SMEs perform even better if NOMA had an active role in innovation facilitation?

Norwegian SMEs seek advice at other European national medicines agencies. So their need for such guidance is not only confined to the formal scientific advice procedures through EMA. SMEs use the more informal scientific and regulatory advice at national medicines agencies to prepare for the more formal and time-consuming one at EMA. For the Norwegian SMEs, lack of access to a more innovation-oriented medicines agency in Norway means limited access to informal discussions, more preparations for more formal meetings and more wasted time on travelling. Consequently, if NOMA had an active role regarding innovation facilitation, Norwegian SMEs would have probably worked even faster and more effectively.

Nevertheless, the effect of a passive role of NOMA may be more serious for the academic research centres since they do not have any understanding or knowledge of the regulatory requirements for the MP development. As described elsewhere in the thesis, national medicines agencies may act as supporting organization, contributing to the entire national innovation environment through knowledge spillover; i.e. lessons learned from SMEs and larger pharmaceutical firms can be transferred to the academia.

One of the first steps in the direction of innovation facilitation and provision of scientific advice is that NOMA actively attends in EMA's SAWP. This aims at strengthening NOMA's scientific competence to find solutions for development challenges rather than to solely evaluate if the developers have done the right things by focusing on the assessment of the final documentations. Parallel to this, NOMA also needs to develop its organization culture to a more innovation-friendly direction. Arranging regular information and educational meetings for the SMEs and academia should become one of the major tasks for several functions and units at NOMA.

3. SMEs needs for information and guidance is on a more basic level than Big Pharma's needs.

To address this need, NOMA could build a national SME office.

This should be a low-threshold service-based office working as the first contact point. The SME office should be in charge of providing rapid and informal guidance and arranging larger information meetings in addition to informal product-specific meetings for the benefit of both SMEs and academic researchers. One way of actively providing information and education of the academic actors and SMEs is to use so-called "nodes" to bring this forward. Examples of such nodes can be research departments at the hospitals.

4. NOMA's strategy should encompass innovation facilitation as one of its main goals.

To be able to achieve the above mentioned goals, innovation facilitation must be included in NOMA's strategy as one of the main points. Otherwise, this will not be prioritized.

Not only NOMA, but also HoD needs to recognize NOMA's responsibility and tasks regarding innovation facilitation. A more holistic innovation and industry development policy is required through better communication and collaboration between NHD, HoD and the ministry of education and research. In Sweden, SwedenBIO has taken initiative for such a meeting between the three ministries resulting in formation of a group at the ministry of trade to develop the project further (SwedenBio informants).

5.4 Limitations of the study and future research

The author is currently employed at NOMA and has earlier been working in one of the successful Norwegian pharmaceutical SMEs. This is probably one of the reasons for somehow skewed analysis towards more weight on the Norwegian situation.

Selection of the informants and secondary data has been significantly influenced by the focus of the study on innovation in the national SMEs. Since MPA is innovation-oriented, none of the informants gave a hint on any controversial role or the resisting institutional forces in Sweden. Possibly, the outcome would have been different had an informant been selected from other segments such as pharmacy, prescribers, etc. The same type of limitation applies to NOMA. Since NOMA has not been active in innovation facilitation, the controversial and overall negative results mostly reflect this aspect, and not NOMA's role on other important tasks of the agency. The controversial responses and facts is the main reason for more weight on analysis of the Norwegian situation.

There are several interesting suggestions for further research in this area.

First of all, the study was not able to give an answer to the main research question about the effect of the innovation facilitation role of the national medicines agencies on the innovative scope and productivity of national SMEs, most probably because of the strong influence of the control variables being different in the two countries of Norway and Sweden. We suggested that such control variables are indicative of the national innovation system. A future research on this subject should be done by comparing the agencies in countries that are more similar with respect to the national innovation systems. It can also be suggested to study the roles of national medicines agencies with the perspective of them being a part of the national innovation system.

If NOMA decides to change its focus and role towards innovation facilitation, a longitudinal case study of NOMA can be suggested to investigate how a regulatory organization is able to change its focus from controlling the industry to acting more as an innovation supporting organization. Such study can also monitor the effect of this change of role on the Norwegian SME's productivity and scope in the longer run.

The most surprising finding in the study was that Norwegian pharmaceutical SMEs within drug discovery and development are in a better position than those in Sweden. It is necessary to emphasize that the results reflect only a "snapshot" of the situation in a limited timeframe.

The in depth study of this observation over time was out of the scope of this thesis and can be suggested as a future research. It will also be interesting to investigate the differences between the two countries in other pharmaceutical segments such as diagnostics and medical devices.

