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Institute of Health Policy and Management

The collaborative practices of the Dutch pharmaceutical regulatory authorities

A qualitative study exploring employee's perspectives

Master Thesis

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by

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Contents

List of Abbreviations

CCMO:	Central Committee of Medical Research Involving Human Subjects
CIBG:	implementation agency of the Ministry of Health, Welfare and Sport
CVZ:	Dutch Healthcare Insurance Board
EMA:	European Medicines Agency
GCP:	Good Clinical Practice
GDP:	Good Distribution Practice
GMP:	Good Manufacturing Practice
IGZ:	Healthcare Inspectorate
IT:	Information Technology
LAREB:	The Netherlands Pharmacovigilance Centre
MEB:	Medicines Evaluation Board
METC:	Medical Ethics Review Committee
RIVM:	National Institute of Public Health and Environment
SCM:	Supply Chain Management
VWS:	Ministry of Health, Welfare and Sport
WHO:	World Health Organization

1. Background and Introduction

1.1 Historical development of drug regulation

The discovery and development of new drugs is a very lengthy and costly process. *(Jensen, 1987)* Before a new medicine becomes available to patients, it will have gone through a long process of research, registration and market introduction. In the Netherlands, the registration of medicines was introduced in 1963 due to a drug catastrophe in the early 1960's. *(Drost and Reijnders, 1987).* Thalidomide, which was highly prescribed as a sleeping pill and morning sickness treatment for pregnant women from1950 trough 1960, caused thousands of birth deformities before it was removed from the market. This disaster was a wakeup call for regulatory authorities creating an increased awareness of drug safety and the introduction of drug regulation. *(Bouvy, 2013)*

1.2 Structure of drug regulatory agencies in general

Concerns related to the efficacy and safety of drugs have caused most governments to develop regulatory agencies to oversee development and marketing of drug products and medical devices. According to the World Health Organization's (WHO) 2002 report 'Effective drug regulation', the aim of drug regulation is twofold: first, to protect public health by keeping low-quality, unsafe, or inefficacious products from entering the market, and second, to promote public health by ensuring drugs reach patients without unnecessary delay. Drug regulation encompasses a variety of key functions including:

(I) *evaluation of safety and efficacy data and control of clinical drug trials,*

(II) *licensing and inspection of manufacturing facilities and distribution channels,*

(III) *product assessment and registration,*

(IV) *monitoring of adverse drug reactions.*

Each of these functions targets a different aspect of pharmaceutical activity. For effective protection, these functions must act in concert. In some countries, all functions related to drug regulation come under the jurisdiction of one single agency, which has full authority over the command and control of these functions. In other countries, drug regulatory functions are assigned to two or more agencies at either the same or at different levels of government. *(Ratanawijitrasin and Wondemagegnehu, 2002)*

1.3 Drug regulation in the Netherlands

In the Netherlands, the drug regulatory functions are assigned to seven authorities: the Medicines Evaluation Board (MEB), the Ministry of Health, Welfare and Sport (VWS), an implementation agency of the Ministry of Health, Welfare and Sport (CIBG), the Central Committee of Medical Research Involving Human Subjects (CCMO), the Healthcare Inspectorate (IGZ), the National Institute for Public Health and the Environment (RIVM) and the Netherlands Pharmacovigilance Centre (LAREB). Officially, these regulatory agencies are working together under the title *'pharmaceutical regulatory chain' ('geneesmiddelenketen').*

Given that there are multiple organizations required to work together to ensure effective and safe pharmaceuticals it is imperative to understand how this complex structure functions and to what extent they are functioning as a chain. To date, there is no empirical evidence regarding the interaction and

collaboration between these pharmaceutical regulatory authorities. This thesis will, on behalf of the National Institute for Public Health and the Environment, contribute to a better understanding of how these regulatory organizations interact from the perspective of the regulatory authorities' employees.

1.4 Supply Chain Management

Supply Chain Management, the coordination between businesses and processes involved in producing and delivering a product or service, has been widely used in other industries for decades. Many of these industries have attributed their success to effective supply chain management. However, supply chain management in healthcare has lagged. There should be efficient transactions between the organizations for SCM to work.

While there is numerous literature validating the importance of supply chain management, there is limited academic literature that addresses the challenges unique to the healthcare industry. *(Meijboom et al, 2010)* Additionally, there is no empirical evidence about the collaborative practices between the Dutch pharmaceutical regulatory authorities. Therefore, the aim of this thesis project is to study the collaborative processes within the drug regulatory chain using a supply chain perspective. This perspective implies a business focus on inter-organizational conditions and requirements necessary for delivering products and service across organizational borders. Finally, a comparison will be made between the practice and the theoretical framework of Supply Chain Management.

1.5 Problem

The Dutch drug regulatory chain is a complex structure, which consists of seven different organizations required to work together to ensure effective and safe pharmaceuticals. It remains unclear how this complex structure functions and to what extent they are functioning as a chain.

1.6 Objective

The primary objective of this thesis is to study the collaborative processes of the Dutch drug regulatory chain from the employee's perspectives and provide a comparison with aspects from supply chain management.

Research question(s)

How do employees of the Dutch drug regulatory authorities experience the collaborative practices and how do these experiences relate to supply chain management literature?

I. What are characteristics of good supply chain management?
II. Who are the chain partners and what are their responsibilities?
III. How do employees of the chain partners experience the collaborative practices?
IV. How do these experiences relate to good supply chain management?

2. Theoretical framework

What are characteristics of good supply chain management?

This chapter outlines the theoretical framework used to describe performance of the Dutch drug regulatory chain. It contains an introduction of the Supply Chain Management (SCM) theory and outlines aspects necessary in order to implement SCM.

2.1 Definition of Supply Chain Management

The idea for a chain of care activities performed by multiple organizations emerges from the field of Supply Chain Management. This discipline is rooted in business sectors and addresses inter organizational collaboration problems by using a supply chain perspective. *(Meijboom et al, 2010)*
The framework emphasizes the interrelated nature of SCM and the need to proceed through several steps to design and successfully manage a supply chain. The members of a supply chain include all companies- /organizations with whom the focal company interacts directly or indirectly through its suppliers or customers, from point of origin to point of consumption. *(Lambert and Cooper, 2000)*
The supply chain represents a way to visualize all the necessary steps from beginning to end to deliver products or services to the customer. *(Meijboom et al, 2010)* These steps are spread over several organizations involved in the supply chain. Given this fact, there is substantial room for conflict between the perspective of the supply chain and organization boundaries, interfaces between organizations that become barriers to coordination and product flow.

There are different definitions of supply chain. One definition defines a supply chain as a set of firms that pass materials forward, when several independent firms are involved in producing a product, and deliver it to the end user in the supply chain. *(Mentzer et al, 2001)* Another definition notes a supply chain is the alignment of firms that bring products or services to the market. Lastly, supply chain is also defined as a network of organizations involved in the up- and down-stream production of products or services for the ultimate consumer *(Christopher, 1992)*
Given these definitions, for the purpose of this paper, the supply chain is defined as a set of organizations (the regulatory authorities) directly involved in the flows of products, services and/or information from a source (development of a pharmaceutical) to the patient (having access to the pharmaceutical). Implementing the SCM theory can be seen as an organizational process that seeks to achieve seamless and coordinated service.

2.2 Aspects of Supply Chain Management

Successful supply chain performance requires a couple of factors. Since the SCM theory is primarily business oriented, aspects like contracts, payment schemes and other arrangements are out of scope of this thesis. Our focus is on inter-organizational aspects and requirements necessary for delivering services across organizational borders. Below, eight factors are outlined which will be used to study the interaction and collaboration within of the Dutch pharmaceutical regulatory chain.

Agreed vision and goals

Min and Mentzer (2004) identify the concept of SCM as including an agreed vision, goal and supply chain leadership. The literature describes SCM practices from a variety of different perspectives, but all with a common goal of ultimately improving organizational performance. Before SCM can be developed, a common vision and goals is required for the supply chain members. *(Sing, 2013)*

Partnership

Strategic partnership is defined as the long-term relationship between the organization and its suppliers. It is designed to leverage the strategic and operational capabilities of individual participating organizations to help them achieve significant ongoing benefits. Effective partnership emphasizes direct, long-term association and encourages mutual planning and problem solving efforts. Such strategic partnerships are needed to promote shared benefits among the parties and ongoing participation. Strategically aligned organizations can work closely together and eliminate wasteful time and effort. *(Li et al, 2004)*

Inter-organizational power

Power is defined as the ability of one firm to influence the intentions and actions of another firm. *(Maloni and Benton, 1999)* Inter-firm power often plays a critical role in the supply chain. Given that power may influence the inter-firm relationships driving supply chain integration, such power may thus also affect the performance of the chain. Performance is defined as the ability to effectively attain desired goals and objectives and empirical research has demonstrated that integrated relationships can significantly enrich performance. *(Maloni and Benton, 1999)* If performance is significantly dependent upon the relationship, the awareness of the importance of power is magnified. Many practitioners would consider power to be an omnipresent, unmanageable part of everyday business. Inter-firm power could be a barrier to the win-win integration process by upsetting the mutuality of supply chain relationships. Thus, power plays a significant role in the supply chain and different sources of power have contrasting effects upon inter-firm relationships in the chain. *(Maloni and Benton, 1999)*

Coordination of the supply chain

Coordination among independent firms is key to attaining the flexibility necessary to progressively improve processes in response to changing market conditions. *(Simatupang et al, 2002)* Poor coordination among the chain members results in dysfunctional operational performance. Some of them include higher costs, longer delivery times, higher levels of loss and lowered customer service. *(Simatupang et al, 2002)* Changes occurring in any of the chain partners are likely to affect the performance of the other supply chain partners. Coordination of fragmented services is necessary in order to improve efficiency. To be able to deliver more efficient, transparent and trustworthy service either differentiation has to be reduced or integration increased.

