Demanding Dynamics

Samenstelling beoordelingscommissie:
Prof.dr. R. Bal
Prof.dr. J.F.G. Bunders
Prof.dr.ir. C. Leeuwis
Prof.dr. H.G.M. Leufkens
Prof.dr. N.E.J. Oudshoorn
Prof.dr. J. Tait

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Cartography, figures, DTP and graphic design: Ton Markus, Fred Huurdeman and Rien Rabbers (GeoMedia Faculty of Geosciences, Utrecht University)

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Demanding Dynamics

Demand articulation of intermediary organisations in emerging pharmaceutical innovations

Vragende dynamiek
Vraagarticulatie van intermediaire organisaties in opkomende farmaceutische innovaties

(met een samenvatting in het Nederlands)

Proefschrift

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Wouter Pieter Christiaan Boon

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Promotoren:
Prof.dr.ir. R.E.H.M. Smits
Prof.dr. S. Kuhlmann

Co-promotor:
Dr. E.H.M. Moors

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Glossary

Term	Definition
Demand articulation processes	Iterative, inherently creative learning processes in which stakeholders try to address what they perceive as important characteristics of, and attempt to unravel (sharpen, make more concrete) preferences for an emerging innovation.
Demand articulation mechanisms	Distinct internal first-order learning loops that intermediary user organisations go through depending on differences in organisation characteristics, and situations that these organisations face.
Event category	Distinct stage of the first-order learning loop, i.e. agenda-setting – demand synthesis – expression – evaluation, or second-order learning loop, i.e. self-positioning – other-positioning.
Event theme	The sequence of events related to a single coherent topic.
First-order learning	Development (sharpening and making more concrete) of demand statements.
Innovation arena	Functional area of action in which stakeholders articulate their demands about (certain aspects of) new technologies.
Interfaces	Media of interaction; foci of communication between an intermediary user organisation and its interacting partners.
Interface strategies	Strategies that intermediary user organisations deploy in order to communicate effectively with interacting partners in an innovation arena. Focusing on access, empowerment, and impact.
Intermediary user organisation	Stakeholders that facilitate interactions between users and one or more other actors.
Joint construction of demands	Convergence and divergence on demands and underlying assumptions between different actors.
Other-position	Underlying assumptions attributed by other actors to an organisation.
Second-order learning	Development of underlying assumptions by the organisation itself (self-positioning) in relation with the position that is granted to the organisation by others (other-positioning).
Self-position	Underlying assumptions as proposed by the organisation itself.
Underlying assumptions	A complex of organisational norms and values that frame the day-to-day decisions on operations and demands consisting of the objectives, strategies and ultimate preferences (being the desired identity and social order).

"You will never hear me advocating those puerile Emanations which detail nothing but discordant Principles incapable of Amalgamation, or those vapid tissues of ordinary Occurrences from which no useful Deductions can be drawn. – In vain may we put them into a literary Alembic; – we distil nothing which can add to Science. – You understand me I am sure?"

Sir Edward Denham in 'Sanditon' by Jane Austen

Wield was the best systematic searcher of premises he'd met, though if you knew what you were looking for, there was no one to beat Andy Dalziel. No system, but he had a nose for going straight to the spot. As for himself, Pascoe acknowledged a deep-rooted distaste for this hands-on invasion of privacy which rendered his searches pain-giving as well as painstaking. Dalziel had once remarked, 'Pete, lad, I'll always know if you've been searching my room 'cos you'll leave it tidier than you found it!'

'Pictures of perfection' by Reginald Hill

Preface

This PhD thesis is called "Demanding dynamics – Demand articulation of intermediary organisations in emerging pharmaceutical innovations". It is about the role of a particular kind of users, intermediary user organisations such as patient advocacy groups, in the emergence of new technologies. Over time, these organisations engage in learning processes of demand articulation in an attempt to influence innovation processes and debates about innovations.

As the title suggests, the focus is on the processes (dynamics) of demand articulation. At the same, these articulation activities are exacting and put pressure on actors, like these intermediary user organisations, to engage in them and to make an impact. If well-applied, though, the results of these activities can turn the users into demanding actors. All in all, the explanation of the title is as fluid as the tasks of intermediary user organisations, the demand articulation processes and the emerging technologies themselves. This thesis hopes to shed light on all these three aspects.

Work on this thesis was done as part of a larger project called 'User-producer interactions in functional genomics' conducted by the Department of Innovation and Environmental Studies at Utrecht University. Apart from this thesis, which focuses on emerging pharmaceutical innovations like pharmacogenomics, the larger project also includes work on: emerging nutritional innovations, theorising on user-producer interaction in emerging genomics innovation in general, action research, and the dissemination of the research results to the wider world; the latter two items being conducted by the Kluyver Centre for genomics of industrial fermentation at Delft University of Technology. The project is financed by the Netherlands Organisation for Scientific Research (NWO) as part of their programme 'the societal component of genomics research'. The Netherlands Graduate School of Science, Technology and Modern Culture (WTMC) is acknowledged for their training programme and financial support of the printing of this thesis.

Chapter 1
Introduction

"What others see as a theoretical model is for us and our members a harsh reality." This is one of the last sentences of a letter that the Dutch Neuromuscular Diseases Association (VSN[1]) sent to the Ministry of Agriculture amidst fierce political discussions at the beginning of 1998. Scientists and companies were working on genetically-modified animals intended for the production of medicines, including medicines for neuromuscular diseases. According to another letter by this patient advocacy group, the media and animal rights groups were heavily influencing the politicians to turn to stricter regulation. Ultimately, the Ministry of Agriculture chose for a consensual solution: animal biotechnology is prohibited unless certain conditions are fulfilled. This debate developed in a different way than the one on genetically-modified food that was also taking place in the 1990s. Scientists and companies aligned in the food debate as well but there were no intrinsically-motivated proponents like the patient organisations that supported them.