5 CONCLUSION

The main objective of the study was to better understand the role of national medicines agencies in promoting innovation within national (bio) pharmaceutical SMEs, by studying the case of Norway and Sweden.

The main research question and the related sub-questions to be answered were:

5. What role do national medicines agencies play in promoting the innovative scope and productivity of the pharmaceutical innovation performed by SMEs in their own countries?
 - a. How can national medicines agencies facilitate and contribute to (bio) pharmaceutical innovation in terms of innovative productivity and scope?
 - b. How does the institutional environment of the national medicines agency influence its role?
 - c. What strategic resources at national medicines agencies are important in facilitating innovation?
 - d. What other factors in the national innovation environment contribute to the innovative productivity and scope of SMEs?

The overall results to the main question indicate that, in case of Norway and Sweden, there was no direct relationship between the active innovation facilitation role of the national medicines agency and the innovative scope and productivity of the national (bio)pharmaceutical SMEs. It was concluded that the influence of other factors in the national innovation environment (sub-question d) were stronger than the innovation facilitation role of the national medicines agency. This, however, does not mean that national medicines agencies do not have a role in positively influencing the innovative scope and productivity of national actors. To the contrary, national medicines agencies can play a significant role in guiding SMEs and academic environments how to do the right things first time. This is supported by the fact that Norwegian SMEs seek advice and guidance in other European countries. In addition, by acting as supporting organization, national medicines agencies can contribute to

the entire national pharmaceutical innovation environment through knowledge spillover. Consequently, if NOMA had an active role regarding innovation facilitation, Norwegian SMEs probably would have worked even faster and more effectively.

The study described the influence of the European and national institutional environment on the different roles that the two agencies have taken and concluded that in Sweden the European and national institutional forces seem to be aligned along the same axis and both work in the same direction of contribution to innovation, while in Norway the national institutional forces strongly moderate the influence of the EU's institutional framework resulting in NOMA's predominantly controlling role on the pharmaceutical industry (sub-question b).

We also demonstrated the evidence that strategic resources and competences, including the vision of the management and their ability to take advantage of the right timing at the time of establishment of EMA and/or official entrance to the EU/EEA collaboration in both countries have probably been important factors in selection of the roles and building their sustained competitive advantages in completely different fields (sub-question c).

The "practical implications" section addresses the "sub-question a" with several suggestions on how it is possible for NOMA to contribute actively to innovative productivity and scope of the national SMEs.

The time has long passed when a pharmaceutical company could perform all stages of product discovery and development on its own. Today's complex medical challenges and scientific progress demand an entire network of collaborations to deliver new therapies. In the context of development of a knowledge-based industry for a future sustainable national economy, the important role of a national medicines agency cannot and should not be underestimated. Further study in this area, as elaborated in the discussion part, is therefore recommended.

APPENDIX

Appendix A- List of SMEs in Norway and Sweden involved in Drug discovery and development

Norway:

Affitech research, Algeta, APIM Therapeutics, Algipharma, Avexxin, BerGenBio, Biolink, Bionor Pharma, Biosergen, Biothec Pharmacon, Clavis Pharma, Lytix Biopharma, Nordic Nanovector, PCI Biothec, Pharmaq, Photocure, Pronova Biopharma, SantoSolve, Serodus, siRNAsense, Targovax, Vaccibody.

Sweden:

Active Biotech, Adenovir Pharma, Affibody, Albiero, Allenex, Alligator Bioscience, Aprea, Athera Biotechnologies, Avaris, Axcentua Pharmaceuticals, Axongen, Betagenon, BioArctic Neuroscience, BioInvent International, Camurus, Cantargia, Cardoz, Cebix, Chemilia, Chronotech pharma, Creative Antibodies Sweden, Dermagen, Dyamid Medical, Dilafor, Eribis Pharmaceuticals, Essentys, Eurocine vaccines, Glucox Biothec, Hansa Medical, Imed, Immunicum, Index Pharmaceuticals, Isifer, Kancera, Karo Bio, Laccure, Lidds, Mivac, NeuroNova, NeuroVive Pharmaceuticals, NovaSAID, Oasmia Pharmaceuticals, Omnio Healer, OncoPeptides, Oxthera, Oxypharma, Pergamum, Pharmalink, PharmaSurgics, PledPharma, Premacure, Redoxis, Respiratorius, SentoClone, TikoMed, Umecrine Mood, Vicore, WntResearch, Ximmune, Isconova, Medivir, Simplexia.

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