So far, this chapter conceptually presented how some of the problems mentioned in the introduction chapter can be dealt with using supply chain perspective. The objective of SCM is to create the most value, not simply for the company, but for the whole supply chain network including the end customer. Consequently, supply chain process integration should be designed to increase process efficiency and effectiveness for the entire supply chain.

Information sharing

Information sharing is cited by many studies as the most critical agent in the trust building process of supply chain implementation. A positive relationship is confirmed: information sharing reduces the degree of uncertainty which in turn indirectly improves the level of trust among the supply chain partners.

Partners in the supply chain may be reluctant to share information because of costs. Many companies think that owing information gives them a crucial competitive advantage, and therefore, fear sharing it freely, though companies in the supply chain would benefit if they did. *(Agrawal and Pak, 2001)* This hesitancy can be due to different factors including the sharing of sensitive information and, the perceived threat of giving away a competitive advantage to other firms. Ambiguous regulations and ineffective lines of communication may also inhibit the trust-building process necessary for a successful and ultimate commitment. As a result, the information that each participant uses to make its decisions doesn't reflect conditions in the industry as a whole.

Continuous and open communication between and among supply chain partners minimizes any degree of uncertainty and/or misunderstanding. The dispersal of information by chain partners will increase the speed with which it is shared, its accuracy, quantity and the transparency of the whole chain. *(Agrawal and Pak, 2001)*

Information technology

Gunasekaran and Ngai (2003) argue that Information technology is like a nerve system for SCM and that it is impossible to achieve an effective supply chain without information technology (IT). Moreover, it is essential to integrate the activities from both inside and outside of an organization. This requires an integrated information system for sharing information on the different value adding activities of the supply chain. Increased information sharing between members of a supply chain using electronic data interchange (EDI) technology reduces uncertainty and greatly improves the performance of the supply chain system. Companies need to invest large amounts of money in redesigning organizational and technical processes of traditional and fundamental product distribution to achieve an IT-enabled supply chain system.

Integration of processes

Thousands of activities are performed and coordinated within a company, and every company is in some way involved in supply chain relationships with other companies. When two companies build a relationship, some activities will be linked and managed between the two companies. *(Lambert and Cooper, 2000)* Since both companies have linked internal activities with other members of their supply

chain, this link might be considered as a supply chain network. Hakansson and Snehota (1995) illustrated that the structure of activities between organizations is a critical cornerstone for creating unique and superior supply chain performance. “Successful supply chain management requires a change from managing individual functions to integrating activities into key supply chain business processes.” *(Lambert et al, 1998)*

Furthermore, cross-functional and cross-organizational teams are proposed. It is widely recognized that expertise from various functions is required to address the wide range of product and process related problems*. (Meijboom et al, 2010)* A lack of intercompany consistency causes significant friction and inefficiencies in supply chains, for instance when companies use different names for similar processes and similar names for different processes.

Thus, cross-functional or cross-organizational teams facilitate short and direct information lines, particularly if communication needs to cross-functional or even organizational boundaries. *(Li et al, 2006)* Short and direct communication lines combined with standardizing the format in which information exchange takes place between departments or organizations can minimize such misunderstandings. To this end, integration should be a continuous process. *Kannan and Tan (2005)* emphasize the need to continuously improve the integration of activities across the supply chain and to keep searching for new ways to integrate supply chain activities. Meetings should therefore not only focus on the content but also on how to improve the integration between different departments and organizations. Focus should lie at the interface between providers. *(Meijboom et al, 2010)*

Cycle time

Cycle time is central to a firm’s strategic success. Cycle time here is defined as ‘the length of time between taking an order and delivery of the needed product to the customer.’ *(Hult et al, 2007)* It is a key metric for directly assessing supply chain function. Excellence in cycle time allows firms to grow faster, control overhead and inventory costs, and get new products introduced early on the market. *(Hult et al, 2007)*

3. Methodology

This chapter outlines the methodological framework used in this thesis project for describing the performance of the Dutch pharmaceutical regulatory chain. It starts with an introduction of the data used in the research. Next, it describes the focus group interviews done with the seven Dutch regulatory authorities concerned with ensuring quality and safety of a pharmaceutical. Finally, it concludes with a description of the method used to analyze the transcripts and interpreting the output of the respondents.

In order to answer the research question concerning the drug regulatory chain, focus group interviews with the employees of the chain partners were conducted. The computerized PubMed system was used to identify studies regarding drug regulation and the registration procedures. Additionally, ATLAS.ti qualitative data analysis software was used to code and analyze the data.

3.1 Literature review

A literature review was conducted for three reasons: to understand the topic of the research more thoroughly, to identify whether there is previous research done on the topic, and to answer the first sub question concerning tasks and responsibilities of the regulatory authorities. The PubMed database was used to identify studies concerning drug regulation in the Netherlands or elsewhere. The search strategy was developed using combinations of search terms relevant to pharmaceutical regulation. The following search terms were used: pharmaceuticals, medicines, drug regulation, drug policy, and Netherlands. Once the relevant articles were selected, bibliographies of these articles were searched for additional references. Moreover, the seven organizations' websites were consulted to identify their main tasks and responsibilities.

3.2 Focus group

We undertook a qualitative study using focus groups to explore employee's experiences, opinions and beliefs concerning the collaboration between the different organizations. Focus groups are an efficient way of gathering views from several individuals simultaneously and providing insights into issues that would be potentially less accessible without the synergy produced from group discussion. The aim of the focus groups was to ask participants/employees for their perspectives on the collaboration and interaction between the different organizations. Focus group sizes were limited to between six to eight participants.

3.3 Recruitment and participants

Over a period of 13 weeks from 2012-2013, a total of seven focus groups were conducted. The focus groups were held at the employees work location. The respondents were contacted through the directors of the seven organizations, who were asked to distribute to their staff the invitation to participate. Potential participants were followed up by a telephone call several days later. The invitations issued to participants included detailed information about the background, aims and researchers conducting the study.

3.4 Focus groups conduct

Upon arrival at the focus group location, participants were provided with a PowerPoint presentation. The presentation started with an introduction screen, explaining the purpose and subject of the interview. Participants were informed that they could withdraw from the discussion at any time. We moderated each focus group interview using a semi structured topic guide. Interviews were conducted by two study members, one acted as the primary interviewer and the other focused more on taking supplementary notes. The primary interviewer encouraged participants to relay experiences, exchange opinions and discuss issues with their peers about their experiences of the different aspects of SCM.

Interviews were structured around a set of root questions concerning the following collaborative aspects: 'agreed vision' (as an indicator of whether people worked with a chain perspective), 'collaboration', 'information sharing', 'information technology', 'timelines', 'inter-organizational power' and 'coordination'. (**Table I**) There were three main questions. The first question was more an introduction question where participants were asked to tell something about their tasks and responsibilities. The second root question concerned their experiences with the above mentioned aspects. Finally, the respondents were asked whether they had ideas for improvement or other additional suggestions. Where necessary, further questions were asked to extract additional information, clarify unclear comments and probe issues raised. Discussions lasted 60 minutes and were audio recorded with permission. After each focus group, a debrief followed to discuss the emerging themes, and notes were checked for consistency and merged.