A decade later, part of the biomedical community is occupied with the stem cell therapy debate. The pro-life movement is guarding the protection of human embryos, mostly based on religious arguments. Scientists and companies, again, emphasise reasons for continuing work on these embryos, such as expectations of finding a cure for diseases like Parkinson's. Especially in the US fierce discussions are taking place on this topic. Although the federal government takes a rather strict stance on the issue, some states are supporting scientific research. Disease advocacy groups had largely contributed to convince people to back the California $3 billion stem cell research initiative that was approved in 2004 (Wadman and Abbott, 2006). Again, this debate has never been one-sided, and demands from a broad range of stakeholders are taken seriously.

These two examples show that many actors are trying to influence health care technologies that are in an emergent phase of development. This results in constant converging and diverging moves in debates about these technologies. The actors constantly articulate their demands in an attempt to increase their influence on the innovation processes.

The examples also illustrate the significance of patient advocacy groups or – broader – organised users in these advocacy activities, which was not so evident only a few decades ago. The VSN influenced the debate on genetically-modified animals for the production of drugs by sending letters to parliament and the media. In the case of the California stem cell research programme, disease advocacy groups sat on the board of the programme committee and campaigned during voting for the project.

Interest in the role of users in innovation is fuelled by a broad and diverse range of user involvement literature in innovation sciences, organisational studies, and science and technology studies (Von Hippel, 1988; Lundvall, 1992; Smits, 2002; Moors et al., 2003; Oudshoorn and Pinch, 2003). These scholars claim that a better quality of interactions

1 The abbreviations found in this thesis are listed in Appendix A.

between users and producers enhances the innovation processes in which they are engaged and might even lead to more successful innovations. Users sharpen their demands about these technologies and express them during the development of new technologies. This process is called demand articulation.

In line with the emphasis on organised users articulating their demands about emerging technologies, the ***central research question*** of this thesis is: *How to understand the demand articulation processes of organised users in the context of emerging pharmaceutical technologies?*

1.1 Putting organised users central

The innovation processes in the pharmaceutical industry are traditionally characterised by their *technology-push and science-push orientation*. Pavitt (1984), who described sectoral patterns of technical change, regarded the industry as science-based because pharmaceutical companies rely on the strategy of technology accumulation by focusing on basic science, intensive university-company relations, and corporate R&D laboratories. Therefore, innovation in this industry is organised from the perspective of the linear model, i.e. basic science findings are translated into clinical compounds that are subsequently marketed as drugs. This model is partially defined by regulatory (safety and efficacy) milestones. The 'drug research and development pipeline' model of pharmaceutical companies is a clear demonstration of this. The reason for this R&D dependency lies in the industry's emphasis on product innovation and the knowledge-intensive character of drug innovations.

Many scholars have breached this perspective over recent decades. Not only are important feedback loops discerned inside the pharmaceutical company (Schmid and Smith, 2004), e.g. by forming small, decentralised task groups that are able to accelerate internal decision-making. Also the interaction with external actors became apparent (Smits and Boon, 2008), including small dedicated life sciences businesses (Van der Valk, 2007), medical professionals (Blume, 1992), and reimbursement agencies.

The category of *users of health care and pharmaceutical innovations* is one type of external actor, which takes the centre stage in this thesis. In this sector, users are rather heterogeneous: there are several actors engaged in decisions about the use for pharmaceutical innovations, including patients, physicians, medical specialists, (health) insurance companies, and the representatives of these actors.

These representative actors are examples of organised users, or what we call intermediary user organisations, such as patient advocacy groups, steering committees, and medical professional groups. Compared to other actors in the innovation system the role of these organisations is not as well-defined as that of other actors, such as companies. They act in the middle of all these actors and their interests. They need to legitimise their existence and obtain access to debates. We focus on intermediary organisations that are users in the context of technological development or act on behalf of these users.

Arguments in favour of including users in innovation processes are, first of all, to a certain extent instrumental. A better mutual understanding of needs, visions, goals, and ethical issues provided by intermediary user organisations changes the context in which innovation processes take place and by this increases their chances of successful adoption and implementation of innovations, e.g. by decreasing the risk of provoking resistance just as we have seen in the two examples presented at the start of this chapter. Utilising users' creative potential might improve the innovations themselves and might even lead to new

innovations. In the context of pharmaceutical innovations, the lay knowledge that patients have is often cited under the term "experiential knowledge" (Caron-Flinterman et al., 2005).

Two other reasons (Fiorino, 1990; Collins and Evans, 2002; Caron-Flinterman et al., 2007) for user involvement are: a political one based on the idea of democratisation, and a moral one based on the fact that users have a right to participate in decisions that affect their lives. The latter argumentation is augmented by various macro-developments, such as late modernity and the decline of trust in expertise, e.g. in doctor-patient relations, their 'growth to maturity', and an increase in commodification and individualisation of health care.

1.2 Health care sector challenges and users

The involvement of users remains significant in the light of current challenges that various actors in the health care and pharmaceutical sector face. We focus on two major problems related to innovations: the decrease in pharmaceutical innovations, and the adoption and implementation of these innovations by society.

Firstly, the health care industry is traditionally an innovative one and constitutes a diverse range of companies and related products, such as pharmaceutical products, diagnostics, and medical appliances. In the pharmaceutical industry, for example, firms are expected to maintain a double-digit percent growth, which they can only realise by introducing potential 'blockbusters'[2] on the market on a regular basis (Gassmann et al., 2004).

Recently, some scholars have questioned the innovative capacity of pharmaceutical companies and fear for the viability of the blockbuster future. They base themselves on macro-trend figures, showing the existence of an "innovation deficit" [3] (Drews, 1998), or on moral arguments that claim too much reliance on so-called 'me-too'[4] and generic drugs (Angell, 2004). On the other hand, others criticise the existence of such a deficit (Cohen, 2005; Schmid and Smith, 2005).

Many scholars have since then tried to find reasons – and solutions – for this decreasing productivity (Booth and Zemmel, 2004; Belsey, 2007; Frantz, 2007; Owens, 2007; Tait, 2007), in which problems are often combined with great expectations of new technologies. These include:

- Diseases for which there are easy solutions were already accommodated with treatments. In other words, the 'low hanging fruit' had been picked. Diseases that remain untreated are most of the time multifactorial and rather complex, such as cancer, for which no ready 'silver bullet' solution exists.