3.5 Empirical evidence for questions

Table I: Empirical evidence

Research object	Literature quotes	Sources	Main interview question
ORGANIZATION BACKGROUND			
Structure of activities	*"Our research further suggested that the structure of activities/processes within and between companies is vital for creating superior competitiveness and profitability."* *"The implementation of SCM involves identifying the supply chain members with whom it is critical to link, what processes need to be linked, and what type/level of integration applies to each process link."*	D. M. Lambert and M. C. Cooper. Issues in Supply Chain Management, 2000	What are the key competencies of your organisation?
TO PROVIDE EMPIRICAL EVIDENCE ABOUT THE COLLBABORATIVE PRACTICES OF PHARMACEUTICAL REGULATORY CHAIN			
Agreed vision	*"The literature portrays SCM practices from a variety of different perspectives with a common goal of ultimately improving organizational performance. Before SCM can be developed, a common vision and goals is required for the supply chain members. It is observed that global weightage of top management*	Min, S., & Mentzer, J.T. (2004). Developing and measuring supply chain management concepts. *Journal of Business Logistics, 25*	Do you think there is a common vision within the chain? (If yes, how can you tell there is? What are benefits? If not, why and do you think it is desirable?)

	commitment is highest among strategic factors and agreed vision and goal of supply chain members among sub factors."		
Collaboration	*"Strategically aligned organizations can work closely together and eliminate wasteful time and effort."* *"True collaboration needs more complex forms of communication that go beyond simply sharing numbers and words – but requiring shared thinking, planning, and working together towards a common goal."*	S Li et al, 2006	Do you think the medicine supply chain has a common goal? (If yes, how do the partners try to achieve the desired aligned goals?) How is the relationship between your company and the other chainpartners? Does your company collaborate with the supply chain partners? (If yes, in what kind of situation? If not, why not?)
Power	*"a strong leader firm may use its power to influence, rather than dominate, the supply chain behaviors of other firms; in either case the leader's power will influence the other members of the supply chain, with either a beneficial or injurious effect depending on the power bases used. Positive uses of power tend to lead to stronger supply chain relationships, which in turn lead to improved performance".*	Defee and Stank, 2005	Which factors do you think can affect the supply chain collaboration? Does your organisation think that its partner's power can affect the supply chain collaboration? (Who? Why? How?)
Coordination	*"Coordination among independent firms is the key to attaining the flexibility necessary to enable them to progressively improve logistics processes in response to rapidly changing market conditions."* *"Poor coordination among in the chain members can cause dysfunctional operational performance."* *" Simply because there is an apparent need for someone to take a helicopter view of the whole terrain doe not mean this happens in practice."*	T. M. Simatupang, A. C. Wright and R. Sridharan, 2002 J. Storey and C. Emberson. Supply chain management: theory, practice and future challenges. 2006	Is there anyone responsible for managing/coordinating the activities of the medicine supply chain? Which individuals or groups are actually engaged in such practice? How?
Informationsharing/ Transparency	***Level of information sharing:*** *"Virtually every author indicates that the information flow facility structure is key. The kind of information passed among channel members and the frequency of information updating has a strong influence on the efficiency of the supply chain."* *"Management believed that an improved information flow would naturally lead to an improved product flow."*	Lambert and Cooper, Issues in supply chain management, 2000. S. de Treville, R.D. Shapiro and A. Hameri, 2003	Given the shared common goal, does your organisation get information/data from the supply chain partners? (If yes, when and how? If not, why not) What information does your organisation (want to) transfer to your supply chain partners? (Why?)

	Quality of information sharing *"Regarding the content and quality of information to be exchanged, it is important to include information that is critical and proprietary of nature. Moreover, it should be accurate, timely and adequate."* *"While information sharing is important, the significance of its impact on SCM depends on what information is shared, when and how it is shared, and with whom."*	Li et al, 2006 Li et al, 2006	Regarding the content of the information, what can you say about the quality of the information shared?
Information technology	*"Information systems should be linked across functional departments as well as organizational boundaries, so that records can be accessed and updated by every provider. This will reduce the likelihood of duplicated tests, because everybody can check whether or not a test has been conducted"* *"Successful implementation of IT as an enabler of SCM depends upon the support of top management and overall organizational structure."*	A. Gunasekaran and E.W.T Ngai. Information systems in supply chain integration and management. 2004	Are the information systems linked across the chain partners? (If yes, which systems? What is perceived benefit?) (if not, why not?)
Process Integration	*"Short and direct communication lines, combined with standardizing the format in which information exchange takes place between departments or organizations can minimize misunderstandings. To this end, integration should be a continuous process."* *"When employees from different departments or organizations are united in one team, their decisions will be less focused on the short-term benefit for their own department or organization, and more focused on the consequences of each decision for each department or organization."* *"Different names were used for similar processes, and similar names for different processes. We believe that this lack of inter-company consistency is a cause for significant friction and inefficiencies in supply chains."*	B. R. Meijboom, S. Bakx and G. P. Westert. Continuity in health care. 2010 D. M. Lambert and M. C. Cooper. Issues in Supply chain management. 2000	Do you think processes in the medicine supply chain are integrated? (If yes, to what extent and what is the benefit? If no, why not? do you think it is necessary?) Are there cross-functional teams?
Cycle time: **The length of time between taking an order and delivery of the needed product to the customer**	*"Cycle time is a key metric for directly assessing supply chain functioning. More importantly, cycle time is central to a firm's strategic success"*	G.T.M. Hult, D. J. Ketchen and M. Arrfelt. Strategic Supply Chain, 2007	What is the length of time between taking an order and delivery of the needed products?

3.6 Data analysis

The audio recordings were transcribed and supplementary notes were reviewed prior content analysis. The seven transcripts were initially open coded using Atlas.ti, which was followed by a second level of coding to categorize the open codes into categories of SCM. Statements not fitting the framework of supply chain management were grouped in a separate category. The coding was reviewed for consistency and to ensure that no significant concepts had been overlooked or statements left uncoded. This resulted in seven coding schemes, each containing one organization/focus group. Similar codes in the coding schemes were grouped and regrouped to further refine the data. Finally, to obtain an overview of all the codes, all codes from the seven organizations were put into a matrix. Two researchers independently conducted the analysis, which was then cross checked and reviewed for consistency. Discrepancies and theme overlaps were reconciled through discussion between researchers and refined until consensus was reached.

Given my a priori descriptive goal, I did not seek to generate new theories about supply chain management; rather, I focused on describing common experiences and identifying barriers that might be amenable to interventions to improve chain processes.

4. Results

This chapter describes the results of the thesis research. First, it presents the results of the literature review. Second, it continues with a description of the results from the focus group interviews with the employees of the seven regulatory authorities.

4.1 Who are the different chain partners and what are their responsibilities?

- **Central Committee on Research Involving Human Subjects (CCMO)** Before someone is allowed to market a medicine in the Netherlands, one must conduct research or arrange for research to be conducted to test that medicine. In case this research comes under the Medical Research Act or the Embryos Act, one is required to submit the research protocol to a recognized medical ethics review committee (METC). Without the committee's approval, research cannot go ahead. In some cases, for example, study protocols in which gene therapy, xenotransplantation, substances that fall under the Opium Act, cell therapy, vaccine development or interference DNA is used, the CCMO acts as the research committee. Both committees protect subjects taking part in medical research by reviewing the research based on statutory provisions laid down for them and taking account of the interests of medical progress. The central Committee on Research Involving Human Subjects oversees medical research involving human subjects in the Netherlands and supervises the local METC's.

- **Health Care Inspectorate (IGZ)** The Healthcare Inspectorate forms the Public Health Supervisory Service, and promotes public health through the enforcement of qualitative health services, prevention measures and medical products. Manufacturers, distributors and importers of medicines intended for human use must hold a manufacturing or wholesale authorization. The inspectorate enforces this legal obligation in the Netherlands. The inspections are primarily concerned with compliance of Good Manufacturing Practice(GMP), Good Distribution Practice(GDP), and Good Clinical Practice (GCP) guidelines.
    - Good Manufacturing Practice (GMP) is part and parcel of quality management. It ensures that products are always produced and inspected in accordance with the established quality norms for the intended application, as well as the terms and conditions of the marketing authorization.
    - Proper storage and distribution (GDP) is also part of quality management and ensures that quality is maintained at the level prescribed by the marketing authorization or product specifications throughout the distribution chain
    - The Healthcare Inspectorate carries out inspections to verify whether clinical studies are carried out in accordance with the principles of Good Clinical Practice (GCP).

  If the Inspectorate finds that a manufacturer is indeed complying with the GMP guidelines, it will issue a GMP certificate. The Inspectorate also advises the Minister of Health on issuing or revising Manufacturing or Wholesale Authorizations. On request, the Inspectorate also advises the Medicines Evaluation Board regarding licensed manufacturers. Manufacturers of

active pharmaceutical ingredients do not need a manufacturing authorization. Nevertheless, GMP inspections of these companies will be conducted at the request of the MEB or the manufacturers themselves**.**

- **CIBG.** Farmatec, part of the Ministry of Health, deals with applications for manufacturing and wholesale authorizations. Application for a license to manufacture pharmaceutical products is made to the Minister of Public Health. The application is assessed by Farmatec after approval by the Healthcare Inspectorate.

- **Medicine Evaluation Board (MEB)** The Medicines Evaluation Board (MEB) assesses and guards the efficacy, safety and quality of both human and veterinary medicinal products. The MEB has autonomous power to make decisions regarding the availability of human medicinal products. The MEB is responsible for authorizing and monitoring safe and effective medicinal products on the Dutch market and shares responsibility for authorizing medicines throughout the European Union.It is an independent board that makes decisions about what medicines will be admitted to the market. By doing so, the MEB promotes the proper and safe use of medicines in the Netherlands.

- **National Institute for Public Health and the Environment (RIVM).** RIVM has an important role in the approval, inspection and release of medicinal products in both the Netherlands and Europe. It tests the quality and safety of medicinal products or vaccines based on laboratory and animal studies. The institute is an independent branch of the Ministry of Health, Welfare and Sport (VWS) and conducts scientific research on behalf of government policy. It undertakes structural batch checks to monitor whether medicinal products continuously comply with authorized requirements. The quality and safety of a new medicinal product is assessed based on various studies. Moreover, the RIVM analyses medicinal products like fake and illegal products, to identify potential hazards.

- **Netherlands Farmacovigilance Centre (LAREB)** The Netherlands Farmacovigilance Centre collects and analyses reports of adverse reactions of medicines and vaccines, which is collected in a central database. The MEB has online access to this anonymous data. Healthcare professionals, patients and also manufacturers can report an adverse reaction. Each quarter, Lareb writes a report concerning these details and sends it to the Medicines Evaluation Board, the European Medicines Agency and the World Health Organization in order to help monitor global drug safety.

- **The Ministry of Health, Welfare and Sport (VWS)** Based on the interviews, the Ministry of Health, Welfare and Sport is mainly responsible for the legislation and policy regarding health care. In that sense, it has a different position in the chain relative to the other organizations. The Ministry of Health, Welfare and Sport is perceived by the employees of the chain members as the coordinating partner in the pharmaceutical regulatory chain.

In conclusion, the regulation of drugs , as mentioned in the introduction, encompasses a couple of key functions. Trying to allocate the different Dutch regulatory authorities to these different key functions gives us the following picture:

(I) *evaluation of safety and efficacy data and control of clinical drug trials (CCMO, Inspectorate)*

(II) *licensing and inspection of manufacturing facilities and distribution channels (CIBG, Inspectorate)*

(III) *product assessment and registration (MEB)*

(IV) *monitoring of adverse drug reactions. (MEB, LAREB)*

4.2 How do employees of the chain partners experience the collaborative practices?

The findings of the focus group interviews were grouped into eight key categories identified from the supply chain management literature. The category headings discussed below provide structure for the findings and a focal point under which to order the sub-themes and central perspectives associated with each category. Overall, there were few observed differences between the different chain partners. Where differences were observed, they have been highlighted. An overview of the focus group interviews is given in Table 1.

Table 1. Focus group interviews

Date	Organization	Participants
02.11.2012	**CIBG** *(implementation agency of ministry of Health, Welfare and Sport)*	2
13.11.2012	**RIVM** *(National Institute of Public Health and Environment)*	3
15.11.2012	**IGZ** *(Health Care Inspectorate)*	4
19.11.2012	**CCMO** *(Central Committee on Research inv. Human Subjects)*	3
26.11.2012	**LAREB** *(Netherlands Farmacovigilance Centre)*	6
13.12.2012	**VWS** *(Ministry of Health, Welfare and Sport)*	2
10.01.2013	**MEB** *(Medicine Evaluation Board)*	6

Agreed vision and goal

First, participants were asked to tell whether they were familiar with the pharmaceutical regulatory chain and whether they felt a part of it. Based on these answers, we followed up with questions concerning the existence of an agreed vision. For objective reasons, the respondents were not told beforehand which organizations the chain consist of (according to the official paper of the pharmaceutical regulatory chain members).

A majority of participants reported to not have a clear definition of a pharmaceutical regulatory chain. It was noticed that the term ‘pharmaceutical regulatory chain’ has different meanings to different people of the different chain partners.

MEB, 10th January 2013

According to me, nobody here thinks that we can do our things in our divine isolation and there is a kind of black box, the outside world, and sometimes there comes something in and then we throw it outside again. However, the definition of the chain, I suppose one can think anything of it. I think you should give us the definition. Or one could say, everyone who has to do with medicines. However, that does not mean a lot…

CCMO, 19th November 2012

Do you think people are aware of the fact they are working from a chain perspective? In other words, do you think people have the feeling they are part of the chain? (interviewer)
Ehh well, the chain perspective, what is that? To be honest, I need to ask that…

Yes, the chain does tell me something, but I am not aware that I am part of the chain. At least not every moment. But the reason for that is because the CCMO fulfills a very specified task. Doing my work, I do not feel dependent on the rest of the chain partners.

There was also indistinctness about the start and endpoint of the chain. According to some, the chain begins from the development of an active pharmaceutical ingredient and ends when the patient receives the medicinal product, so the reimbursement authority (CVZ) needs to be included as a chain partner. According to others, the pharmaceutical industry has to be included in the chain as well. A substantial minority reported to be unsure whether or not, and to what extent, they are part of the chain.

MEB, 10th January 2013

What do you understand by the pharmaceutical regulatory chain? (interviewer)
I would prefer it if you could tell us that. Because I think that, for instance, CVZ absolutely should be in the drug regulatory chain, but it is not.

Ministry, 13th December 2012

You had to ask everyone to draw the chain beforehand
That had to be one question.
Than probably, you would have gotten five different drawings.

Most of the participants assume that there is an agreed goal within the chain, but overall they were not sure about the precise definition of the goal. Those who tried to give a definition of the shared goal gave, although a little different, a similar definition: safe and qualitative good medicines, promotion of pharmaceutical safety, and optimal use of medicines. Nevertheless, for most of the participants it remains an abstract goal.

Lareb, 26th November 2012

Do you think those chain partners work from a common goal?
Well, I assume the common goal is the promotion of safe pharmaceutical. And basically, that is what I think everyone stands for.

Well, not only safety. I think optimal use. For instance, also the determination of a pure indication and the effectiveness within.
Yes, it is much broader.
The common goal is optimal use I think.

Healthcare Inspectorate, 15th November 2012
I think if you just go high enough, the common goal is safe medicines and that steps taken to ensure this are performed safely and according to the rules, which we think they guarantee safety. But the more you go down and try to sub define the common goal, like what are safe studies? What is safe production? What is… Than the goal differentiates more.

The reason why most respondents had difficulty in defining the pharmaceutical regulatory chain goal lies in the fact that most of them feel there is no chain. The term 'chain' is a misnomer according to some participants:

National Institute for Public Health and the Environment, 13th November 2012
But what do you then understand by the chain? (interviewer)
Well, in this case the chain concerns the fact that they are all rings related to the same thing. But it is not a chain where at one end something comes in and at the other end something comes out. There are things, which both start and end at the MEB. There are things, which have been at the MEB for years and currently ongoing at the Healthcare Inspectorate. There are things, which have been ongoing for years and eventually only CVZ has something to do with it. Everything has another point. And there are islands and everyone knows at which desk he has to be for which kind of problems and which kind of questions. But there is little necessity to go on or to link the chain together.

MEB, 10th January 2013
Do you think you operate as a (link) in the chain?(interviewer)
I think that is very difficult. A link means indeed that you get something and then you pass it on again, while in fact there is much overlap at the different areas. The CCMO or other METC's approve clinical trials but in the meantime, those manufacturers could come to us for scientific advice. It is not that we only start at the moment a manufacturer submits his dossier, while submitting a registration dossier is indeed the endpoint of METC's. The same goes for the adverse reactions and also the inspection of clinical trials, there, the Healthcare Inspectorate has a role too or when it concerns inspection of not-registered pharmaceuticals or label use. It is not a linear process in the sense that you can put all those part in succession and then you are finished.
It is more a chain puzzle.
Yes, or a braid. And then one time you see the red ribbon more and the other time you see more of the blue ribbon.

The participants from the Ministry of Health, Welfare and Sport confirmed the abovementioned reasoning and explained that the term *'pharmaceutical regulatory chain'* is chosen only to improve collaboration in the management board, as there are chronic tensions between board members of the different chain partners.

Ministry, 13th December 2012

*But the question is what do you understand by that chain? Because the last few years, we are indeed talking about the medicine regulatory chain, but we are talking about the collaboration between the parties rather than about the actual process which the products has to go through**.***

I think that, throughout the years, things on the employee level are going quite good. It is more on the level above where the tensions are. The aim of the chain meeting is more an issue of governance. Hey guys, we have to go together through one door on the field of this and that. People higher in the trees do not really like each other and that has an effect and that has everything to do with that what I said before: power, money, how much personnel one has, whether you have more competence etc.

Given the fact that people were either unfamiliar with the term pharmaceutical regulatory chain or felt the term was a misnomer, participants were told about the official chain members according to the declaration signed by the different management boards. For consistency reasons, we continued the focus groups by questioning participants about the remaining aspects of collaborative practices by referring to the seven organizations mentioned in the declaration.

Partnership

Different experiences concerning partnerships between chain partners emerged from the focus group interviews. The feeling of working on the same product, good contacts with employees of different organizations, fixed work appointments and dependency on each other's input are aspects mentioned to contribute to good partnership. However, participants also cited experiences where partnership is lacking. For instance, the absence of fine tuning related activities between CCMO and MEB (e.g. approval for performing clinical drug trials and assessment of clinical trial outcomes) is a factor that hampers good partnership. Participants experiencing this say they are willing to collaborate in order to tune these activities, but cannot. Trying to communicate about this is exhausting and because of the unfamiliarity which each other, they feel like the organizations are two different islands.