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2 Blockbusters are defined as drugs that surpass the one billion US dollar annual sales mark. Investing in these drugs has been the default strategy for pharmaceutical companies.

3 Related to this is the so-called 'productivity paradox': notwithstanding high investments in research and development, the amount of successful, marketable products is declining at least from the early 1970s onwards (Booth and Zemmel, 2004). This has led to an increase in development costs per marketed drug from 138 million in 1975 to 802 million US dollars in 2000 (DiMasi et al., 2003). Other authors criticised these figures (Goozner, 2004; Adams and Brantner, 2007).

4 Me-too drugs are only marginally different from medicines that have already been on the market for some time.

- Many scientific and technological advances have not (yet) delivered on the promises of being beneficial to drug innovation, although they implied large investments. Examples include combinational chemistry, high-throughput screening, molecular design, proteomics and pharmacogenomics.
- The regulatory hurdles are often cited as being detrimental to innovation. A large portion of drug development costs need to be allocated to comply with safety and efficacy testing in clinical trials, and the organisation of post-marketing research.
- Pharmaceutical companies might be too large to be properly managed and their organisations might not be appropriate for efficient R&D. The organisation of innovation processes inside pharmaceutical companies has also been criticised, e.g. the way in which R&D departments are organised, funds are prioritised and pipeline decisions are made.

As part of the instrumental reasons for involving users, mentioned in the previous section, users might contribute to increasing the effectiveness of the drug innovation process, e.g. by co-producing clinical trials and co-operating on regulatory issues.

Secondly, the health care sector faces challenges related to the adoption and implementation of pharmaceutical innovations by society. The rising drug development costs inevitably lead to higher prices for drugs, which in turn form a heavy burden on public and private health care costs. Already, pharmaceutical products constitute an increasing portion of health care expenditure (OECD, 2003). These growing costs can be problematic when poled against the still unmet medical needs for therapies for complex diseases, and ailments that are prevalent in low-income countries, like cures for Parkinson's disease or malaria (Schmid and Smith, 2007). These developments pose questions about drug access and reimbursement, the equal distribution of benefits and costs, the maximum costs per treatment, the demands for an increasing level of safety, and the prioritisation of drug R&D.

The involvement of intermediary user organisations in debates about these questions might be beneficial (Lyall et al., 2004; Bal and Van de Lindeloof, 2005; Abraham and Davis, 2007). They can broaden, enrich and articulate the range of arguments in the debates by putting forward their demands, and their inclusion in debates might increase the democratic value and legitimisation of the outcomes.

Although this thesis focuses on pharmaceutical innovations, the user involvement in health care in general should not solely be concentrated on aiming at pharmaceutical solutions. This raises questions about medicalisation and 'disease mongering', in which actors envisage ordinary, mild, potential, personal or social ailments as medical problems (Moynihan et al., 2002). Recently, several scholars explicitly cast doubts on the influence the pharmaceutical companies have on organised users, like patient organisations (Herxheimer, 2003; Angell, 2004; Bouma, 2006; Dehue, 2008). Some companies even create patient groups by themselves or fund organisations in order to influence disease advocacy. O'Donovan (2007) called this "corporate colonisation" but at the same time warned against treating every patient organisation as suspicious. These organisations can also broaden and enrich debates without necessarily having to align with corporate actors.

In conclusion, the challenges faced by the health care sector in the context of drug innovation processes, and discussions on pharmaceutical products in society at large might benefit from user involvement. Users might also benefit in return. Therefore, it makes sense to study involvement by organised users in the context of (emerging) innovations.

1.3 Emerging pharmaceutical technologies and users

This thesis deals with the emerging technology-related challenges of innovations in health care, more in particular the pharmaceutical sector. *Emerging technologies* are technologies that are in the early phase of their development (Van Merkerk and Van Lente, 2005). A lot of aspects remain uncertain, abstract and 'fluid' in these early stages. At the same time, these technologies attract a rather large share of attention. They are often eye-catching and through projections involve great expectations, promises and even beginnings of hypes. Examples of emerging pharmaceutical technologies include stem cell therapy, gene therapy, nanotechnology, and pharmacogenomics.

Here, the focus is on pharmacogenomics[5]. The advent of the publication of the human genome (Evans and Relling, 1999; The Celera Genomics Sequencing Team, 2001; The International Human Genome Mapping Consortium, 2001) led to investigating the functional manifestation of genomics; which genes do what, when and why? Pharmacogenomics is the functional expression of genomics in pharmaceutical research and development. Hopkins and colleagues (2006) defined pharmacogenomics as: "the science and technologies associated with dividing patients or populations into groups on the basis of their biological response to drug treatment using a genetic test" [not only relying on DNA analysis but also including phenotypic tests]. This might ultimately lead to more tailor-made medicines.

Pharmacogenomics is an emerging technological field. Major introductions of product innovations could be at least fifteen to twenty years away (Royal Society, 2005), although it is currently uncertain whether this will eventually be realised. At the same time, the technology makes a mark on current practices because a diverse set of actors construct strong expectations on this topic and some exemplary products have been introduced.

Emerging innovations are shaped as a result of co-evolution of technology and society (Nelson and Winter, 1977; Bijker et al., 1987) that spirals its way from early-stage to more established stages, leaning on several articulation processes (Rip, 1995). User involvement and user-producer interactions in emerging technological fields are carried by so-called *demand articulation processes*. These processes are defined in this thesis as iterative, inherently creative processes in which stakeholders try to address what they perceive as important characteristics of, and attempt to unravel preferences for an emerging innovation. Demand articulation takes place when thoughts of stakeholders, in terms of content and position (in favour or against), are made explicit, in such a way that other actors are prompted to (re-) act. It is a learning process that takes time. In the early phase of technology development stakeholders only have 'vague' ideas that become more concrete during the course of the demand articulation process. In this sense, these processes play an important role in clarifying needs for an emerging technology, and are especially prominent for stakeholders who are positioned on the user side of the innovation system, such as the intermediary user organisations.

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5 The emphasis on pharmacogenomics is influenced by the financing of this project organised through the programme on the 'Societal component of genomics research' of the Netherlands Organisation for Scientific Research (NWO). It would be difficult and even nonsensical to motivate the choice for concentrating on this emerging technology above others because of the inherent uncertain and fluid characteristics of these technologies.