> ***MEB, 10th January 2013***
> *I certainly want to mention CCMO here. As a pre-clinical assessor, we see mainly dossiers in the registration phase and from all corners there is pressure, for instance to reduce laboratory animals. We are stopped on that and therefore we would like to have communication about that. I think there is total unfamiliarity. I think there is much to gain if one shares information en does collaborate to discuss which kind of studies one would like to see, particularly when it concerns laboratory animals. With regularity, we see dossiers where too and too many animal experiments are performed. In such a case, one could have communicated in an earlier phase that certain studies don't need to be performed. That could be resolved in another way or that could be combined. In addition, regarding biotechnology, the assessment both chemical pharmaceutical as pre-clinical is performed on a very different level and on totally other aspects then the aspects required during registration.*

> ***MEB, 10th January 2013***
> *You recognize a certain desire. Are you in dialogue with CCMO considering this? (interviewer)*
> *No actually not, it is an exhausting happening. I really got the feeling that we (MEB and CCMO) are two different islands.*
> *What do you think is the reason for that?*
> *I think it is primarily unfamiliarity with each other, but I suppose they are consciously held apart. They are two different organizations. We do our part, you do yours.*
> *Yes, and in that sense I think it has to do with power and pegs. But ok, it is also very hard, at least from the work floor, to make those contacts. Of course one could say, let them come to us, but you have to be able to supply it. And I have the idea that in that way, one doesn't communicate with each other.*

It seems like the CCMO employees share the same opinion considering the need for more balance between the requirements of clinical trials and registration:

> ***CCMO, 19th November 2012***
> *But I think, and maybe I am running ahead on other things, but sometimes there could be more balance (between registration requirements and clinical trial requirements). I mean, particularly the advices the registration authority gives to manufacturers and then the manufacturer comes to us and then a random METC tells them: We cannot approve this study as it is performed now. Well then eh… I don't say it happens too often, but it happens.*

Additionally, some participants also mentioned ‘fear of each other’s territory’, lack of coherence, lack of interest and unknown employees and/or organizations as reasons for experiencing no or insufficient partnership with chain partners. Other reasons given are the (physical) distance between the different organizations and the fact that the various partners are steered separately. Also, there is the perception among employees that there is no need for collaboration, as a few participants noted that at some point their responsibility ends and the responsibility of others begin.

> ***National Institute for Public Health and the Environment, 13th November 2012***
> *Well, then Lareb remains. Do you have any kind of contact with Lareb? (interviewer)*
> *No, we have nothing to do with what comes on the market nor when it is on the market, as then our responsibility ends. Within our organization, we look at a small part of the vaccines/blood products that are manufactured, before they are allowed to be sold. Only afterwards, there might be a chance that the healthcare inspectorate comes back to ask us whether there is something to announce. Or when it doesn’t succeed with the assessors, one could imagine that a pallet comes back. But those other fields are really apart from our field.*

Some participants expressed a desire to clarify the overlap between the different organizations clarified. Others mentioned that bundling knowledge within the chain would be helpful; if the knowledge is bundled, it is easier to access. Increased coherence is also desirable according to some participants.

Respondents of Ministry of Health and Welfare report there is good collaboration on the work floor. According to them, the tensions are more between the boards of the different organizations involved.

> ***Ministry, 13th December 2012***
> *When talking about the collaboration, the existing problems are at the managerial level. If you ask them about their collaboration, that really differs from the mutual collaboration of the chain partners. Because in my point of view, those chain partners are the key of the chain, which works in the chronology of a product of pharmaceutical. From testing until monitoring. They really need to collaborate a lot on the content of the pharmaceutical. Whether they do that in a proper way, well that is another issue. I think that on the employee level, the collaboration goes well, but at the higher level, they often have conflicts.*

Inter-organizational power

Findings reveal that, to a certain extent, there is inter-organizational power within the chain. There are organizations, that influence the relationship with others partners. Reasons cited for the existence of power are authority given by law, reputation and self-preservation. Different experiences were reported concerning the power of partners within the chain. According to one group of the employees, MEB is the most powerful authority. It is a large organization financed by third parties and therefore financially independent of other chain partners.

> ***CIBG, 2nd November 2012***
> *Look, the MEB has much power within the chain. What sets this organization apart is its managerial status. It is an independent administrative body, which is wholly financed by third parties. As a result, the organization has certain capabilities, particular possibilities and certain influence. I think it is a big organization. And of course, they are the portal for the pharmaceutical industry to make a pharmaceutical available, and in that sense the MEB has a major role which gives them relatively much power. However, I think that they are allowed to have that power, because they simply one of the most important chain partners.*

However, some participants also perceived the power of the MEB as problematic. There seems to be tension between the power of the MEB and the Inspectorate. They differ in opinions about how power should be divided, especially when it concerns issues with products on the border line of the organizations. According to both the MEB and the Healthcare Inspectorate, most of the time, power issues are about reputation and self-preservation.

> ***Healthcare Inspectorate, 15th November 2012***
> *MEB and Healthcare Inspectorate, hmm.. sometimes that really gives struggle. There where it concerns parties which need to be recalled, where we think that MEB sits on our chair and they think we sit on their chair, that really gives struggle, especially between our director and director of MEB*
> *Where does that relate to? (interviewer)*
> *Well there when it concerns products on the market which do not meet the quality requirements anymore. If it concerns batch level and the products are recalled than we are the authority which is responsible to re call the batch. However, sometimes it transcends batch level and then it comes to product level. If there are issues with the product on product level, you are at the dividing lines which gives struggle. We often have debates about that. Who puts it on his website (because MEB and Healthcare Inspectorate have around the same text on their websites)? Because that is also a matter of reputation, 'we have done something', 'we are strong'.*

> ***MEB, 10th January 2013***
> *The Healthcare Inspectorate performs the inspections (on efficacy clinical data for example) and then they find it ok or not but eventually the decision whether to go on with the data or not is to us. We take into account their standpoint when looking at the whole picture. But I have the idea that we have a kind of power to say yes or no, which they do not have. Their role is to see whether it is ok or not, but the final decision is up to us.*

Others claim the Ministry of Health might be the authority with the most inter-organizational power. Although there might be inter-firm power within the chain, most of the partners are not bothered by the power, mostly because the different responsibilities are clearly fenced off by the law and cannot be threatened by expressed power.

> ***National Institute for Public Health and the Environment, 13th November 2012***
> *The Ministry of Health, Welfare and Sport has finally the power to enforce change, to install the chain, to fill it in and to refill it.*
> *Yes, when it concerns putting together organisations, the only one who can initiate that or enforce that is the Ministry of Health, Welfare and Sport. That is concerning the power to enforce the most powerful chain partner.*
> *And that is also the way it has to be.*
> *Yes, I feel that the Ministry eventually has the final word.*

> ***National Institute for Public Health and the Environment, 13th November 2012***
> *I think if you look at MEB, Healthcare Inspectorate and us, then I think we are in a very clearly defined part. One operates within the borders of the organisation. If a manufacturer asks the Inspectorate about release of blood products, the you see in the minutes: This is a task of RIVM, we keep ourselves out of it. We do not address this. So there is a defined area. When the defined area is clear, power does not matter. In that case you can be powerful on your own area, but I do not have the impression that I am threatened in my work by one of the other partners and the other way around. I think the fencing off is done.*

According to respondents from the Ministry of Health, financial flows within the chain determine existing inter-organization power relations. For example, between MEB and Lareb there is a subsidy relation, which practically means that MEB is able to stop the collaboration with Lareb anytime they want. Additionally, power issues are often related to particular persons and roles.

> ***Ministry, 13th December 2012***
> *Of course, power has impact. One should not think it is a technically snarled process. For a part it is, but it is obviously a collaboration between big and small organisations, where certain organisations are principal for others or do work for each other, but again with own responsibilities. It is complicated. It has to do with many things and power is one of those things, which is also present in this chain. Not different from elsewhere.*
> *Well, here it might be worse than elsewhere (laugh)*
> *Yes, ok. But power plays a part just like it does elsewhere. Maybe a little bit more.*

> ***Ministry, 13th December 2012***
> *For example, Lareb is financially dependent of MEB, which results in a certain power relation. The MEB has conceptualized a bypass, but in fact Lareb gets money from MEB, which is a subsidy relation. You get money if you do something for me. You need to do that and that, and if you do not do that, then…*

Coordination within the pharmaceutical regulatory chain

Participants report that there is neither coordination within the chain nor is there need for it. They say that there is no benefit of coordination since the different tasks and roles are considered known and clearly stated by the law. As one group of participates puts it: 'the law coordinates'. However, most of the respondents refer to the Ministry of Health as the organization, which need to have a helicopter view on the whole chain process.

> ***National Institute for Public Health and the environment, 13th November 2012***
> *Do you think there is coordination within the drug regulatory chain, whether by a partner or person*
> *I think the law coordinates. The law legislates there has to be a registration dossier, legislates that pharmaceutical companies have to have a license and legislates release of products ,*

> ***National Institute for Public Health and the environment, 13th November 2012***
> *For coordination, you need to be at the Ministry of Health, Welfare and Sport, I think.*
> *Let us say, the pharmaceutical companies know what to do to bring a product on the market and with which agencies they have to deal with. One could argue whether the information needed is easy and accessible. But if there should be a helicopter view within the chain, it is definitely the Ministry of Health which should provide that.*

> ***CIBG, 2nd November 2012***
> *No, to be honest there is not much coordination.*
> *Do you think coordination is desirable? (interviewer)*
> *At least we do not need it.*
> *It is not necessary, no.*
> *We could do it ourselves as well.*

> ***MEB, 10th January 2013***
> *There is no overarching agency, which monitors like: "oh pharmaceutical company A comes in a certain period with a new pharmaceutical for the treatment of disease X, let me prepare the people in the chain for it." That is not the case, no.*

The Ministry of Health says it understands the fact that the chain partners point to the Ministry as the coordinator of the chain. However, they say their coordination role is limited to periodic consultation with chain partners. The Ministry is involved only when problems arise. Essentially, the chain partners need to coordinate among themselves.

> ***Ministry, 13th December 2012***
> *"Who coordinates the drug regulatory chain? (interviewer)*
> *That is distinctively the Ministry of Health, Welfare and Sport.*
> *Yes, of course. Actually, we do that by defining by legislation what everybody has to do. Then, everyone has to do what has to be done. Therefore, if we have defined that in a proper way, everyone should understand that. However, sometimes it seems we have to provide more explanation before one understands."*

"What is of importance is that chain partners also have the responsibility to take on the coordination in their mutual collaboration. That is the problem, not everyone has to look at the Ministry of Health for coordination. Basically, all of them are agencies with an autonomous responsibility who have an agency before them and an agency behind them within the process and they have to organize that themselves. So there is a lot of coordination on that level I would say. And if that fails, agencies look at the Ministry of Health – which I think is rightly – and then we address their responsibilities again."

"There are several ways to fill in the role of coordination. We prefer to fill in the role of coordination as limited as possible. Basically, the law contains what the different organizations have to do and sometimes we have conversations with the organizations and then it has to work."

A plainly outspoken coordination does not seem to be desired by the participants. However, there is a wish to evaluate the efficiency of the chain process and the efficiency of the regulation and law.

National Institute for Public Health and the Environment, 13th November 2012

About each law one could wonder: the world changes so is the current legislation still the most efficient one?

I think it is fine to have a look at all those legislations to see how the collaboration could be optimized. But that would fit the helicopter view. But then not so much the question whether the daily practice work, because that works. Everyone does what has to be done. But a helicopter view on the system level; is this still the most efficient way to organize the system?

Information sharing

Both sufficient and insufficient information sharing experiences have been reported. Sufficient information sharing experiences especially concern information sharing during acute/urgent cases. In such cases, people are probably more aware of their mutual dependency, which results in more information sharing. Preventing double work and keeping each other informed were benefits mentioned for sufficient information sharing within the chain.

> ***MEB, 10th January 2013***
> *In case of a big problem with a pharmaceutical, (which cause does not matter for now), the inspectorate may need to do something with the trade of that product within the Netherlands. We, as MEB, need to do something with our dossier, maybe removal of the pharmaceutical. In such a case, we are dependent on each other's information. However, I think in acute cases business is going well. I have the impression we can find each other/ My feeling is that when there is something serious going on, then it all goes well, but when we want to make agreements on structures, processes and collaboration, then it happens with much difficulty.*

Participants also reported incidents of insufficient information sharing. Reasons cited fell roughly into 2 categories: chain partner related and legislation related. Chain partner related are, for instance, disinterest or unwillingness to share information. Furthermore, there seems to be unfamiliarity with each other's work, conflicting interests and in some cases information sharing is perceived as a dilution of firm power. Moreover, some find it difficult to find a balance between sharing useful information and information overload. Legislation restrictions by law also, cause insufficient information sharing.

> ***MEB, 10th January 2013***
> *Well, I think we probably could use the knowledge present on the different work floors. And in certain places, this happens more often than other places. Maybe because sharing information is perceived as adulteration of power, I do not know but that is how I have been fed with information. It could be that we would like to talk with each other, but that is not allowed, well than it comes to an end. It could also be that time is not made free for it, and then it comes to an end as well.*

> ***Lareb, 26th November 2012***
> *Insight in the periodic safety reports (information of MEB) would be very useful for us. But I am not sure how they exactly… whether they could give us access based on the law, I mean there are a lot of catches, because it is information they received from the manufacturers.*
> *It is confidential. Yes, It is indeed confidential. I can also imagine that the legislation framework does limit them in doing that.*
> *You say limited. But do you desire more information sharing? (interviewer)*
> *Yes, for us it would be desirable because we have had situations now and then, where we find a new signal, being glad and then eventually it points out to be already discovered by the manufacturer. In fact, you have done double work and that is a waste.*

A finding worth mentioning is the desire of many chain partners to have better information sharing with MEB.

> ***CIBG, 2nd November 2012***
> *For instance, what does the MEB say about a certain product? Is a product with a certain pharmaceutical form equal to a product with another pharmaceutical form, i.e. Does the MEB consider those pharmaceutical forms identical or not? That is a very specific question. Here, we do not have that kind of knowledge. From my experience perspective I would say they are the same, but that is not legal, that is not based on all those (EU)guidelines. Therefore, you turn to the MEB but that kind of information is not easily accessible. They do not make that kind of information accessible. At least, not to my knowledge. They got certain thoughts on that. And maybe some documents say something about that specific question I mentioned, but we did not receive them nor can we find them easily. So this kind of specific questions, yes, could be sharable.*

> ***Healthcare Inspectorate, 15th November 2012***
> *When MEB got questions concerning a dossier, we do not see those dossiers. We do not know what is applied for in the Netherlands. We know approximately, which studies are on-going, or at least we could get to know that. But which studies result in approval applications and which studies from abroad result in approval applications in the Netherlands, we do not have any idea about. We could ask that, but they will not tell us. Maybe we do not need to know that. But sometimes we receive a request because there appear some issues with a dossier. And then it goes as follows: MEB says, that study is performed there and there and we (MEB) asked for additional information, but we (MEB) fail on making an agreement, so could you go on inspection visit. Only then we receive information about the total application dossier and the study.*

> ***Lareb, 26th November 2012***
> *Is there additional information which currently is missing but desirable? (interviewer)*
> *Safety information of the MEB. Maybe not in the form of databases, but in the form of report or something like that. Their whole chemical-pharmaceutical dossier and preclinical dossier. That is not always relevant. However, if we would indeed have access to what is already known about certain side effects in those documents, which currently is not public, that would definitely be helpful.*

The Ministry of Health, Welfare and Sport is unfamiliar with sharing of information between chain partners of the pharmaceutical regulatory chain. They assume there is information sharing as long as they do not receive signs there are problems. Between the Ministry and the chain partners, there is information sharing when the Ministry gets parliamentary questions concerning the drug regulatory chain.

> ***Ministry, 13th December 2012***
> *We need to answer those parliamentary questions we get about all those chain partners. And of course, we do not always have the knowledge concerning content to answer those questions. So in order to be able to do that, we need input from those organisations. So in that sense, there is information sharing. And actually, those chain partners always co-operate to get the answers.*

Information technology

Most of the respondents reported not having access to one or more databases or not being familiar with existing databases. Often this concerns databases, which are perceived useful or necessary to access. For example, respondents of MEB express a wish to have unrestricted access to Healthcare Inspectorate database. Additionally, the Healthcare Inspectorate would like to have access to the MEB database instead of having to ask for information each time it is needed. Participants mentioned unfamiliarity, conflicting interests, and not acknowledging the benefit of information technology as reasons for databases not being accessible.

> ***CCMO, 19th November 2012***
> *Are you aware of the different databases and do you think they are integrated? (interviewer)*
> *No, they are not integrated.*
> *No, one can not look into each other's databases.*
> *I do not even know which databases there are.*
> *Neither me, does the Healthcare Inspectorate have a database?*

> ***MEB, 10th January 2013***
> *And the Healthcare Inspectorate? They have access to your database, do you have access to theirs? (interviewer)*
> *That is a difficult one. We are currently working on making agreement about certain reports they get about, for instance, a certain problem with a product. When we, as MEB, have a role in that, for instance, because we are a reference member state in Europe for that pharmaceutical, then somehow we need to inform our member states. We are working on it, but it is all done in dribs and drabs. For example, the Healthcare Inspectorate gives us a print out of their system, because we do not have access to it. And this has to do with, broadly defined, why do you have to know that? That is the unfamiliarity, maybe conflicting interest, I do not know.*
> *But do you think access to information technology is desirable?*
> *It is necessary. A pharmaceutical problem is not limited to the Dutch border, most of the pharmaceutical companies are operating at international level. Therefore, a problem which is seen here is the Netherlands can have an impact on the German market.*

> ***Healthcare Inspectorate, 15th November 2012***
> *On the level we are working on, a part of the information sharing has to be better. I mean, on the higher level there is good information sharing, but on the level of details, it could be improved. For instance when you go for inspections or when it considers CCMO for certain documents or certain information. And that has to do with different and entirely separated systems. It has a little bit to do with the legislative restrictions saying what the assessor is allowed to see and what the Healthcare Inspectorate is allowed to see from their point of view. So for us, it is not a case of unwillingness but it is still a little bit powerlessness to share into detail.*

There were also respondents who did have access, but often this access is restricted. Legal issues, conflicting interests, and differing opinions concerning the need for accessibility are reasons cited for the existing access restrictions. Employees noted that having access contributes to better

communication and support within the chain. Information technology improves efficiency through the gain of trustworthy information/data.