1.4 Objective, relevance and central research question

The *objective* of this thesis is to understand demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies, building on existing literature about emerging technologies, intermediary organisations, and demand articulation. Sub-objectives include gaining insight into 1) demand articulation processes inside intermediary user organisations; 2) demand articulation processes in which these organisations engage in interactions with other actors; and 3) recommendations that could be made to governments and intermediary user organisations themselves about conditions under which they can improve the quality of user-producer interactions.

In this way, the *scientific relevance* lies in the contributions this thesis makes in understanding user involvement in emerging innovation processes, a context in which user-producer interactions have not earlier been studied in depth. Furthermore, it adds to more general insights into the concept of demand articulation as proposed by Smits and Kuhlmann (2004) for broadening policy and strategy developments. This study contributes by specifying demand articulation – and related learning processes – while also taking into account the dynamic character of this concept. Moreover, it sheds light on the demand articulation processes on several levels: inside intermediary user organisations, and in the broader context in interaction with other actors. Concerning the intermediaries, we build on literature about representative types of organised users, such as patient advocacy groups (Epstein, 1997; Rabeharisoa, 2003), which has mushroomed from the 1990s onwards (Epstein, 2008).

The *societal relevance* of this study concerns providing intermediary user organisations with recommendations for organising demand articulation processes, as well as their internal learning processes. Moreover, this study also reveals potential strategies to intervene in innovation processes and debates. These strategies centre on access, empowerment and impact these processes and debates. For policymakers, this thesis aims to provide ideas

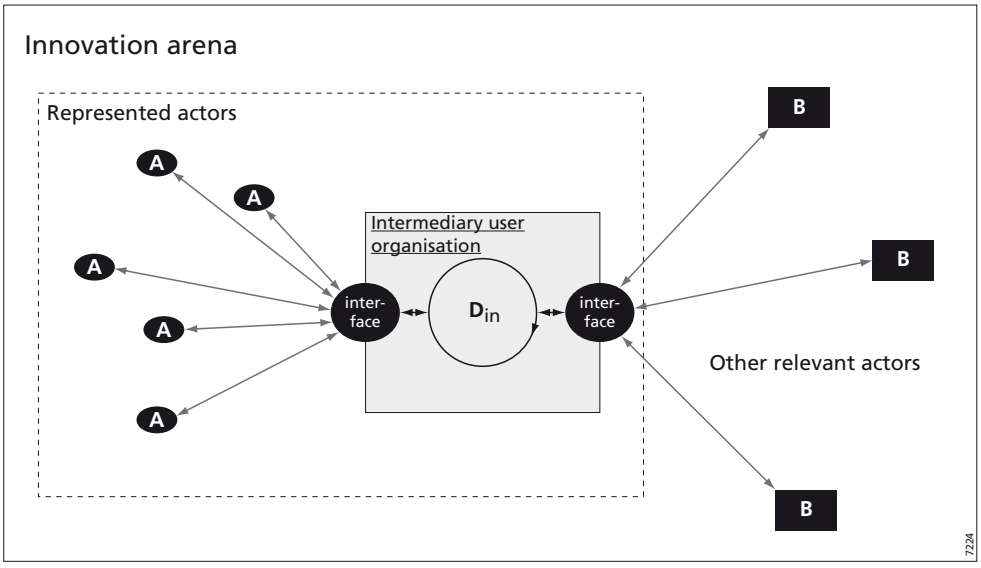

Figure 1 - demand articulation processes inside intermediary user organisations (D_{in}) in the context of two types of interacting partners (As and Bs) as part of a multi-actor innovation arena.

about how to improve conditions for users to participate in demand articulation processes in the pharmaceutical (and health care) sector. Finally, the pharmaceutical industry might learn how to react and act on user involvement in drug innovation processes.

Following these objectives, a more detailed version of the ***central research question*** is: *How to understand the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies?*

1.5 Central conceptual model and research questions

Demand articulation is a process that takes place in interaction between different stakeholders in a multi-actor 'innovation arena', which is a functional area of action in which stakeholders articulate their demands about (certain aspects of) new technologies (Benz, 2007). Internal demand articulation processes of intermediary user organisations (D_{in}) are complemented, initiated or fed by their interacting partners (Figure 1). We discern two types of interacting partners with which intermediary user organisations are engaged:

- Represented actors (As): actors that are embodied by the intermediary organisations, e.g. patients for whom patient advocacy organisations stand;
- Other relevant actors (Bs) with which the intermediary interacts on behalf of the represented actors (As), e.g. governmental agencies, industry, other representative actors.

The communication between intermediary organisation and both types of interacting partners goes through so-called interfaces, i.e. media of interaction or foci of communication between an intermediary user organisation and its interacting partners. Examples of interfaces include a round of consultative interviews or educating actors on a certain topic.

Figure 2 conceptualises the demand articulation process ***inside*** intermediary user organisations and in ***interaction with other*** actors.

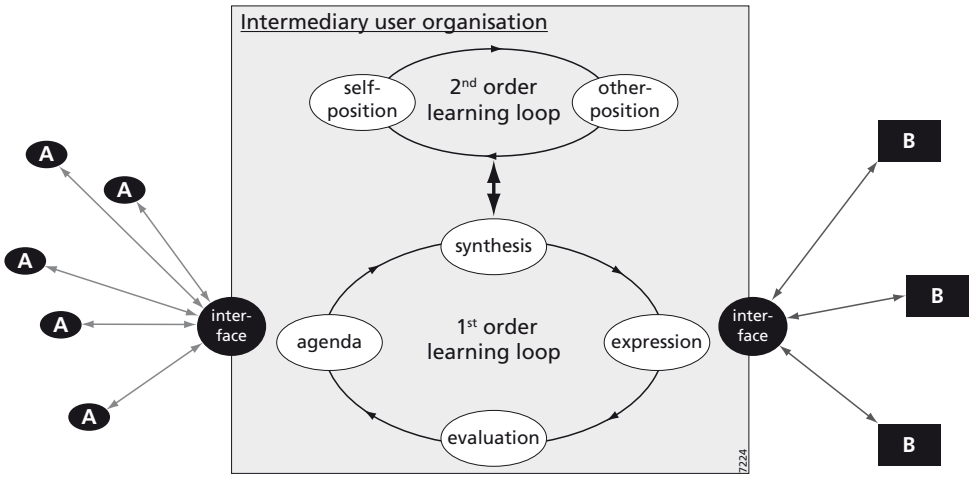

Figure 2 - central conceptual model.

Demand articulation dynamics consist of two intertwined learning processes:

- First-order learning loop about the development of demands, following a cycle of agenda-setting – demand synthesis – expression – evaluation.
- Second-order learning loop about developing underlying assumptions, objectives, ultimate preferences of the organisation itself (self-positioning) in relation with the position that is granted to the organisation by others (other-positioning).

We hypothesise that these two loops are interconnected in such a way that underlying assumptions are influencing demands, and vice versa. Moreover, it is hypothesised that intermediary user organisations go through the learning loops in different ways, owing to distinct kinds of functions and tasks that intermediaries can fulfil, and depending on the issues at stake. These differently-characterised learning processes are called 'demand articulation mechanisms', the identification of which is regarded as an outcome of this study.

The first part of the thesis studies these two interconnected learning processes ***inside*** intermediary user organisations, i.e. inside the grey box of Figure 2. We also take into account that the interacting partners (both As and Bs) influence these internal processes, but in this part the precise background of this influence and the organisation of the interaction remains a black box. The related research (sub-)questions are:

1. *How to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?*

1a. *Does first-order learning take place inside intermediary user organisations?*

1b. *Does second-order learning take place inside intermediary user organisations and how is this connected with first-order learning?*

1c. *What 'demand articulation mechanisms' can be discerned from studying these learning processes?*

The second part of the thesis deals with the way intermediary user organisations ***interact with other actors*** in an innovation arena. Pharmaceutical companies, governmental and regulatory agencies, intermediary user organisations and other stakeholders articulate their demands, which results in either divergence or convergence of demands. Actors agree or disagree on first-order statements, such as demands (needs, expectations). Moreover, they can agree or disagree on second-order statements, such as underlying assumptions. This agreement and disagreement on the two orders leads to four possible states of joint construction (see Figure 3): shared, untuned, congruent and conflicting demands.

Following Figure 2, the focus of the second part lies on the connection between the grey box and the other actors ('A' and 'B'), and the communication between the intermediary and these actors through the interfaces. There are differences in the organisation and strategies employed in these interfaces regarding the two types of interacting partners. The represented actors (As) want to have access to the agenda of the intermediary organisation. At the same time, in order to increase their empowerment and their ability to articulate their demands these actors wish to receive sufficient information. This requires interface strategies focused on 1) agenda access; 2) empowerment and provision of resources (knowledge) for represented actors; and 3) impact on the agenda of intermediary organisation. Regarding the other actors (Bs), the intermediary wants to have an influence on the debate. This requires interface strategies to ensure 1) arena access; 2) sufficient empowerment of the intermediary that makes it possible to engage in the debate; and 3)

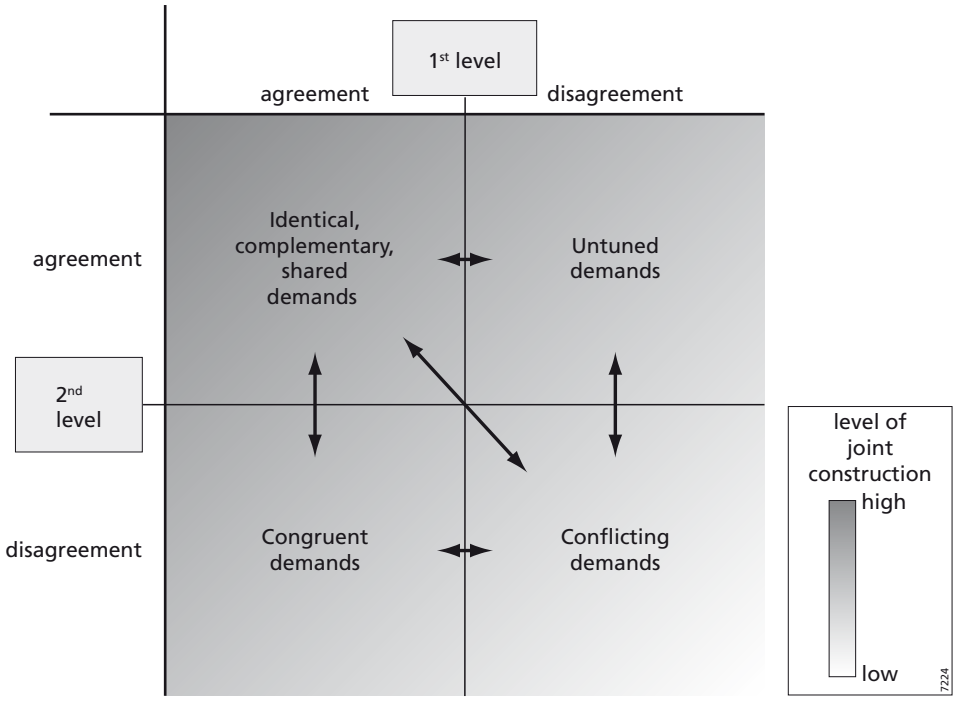

Figure 3 - different states of joint construction in a multi-actor innovation arena.

impact on the debate. It should be stressed that the interactions between actors A and the intermediary, and actors B and the intermediary are bi-directional.

These two types of interacting partners and related interfaces result in the following research (sub-)questions:

2. *How to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies?*

2a. *Does demand articulation take place in a multi-actor innovation arena involving interactions between an intermediary user organisation and its representing actors (As) and other relevant actors (Bs)? In other words, following shifts in Figure 3, to what extent is joint construction of demands occurring?*

2b. *What strategies do intermediary user organisations deploy in the different interfaces with representing actors and other relevant actors?*

2c. *To what extent can the joint construction of demands by the intermediary user organisation and their interacting partners (following shifts over time in Figure 3) be attributed to the interface strategies used? And how effective were those interface strategies?*

Lastly, more ***evaluative*** research sub-questions are:

3a. *In what way did intermediary user organisations influence technology development, and vice versa?*

3b. *What lessons can intermediary user organisations learn from the analysis of demand articulation processes and to what extent are the 'demand articulation mechanisms' and the 'interfaces' (strategies and organisation) of use for these intermediaries?*

3c. What role can the government play in order to improve the conditions under which intermediary user organisations function in the context of user-producer interactions?