> ***MEB, 10th January 2013***
> *There are things where we would like access to, like the signal database of Lareb. Despite affirmations and whatever, we still do not have access to the database. For instance, the EMA (European Medicines Agency) provides us monthly a 'IRMR' which also concerns signals. If we had access to the Lareb database, we could have a look into it to see whether they have seen the signal (of the EMA) as well. Because not all things studied by the EMA are in the Lareb quarter message (an informative message Lareb they send each quarter to the MEB concerning probably new side effects of pharmaceuticals or other relevant signals). That would be useful.*

The respondents from Ministry of Health, Welfare and Sport say free access to the different systems is legally impossible. They think that system access within the chain is not desirable and report that there is currently no policy for integrating the information systems, unless the chain partners themselves have the desire to do so.

> ***Ministry, 13th December 2012***
> *Of course we think that the partners need to collaborate, but it cannot be the case that everyone just can access all those information systems. That is also legally not allowed. In fact, who is allowed to have access and who is not is regulated in the European guidelines.*
> *You say you do not see a link between integrating those information systems and efficiency. Why do you think that? You just mentioned the legal frameworks, are there other things?*
> *I have no reason to assume that at the level of the content of pharmaceuticals, people do not inform each or that there are ICT problems or whatever.*
> *There are also no notifications.*

Integration of processes

Most of the respondents report having periodic consultations with chain partners they work with. Most of the time, this is done to balance the common aspects and trying to integrate the processes. Integration of processes contributes to having a shared vision, getting to know your colleagues, for public relations and to remain in sight.

> ***CCMO, 19th November 2012***
> *Do you have periodic consultations with the Healthcare Inspectorate? (interviewer)*
> *Yes, sure.*
> *And when do you have these meetings?*
> *We meet for such structural consultations four times a year. At two levels. On the employee level we often have meetings with the Healthcare Inspectorate. At the organization level two times a year.*
> *What do you think is the added value of such meetings?(interviewer)*
> *Well, being updated about things which have common aspects. Another goal is framing the policy in such a way that it is feasible.*

> ***National Institute for Public Health and the environment, 13th November 2012***
> *Sometimes you have a specific question, but if you have a specific question it is easier to pick up the phone. Besides , it is useful to see each other every now and then to know, for instance, who you get on the phone. Currently, we know that because the assessors of MEB are our ex-colleges, but after 5 years there is maybe a whole new pool of people. It is possible. But that is why I think it is useful to see each other from time to time.*
> *What is the added value of this integrated meetings? (interviewer)*
> *To invest in relationships.*
> *So you can more easily phone with each other.*
> *In order to be feasible. I can imagine that one would like to stay in the picture, so when the MEB hears something concerning vaccines they will share it with us. That they will think of us in such cases.*

Some participants expressed a wish to set up meetings on a regular basis (either between parties that closely work together or an annual meeting with all parties). For example, a MEB employee reported that they would like to have more periodic consultation with the Inspectorate of Health. However, there seems to be no time to schedule such meetings. The management of the chain organizations needs to see the value of such meetings first before they can be organized.

> ***MEB, 10th January 2013***
> *Collaboration with inspections, that we can perform them together, that is really integration of processes I think, which is very desirable.*
> *What kind of benefits does that contain? (interviewer)*
> *Currently we get reports with the perceptiveness of the inspector, which is a level above you know.*
> *And eventually we get the question of: you need to tell me what kind of impact it eventually has on your data. Whether or not it is useful.*
> *While if I join the inspections, one can watch along and look with one's own perspective at the findings which can be captured mutually in a report. In such a way you can contribute to the contribution in a report.*

Healthcare Inspectorate, 15th November 2012

It would be useful to meet maybe once a year with chain partners about what people exactly do. I mean, very often we have meetings with subgroups but sometimes I think, it is useful to have an annual meeting with the MEB or CCMO, with bigger groups, to talk about the things you do together. That could be done in two ways; one could say you need to do that on very low level or at the very high level, then you have to say to the programme director; we think we would like to have consultations with that chain partner and that chain partner. Well, then of course we get it back, because they have also no time for that, which I can understand…

The interest to do that should come from above or at least they need to see the interest first. I really think it is beneficial.

I absolutely think, and sometimes it is also recognized, added benefit, but when it needs to be made concrete, then suddenly everyone has his/her own daily worries. Nobody has time for that.

Time lines

Timelines in this study concern the time between accepting an order and reaching a decision. (e.g. the time between submitting a registration dossier by a manufacturer to the MEB and the final decision of the MEB, registration or not). Different timelines are set for different types of products. According to the employees, the time lines within which the chain members have to reach their decisions are laid down by the law. There were no problems reported by the respondents. However, sometimes the set time is exceeded but this is due to other factors than to problems in the collaborative practices. Reasons mentioned are problems with the applicant's dossier, and whether or not an inspection is planned. An additional reason mentioned is the possibility to stop the application clock if it is necessary to ask the applicant for clarification or further supporting data.

> ***Healthcare Inspectorate, 15th November 2012***
> *Recently, I have looked up the timelines. It contains a few fixed points and two clock stop periods. Those clock stop periods may last between 3 and six months for the first clock stop period and between one and 3 months for the second one. In these periods things are performed which are not in the standard process. For instance, inspections for clinical trials instance are performed in such a clock stop period.*

> ***National Institute for Public Health and the environment, 13th November 2012***
> *The general timelines are partly dictated by the MEB. But within those clock stops, the party involved dictates. I mean, If they say they want do an inspection, fine, but you have to announce that beforehand. In case there is no inspection, the lead timeline stays fixed. If there are no issues, if the manufacturer submits everything in time, then the lead cycle time stays fixed. But If there appears to be troubles then a subsection comes in between An inspection, additional information or whatever. So the actual cycle time, if you look at it as a … and say, hé, 90 days? Yes, but actually it could have lasted a year (because the clock is stopped for additional information), but still it is within the actual cycle time.*

> ***MEB, 10th January 2013***
> *The cycle time surely has to do with the quality of the dossier. A rattling dossier results in a list questions and making objections. So anyhow, the applicant needs more time to repair it all. But other problems related to the dossier could appear too. For instance, an inspection needs to take place. Than you need to schedule that again. That prolongs the cycle time.*

However, participants from the Ministry of Health noted that speeding up the cycle time is good for the innovation climate. According to them, there might be room for accelerating the cycle time of clinical trials, which probably could lead to patients having faster access to new pharmaceuticals. Speeding up the cycle time also has advantages for the Netherlands from the view of the pharmaceutical industry. A country with faster cycle times is probably more attractive for the pharmaceutical industry to settle, as it means fewer costs for the industry, which in turn may result in cheaper pharmaceuticals.

> ***Ministry, 13th December 2012***
> *There is always discussion about the cycle times. That is because of the fact that it is interesting for the pharmaceutical industry and that in turn is interesting for the innovation climate in the Netherlands concerning this field. Would you like as a country to perform well on that, than cycle times are definitely*

something which is considered. The goal above which we strive for is that patients have faster access to the pharmaceuticals they need and which are useful for them. In fact, you would like to accelerate the cycle time. That is beneficial for the patients as well as for the industry, as they have reduced costs during the process and probably could bring their product on the market at a slightly reduced price. Additionally, pharmaceutical industries would like to establish in the Netherlands, which would be favorable for our economic climate. So in fact, these factors are mutually dependent. Those cycle times are certainly a point for us. There is always discussion about the cycle times and their calculation method, as you can calculate them with or without clock stops which is always a big deal.

Nevertheless, they say there is tension between balancing faster cycle time and quality/safety. Moreover, an alteration in the law for shorter cycle times does not always result in a change. Nonetheless, the participants think the work can be done more efficiently, as the time laid down by the law needs to be considered a maximum rather than a rule.

Ministry, 13th December 2012

The government wants faster cycle times and our Minister wants the same, but they understand the fact there is time needed to guarantee both quality and safety, which is definitely the field of tension. At one hand you want to do it faster, but at the other hand the products need to be qualitative and safe. (VWS)

Those timelines of the MEB are laid down in European guidelines: 210 days. Tomorrow they could change that the guideline by saying it needs to be in within 110 days. Would that really happen than? I have no idea. It is not like you change something in a law, that it will be really followed up. It is an illusion to think that would happen.