3d. What lessons can other stakeholders learn from the analysis of demand articulation processes?

The empirical part of this thesis consists of three case studies that each focus on one Dutch intermediary user organisation. The organisations we investigated were the Dutch Neuromuscular Diseases Association (VSN[6]), the Steering Committee on Orphan drugs (WGM[7]), and the Breast Cancer Association (BVN[8]). For every organisation the research questions 1 and 2 are answered. In the two final chapters these research questions are answered in a more generalised way, as well as research question 3. The next section provides a more elaborate outline of the thesis.

1.6 Outline of the thesis

This chapter introduces the starting point for this thesis, i.e. the premise of user involvement in the pharmaceutical industry as being beneficial to both users and producers. Moreover, the focus of this thesis on emerging technologies, demand articulation processes, and intermediary user organisations is explained, while presenting the research questions, objectives and central conceptual model of this study.

Chapter 2 develops the central conceptual model on a step-by-step basis by first giving an overview of the role of user involvement in science, technology and innovation studies. Then, the role of users as well as the intermediary user organisations in the pharmaceutical industry is explicated. Furthermore, this chapter deals with emerging technologies and demand articulation processes, inside intermediaries and in interaction with other actors.

Chapter 3 introduces pharmacogenomics, providing definitions, examples, trends and characteristics. Moreover, it discusses how this emerging technology can be studied at present, using metaphor analysis to find analogies, e.g. to drugs for rare diseases with a low prevalence (orphan drugs).

Chapter 4 concerns the methodology, i.e. the case-study selection, design and delineation. Moreover, the data gathering methods, operationalisation of research questions, and data analysis are treated.

Chapter 5 presents results of the first case study on the Dutch Neuromuscular Diseases Association, a patient representative organisation. This organisation is engaged in interaction with scientists, companies, governments and (international) networks. Influencing research and development in the field of neuromuscular diseases is one of their prime objectives. Topics include gene therapy, stem cell therapy, exon-skipping, enzyme replacement therapy for Pompe disease, and clinical trials for idebenone and TCH346.

6 Vereniging Spierziekten Nederland (www.vsn.nl).

7 Stuurgroep Weesgeneesmiddelen (www.wgm.nl).

8 BorstkankerVereniging Nederland (www.borstkanker.nl).

Chapter 6 focuses on the Steering Committee on Orphan drugs, a committee founded by the Dutch government to support the situation of patients with rare diseases. It is made up of representatives of a diverse range of relevant stakeholders in the Dutch health care field. Topics include stimulating orphan drug R&D and the reimbursement of orphan drugs.

Chapter 7 concerns the case study on the Breast Cancer Association. This is again a patient representative organisation that, together with a host of other actors, was engaged in discussions on the reimbursement of and access to expensive drugs used in hospitals, such as the pharmacogenomics drug Herceptin.

Chapter 8 discusses the results from the three case studies in a more generalised way, and draws conclusions for the first two research questions.

Chapter 9 evaluates what different actors can learn from this study, which answers research question 3, and reflects on the conceptual model, the methodology and significance of this study for user involvement in innovation processes in general.

Chapter 2

Building a conceptual framework

The premise of this thesis is the importance of user involvement in technology development. As was sketched in the introductory chapter, user involvement and innovation processes can be interlinked. In other words, the co-evolution of society (or use) and technology are potentially beneficial in several ways to all stakeholders involved. Users can help steer the direction of technological progress in a creative and unexpected way, choosing between different alternatives, and controlling the speed of the innovation process.

The central research question that was put to the fore in the first chapter was 'how to understand the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies?' In this chapter the different concepts used in this question are unpacked and contextualised, and the accompanying central conceptual model (Figure 4) is built following the research questions.

In the first part of this chapter (2.1) we lay the groundwork for the concepts mentioned in the central research question and the model by inferring notions about user involvement from science, technology and innovation studies. They concern the significance of focusing on demand articulation, interactive learning, and intermediary organisations. These notions are subsequently elaborated. Firstly, the role of users and intermediary user organisations in (pharmaceutical) innovation processes are discussed (2.2). Secondly, section 2.3 introduces emerging technologies and demand articulation. Thirdly, section 2.4 deals with demand articulation processes inside intermediary user organisations, related to research question 1 and involving first and second-order learning loops. Section 2.5 is about demand articulation in interaction with other actors and involving communication through

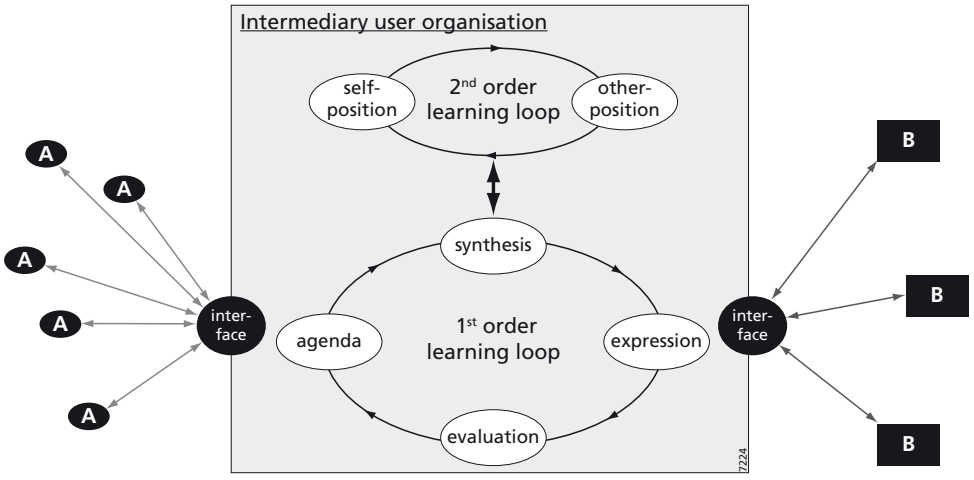

Figure 4 - the central conceptual model.

interfaces, both related to research question 2. The central conceptual model is fleshed out step-by-step throughout this chapter. Section 2.6 presents the final version, which is the same as Figure 4.

2.1 Innovation studies and user involvement

In this thesis we define innovation as a "from an economic and/or societal point of view successful combination of hardware, software and orgware" (Smits, 2002). 'Orgware' refers to the context in which innovations settle. For instance, drug development will not lead to innovations if these drugs are not reimbursed by insurers or accepted by users. Most pharmaceutical companies and industry trade groups regard reimbursement as part of a successful innovation process.

Innovating is a complex process. Despite this, for many years a rather simplistic model of innovation processes dominated the scene. This model became known as the linear model of innovation and was well characterised by the slogan of the 1934 World Expo in Chicago: 'Science finds, Industry applies, Man conforms'. Failures on the market and new insights from innovation theory deepened insights into innovation processes. Scholars such as Nelson and Winter (1977), Rip (1978), Bijker et al. (1987), Etzkowitz and Leydesdorff (2000) and Ziman (2001) emphasised that science and technology co-evolve with social and economic pressures, which is – almost by definition – not a (technological) deterministic process. Furthermore, other authors (OECD, 1992; Gibbons et al., 1994; Rip and Kemp, 1998) point out the numerous and frequent interactions and feedback processes between users and producers in innovation processes. Today, innovation is no longer seen as an autonomous process dominated by scientists and industrialists, but as part of a 'game' in which a heterogeneous set of actors is involved (Dosi et al., 1988; Smits and Kuhlmann, 2004).

Following this co-evolution perspective, a large range of science, technology and innovation studies scholars has increasingly acknowledged the role that society, more in particular users of technology, play in technological developments (Geels, 2002; Smits, 2002; Moors et al., 2003; Oudshoorn and Pinch, 2003; Jelsma, 2005). Oudshoorn and Pinch (2003) provide an overview of four science and technologies studies (STS) approaches to conceptualise and study the co-construction of users and technology: the social construction of technology (Pinch and Bijker, 1987; Bijker, 1992), feminist approaches (Cowan, 1987), semiotic approaches to users (Woolgar, 1991; Akrich, 1992; Akrich, 1995), and cultural and media studies (Silverstone et al., 1992).

We complement this with a fifth strand concerning innovation management and governance studies that are influenced by economics, sociology, organisational and management studies (Hackett et al., 2008). Within this strand we describe three different parts of science, technology and innovation studies: evolutionary economics theories (2.1.1), the search for the origins of innovations (2.1.2), and the innovation systems literature (2.1.3). These parts were partially built on the same theoretical and empirical starting points, and sometimes influenced each other. They all give insights into user involvement in innovation processes, providing building blocks that are used to fill in the conceptual model.

2.1.1 Evolutionary economics theories

The idea of co-evolution of technology and society is deeply entrenched in the (quasi-) evolutionary economics theories discussed here. These theories led to the conceptualisation of co-evolution as a dynamism that leans on several articulation processes, of which demand articulation is one example.

Over the years, economic approaches for studying innovation processes have developed the idea of regarding innovations as endogenous to economic growth. From this, the co-evolution of technology and society evinced, which relates to processes articulating different aspects of new technologies. The discussion in economics started with the *neo-classical economic theory* that regards the role of innovations and technological change as exogenous to economic growth. Schumpeter (1934) introduced the observation that innovations indeed contribute to economic growth in an endogenous way, and needed to be the subject of study. He emphasised the role of entrepreneurs and, later, large companies in propagating innovations, and neglected the part that the demand side could play. Later, Schmookler (1966) brought the importance of market demand in stimulating the direction of technological development to the fore. Other scholars, like Rosenberg (1976) opposed this view. This became the starting point of the technology push versus market pull debate. Although the discussion has still not been completely resolved, both approaches have been criticised as being part of a linear model. From then on, innovation processes have been regarded as iterative in which both demand and supply of knowledge and technology play a role (Mowery and Rosenberg, 1979).

These studies gradually developed into the evolutionary economic and quasi-evolutionary approach to innovation that emerged from the 1980s onwards. Nelson and Winter (1977; 1982) developed an *evolutionary theory of economic change* based on biological evolution including variation and selection of technological options. The selection takes place in a selection environment. Two 'selection layers' guide the variation and selection: the first establishes the direction in which the mutations evolve: the technological trajectory; while the second layer concerns the selection along the lines of this trajectory[9].

The *quasi-evolutionary approach*, developed by Van de Belt and Rip (1987), stressed that variation and selection are not independent. For example, engineers anticipate on the selection environment and are guided by expectations while doing so. Therefore, the technological paradigm of the evolutionary approach is broadened to encompass a nexus in which both the paradigmatic framework of engineers and the selection environment would find a place. They termed this set of rules and beliefs a technological regime, which in this way included cognitive, economic, political and social rules.

This regime later developed into a multilevel perspective (Kemp et al., 1998; Geels, 2002) in which regimes are part of slow-moving technology-external, structural trends in the socio-technical landscape. This turned regimes into meso-level concepts nested into the landscape. At the same time, regimes have assimilated micro-level niches, which act as 'incubator rooms' that are protected from the rigorous selection rules that make up the regimes (Hoogma, 2000). *Niches* are protected spaces in which technologies or markets of

9 Dosi (1982) introduced the term technological trajectory as a translation of Kuhn's notion of a scientific paradigm into a technology analogy and defined it as (p. 148): "an outlook, a set of procedures, a definition of the relevant problems, and of the specific knowledge related to their solution". Within such a paradigm the direction of advancement is programmed, which Dosi referred to as a 'technological trajectory'.

technologies can develop while being screened from 'regular' external influences in order to optimise the technology in the light of a small group of dedicated users. Examples of such policy screening instruments are fiscal measures to propagate the use of a certain product. In the pharmaceutical context, orphan drugs are protected from 'regular' market pressure by special legislation regarding intellectual property rights and market exclusivity.