Of course, one can finish within 200 or even 150 days. If it is possible, one definitely should do that as you are competing with other European Member states.
210 days is a maximum of course.
Yes, that is the maximum indeed. So if you manage to do it much better, you are attracting pharmaceutical companies. I think that is exactly what the MEB does.
They are performing well in Europe so in that sense they are doing well. And if they can do it more better, they get in much more.

5. Discussion

This paper has discussed the collaborative practices of the seven Dutch pharmaceutical regulatory authorities. This study is, to our knowledge, the first qualitative study to investigate and give insight into the collaborative practices of the Dutch pharmaceutical regulatory organizations. Our goal was to develop a supply chain perspective on these practices through the discussion of the practices according to SCM literature, which is primarily business oriented. Our approach focuses on the inter-organizational conditions and requirements necessary for collaboration across organizational borders.

5.1 How do the employee's experiences relate to supply chain management literature?

According to official terms, the Dutch 'pharmaceutical regulatory chain' consists of seven parties: Ministry of Health; Welfare and Sport; CCMO; MEB; Healthcare Inspectorate; CIBG; RIVM and Lareb. The analysis of the collaborative practices between the chain partners demonstrates that the majority of the aspects required by SCM (agreed vision, partnerships, inter-organizational power, coordination, information sharing, information systems, and excellence in timelines) is not or insufficiently present in the current picture of the Dutch pharmaceutical regulatory chain.

A clear agreed vision is lacking. The involved organizations seem to have different perspectives and goals and most of them work independently. The main result is that participants do not feel they are a part of a chain at all. The processes between the regulatory organizations are far more complex (materials are not simply passed forward, but to the applicant; complexity and diversity of products, etc.) and therefore the term 'chain', which suggests a set of organizations that pass material forward, is a misnomer.

Moreover, there are also an inadequate number of *partnerships*, due to the lack of coherence, lack of interest to invest in partnerships, and different management of the organizations. Consequently, attempts to accomplish tasks across organizational borders fail. For instance, both the CCMO and MEB share the same feeling that the requirements for clinical trials and registration are not converged. MEB offers early scientific advice to companies ahead of phase III clinical trials, which might run parallel to the advice provided by the CCMO and sometimes contradicts this. There is growing awareness that this independent assessment of data leads to non-harmonized requirements, which cause the applicant problems. The CCMO and the MEB are willing to discuss this together; however, communication with each other is a very slow and difficult process.

Another finding concerns the *inter-organizational power* experienced by the chain members. The Medicines Evaluation Board (MEB) is perceived as the most powerful organization because of its indispensability for market authorization of pharmaceuticals and its independency due to financing by third parties (the pharmaceutical industry). In general, people report that inter-organizational relationships are not affected by power because each organization has clearly defined responsibilities and tasks. Nevertheless, there are also cases where the power of the MEB does affect relationships.

The Healthcare Inspectorate, for instance, mentions the power of the MEB as particularly problematic when it concerns cases, which are the dividing line of both organizations. Here, the opinions differ about the desirable proportion of power, which in turn is a struggle related to self-preservation and reputation.

Another outcome concerns the absence of chain *coordination.* On one hand, participants feel coordination by an authority is not necessary and has no benefit since the law lays down the different tasks and responsibilities and therefore 'the law coordinates'. On the other hand, participants assume the Ministry of Health, Welfare and Sport to be the current coordinating body to look at, for instance, the overlap between organizations. However, the employees do not experience coordinating in practice. According to the WHO's report 'Effective Drug Regulation', there is no unity of command over drug regulatory functions in cases where drug regulatory responsibilities are divided. The researches argue that drug regulatory structures like the Netherlands, where drug regulatory functions are assigned to two or more agencies, should be designed in such a way that there is a central coordinating body with overall responsibility and accountability for all aspects of drug regulation. *(Ratanawijitrasin and Wondemagegnehu, 2002)*

Furthermore, results indicate that an optimal level of *information sharing* within the chain is lacking. In acute cases, there seems to be information sharing because people are more aware of their interdependency; however, there is insufficient information sharing in general. This has mainly to do with the unwillingness of chain partners, unfamiliarity with each other, and legal restrictions. An interesting point is the expressed desire of most chain partners to have better information sharing with the MEB.

Another point, which might be related to the insufficient information sharing, is the inaccessibility of *information systems* within the chain. The organizations do have information systems, however these are different, separated and most of the time not known and not accessible for partners in the chain.

Integration of processes in the sense of having inter-organizational meetings, seem to be apparent and is perceived as beneficial. Getting to know your colleagues, remaining in sight and public relations are mentioned as benefits. Results concerning *time lines* indicate there are no problems with reaching decisions within the stated timelines. However, according to the Ministry of Health, Welfare and Sport (which is primarily concerned with legislation and policy) there is room for improving the time lines by working more efficiently. They need to consider the stated timelines as maximum rather than a rule. Compared to the other nine countries studied by the WHO, the Netherlands is among the countries where registration of new drugs takes the longest time (12-19 months). According to the WHO, the length of registration time can be used to measure the efficiency of assessment and registration. *(Ratanawijitrasin and Wondemagegnehu, 2002)*

5.2 Research limitations

While this research has provided insights into the collaborative processes between the different drug authority agencies, the research has some limitations which need to be discussed. First, the sample size is relatively small (n=26) compared to the 46 participants which was intended (at least six participants per organization/focus group). However, given the fact that the opinions of the 26 converged, we believe it is unlikely that more interviews would have led to different results. Therefore, we do not consider this a limitation of our study. Second, the interviewers were employees of the RIVM, which is officially one of the chain members. This might have biased the results in the sense that the participants did not fully express their experiences with the RIVM. Third, legislation is not among the aspects studied, while results suggest that it has impact on the collaborative practices. It might be that insufficient information sharing or inaccessibility of information systems for the chain members are related to the laws of different chain members. Finally, the SCM framework turned out to be not the most useful framework since we assumed the seven organizations to be a chain (based on official papers and the chosen term 'pharmaceutical regulatory chain') while results demonstrate that processes are far more complex and are not in accordance with a chain as proposed in the SCM literature. Moreover, SCM does not take into account the legislation. Nevertheless, the aspects studied provide useful information about the collaborative practices between the organizations regardless of whether they are a chain or not.

5.3 What this study adds

This qualitative research has provided an overview of issues concerning the collaborative aspects between seven organizations responsible for protecting and promoting public health. Our results suggest that there are difficulties between the organizations concerning agreed vision, information sharing, information technology, inter-organizational power, and coordination. This raises the question of whether the results of this study will directly or indirectly influence the outcome of drug regulation. One could argue that, for instance, these deficiencies might result in undue delays, which in turn result in a lengthier drug development process. Consequently, a pharmaceutical company is left with shorter time to earn back its investments, which could eventually lead to higher drug prices. *(Bouvy, 2013)* As far as we know, there is no information available regarding if and to what extent difficulties in the collaborative practices result in potential negative outcomes (e.g. introduction of unsafe drugs, substantive delays before public has access to medicines, higher R&D costs etc). This stipulates the need for additional research. However, our results inform policymakers about the views and practices of the different drug regulatory authorities, which should be considered a valuable tool to help policymakers make informed policy decisions in order to meet the needs (e.g. information need, accessibility needs, need to improve cooperation) of regulatory authorities' employees. Additionally, policymakers can use these research findings as a guide when they evaluate the structure of the regulatory authorities and/or review current legislation.

5.4 Further research

Our conclusions could be extended by investigating whether and to what extent the outcomes of this study impact the outcome of drug regulation, both for public health and (development) costs. Here, the perspectives of the pharmaceutical industry and the patient should be taken into account to get an overall picture. In addition, it would be valuable to see how the current deficiencies could be tackled in order to improve the relations between the different authorities. Moreover, CVZ (the reimbursement authority) is not considered an official chain member according to the declaration of the different organizations. Therefore, the reimbursement authority is out of scope for this thesis. However, it would be worthwhile to include this authority in further investigation since empirical evidence suggests that most cases of delayed market authorization are caused by undue delays in the reimbursement process. Moreover, it would be useful to further investigate the efficiency and effectiveness of the current legislation. Evidence suggests that work will be fragmented when drug laws assign different responsibilities to different regulatory bodies. *(Ratanawijitrasin and Wondemagegnehu, 2002).*

6. Conclusion

To conclude, this study highlights issues in the collaborative practices between the different authorities. Given the aim of pharmaceutical regulation to protect and promote public health, it is important that the regulatory authorities collaborate in a way which enables and does not hinder the realization of this aim. Currently, there is no evidence for the potential impact of the results. The presented key issues provide a basis on which to further investigate how these organizations can fruitfully interact in order to contribute to the development of a drug regulation system, which is more efficient, maybe less costly and more responsive to both industry and patient requirements.

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