Building on this quasi-evolutionary approach and the co-evolution of technology and society, Rip (1995) and colleagues conceptualised the dynamics that lead to this co-evolution. 'Societal entrenchment of a technology' refers to "processes in which new technological options, through the interactions between a variety of actors, become viable and established practices in society, both satisfying and modifying needs and interests" (Koch and Stemerding, 1994). This entrenchment constitutes different processes in which several aspects of the technology become articulated over time. In turn, these articulation processes are subject to 'alignment' or mutual attuning as well. Articulation concerns technological options and specifications, cultural and political acceptability, product and maintenance networks, and demands (Koch and Stemerding, 1994; Nelis, 1998). Starting from the perspective of user involvement in technology development, demand articulation processes form a significant element of this. These kinds of processes will be elaborated in section 2.3 onwards.

2.1.2 Search for the origins of innovations

The technology push versus market pull debate also formed the starting point of a second important strand of innovation studies in which users are regarded as sources of innovations, or at least actors who stress their needs for innovative solutions. This section shows that users indeed contribute to innovation in varying degrees, and that zooming in on processes in which users are engaged might also be interesting.

The Science Policy Research Unit (SPRU), founded in 1966 by Christopher Freeman, contributed to the search for the origins of innovations and innovative behaviour. This research group was home to the *SAPPHO-study*. It concerned a pairwise comparison of resembling innovations ('twins') that differed regarding the level of success. The study aimed to unveil explanations ('measures') for these differences by focusing on the characteristics of the organisations behind these innovations. "The single measure that discriminated most clearly between success and failure was 'user needs understood'". Also other marketing-related factors, such as education of users, publicity, and market forecasting appeared to be important (Rothwell et al., 1974; Freeman and Soete, 1997).

Von Hippel built upon product development literature and empirical work of Utterback (1971) and the SAPPHO-project when working on the origins of innovations. He was one of the first authors who showed that in some sectors users dominated the innovation process. Research in the field of scientific instruments led to the conclusion that users can initiate, formulate and even develop new products and processes (Von Hippel, 1976; 1977). Thereby they become what he calls the "*locus of innovation*". Teubal also found, in a similar study to the SAPPHO-project, that understanding user needs was a predictor for successful innovation projects. Moreover, the degree of 'market determinateness' discriminates between successful and unsuccessful projects. Market determinateness is "the degree of specificity of the market signals received by the innovating firm and consequently to the extent to which it anticipates (instead of responding to) demand" (Teubal et al., 1976). Not much later, Pavitt (1984) contributed to the idea that innovations do not solely originate in businesses. He discerned a taxonomy of different companies based on sources of

technology and requirements of users. These categories are: supplier-dominated, scale-intensive, information-intensive, science-based businesses, and specialised suppliers. He found that in different kinds of sectors different sources of innovation predominate.

In subsequent decades Von Hippel and his students (Franke, Herstadt, Lüthje, Urban, Thomke) elaborated on the question why it is important to include the user perspective in the process of innovation. Firstly, they demonstrated the significance of user initiatives[10] in innovation processes (Von Hippel, 2005). In sectors like scientific instruments, process machinery, industrial products[11], and consumer products[12], users appeared to be the "locus of innovation". An example of consumer products are sport-related products (Lüthje, 2004); approximately 40% of all consumers of outdoor-related consumer products ventured at least one idea for innovations. Of these consumers about 30% invented a new product, while the rest made improvements on existing products. A distinction is made between sectors in which users know exactly what they want (sectors in which so-called specials, catalogue items, and mostly industrial products are traded) and sectors in which user demands are more homogeneous (mostly consumer goods, such as food). The former sector leads more often to user-initiated innovation than the latter (Von Hippel, 1978).

Secondly, Von Hippel (1988) explained why users could be highly involved in the innovation process. Based on empirical data, he found that the functional source of innovation resides in the actors "whose analysis lead them to expect a rent they consider attractive". Regarding users, Von Hippel (1986) coined the term of 'lead users' for those who perceive that their expected benefits are significant, and who face certain needs well before the rest of the market or sector.

Thirdly, Von Hippel stressed the importance of including users in the innovation processes. Not only do users point to directions of future needs, they could also have first-hand information on new research directions, ideas, problems, and solutions. This is relevant for new products, processes or services, but also for incremental adjustments to existing ones. The latter is mostly communicated to the producers during the early use of innovations. Knowledge about these problems, ideas and adjustments is not easily transferred to other actors, e.g. because of its situation-related and setting-related character. This is called "stickiness" of knowledge (Von Hippel, 2001). Therefore, it is important for producers to remain in constant interaction with their users.

This strand of innovation studies literature shows that users in some cases can be the origin of innovative ideas, i.e. the 'locus of innovation'. In a less extreme way, users can also steer technology development by stressing their needs. These needs vary regarding the level of concreteness or 'market determinateness'. So, besides demand articulation on a more macro-level, as we have seen in the 'evolutionary economics theories' strand, demand articulation is also an important process in the world of users and other stakeholders on the demand side of innovation processes.

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10 In these cases, users had a need and an idea how to fulfil this need. They even produced a prototype that they introduced to a producer for manufacturing.

11 Printed circuit CAD software, pipe hanger hardware, library information systems, medical surgery equipment, Apache OS server software security features.

12 Outdoor consumer products, extreme sporting equipment, mountain biking equipment.

2.1.3 Innovation systems literature

The role of demand-side actors has also been studied in a more holistic way in the innovation system literature. Here, users – and also intermediary organisations – appear as major actors that are engaged in demand articulation processes. These processes can also be seen as revolving around interactive learning.

A major starting point of innovation studies concerns the observation that organisations are not innovating in isolation, as profit-maximising firms, but in the context of other actors and institutions (Freeman and Lundvall, 1988; Lundvall, 1992; Nelson, 1993). Lundvall (1988; 1992) opposed the transaction cost theory or neo-classical economics view that would expect a strict division between users and producers. Here, the only possibility for knowledge exchange is through vertical integration of organisations (resulting in the transformation of product innovations into process innovations). The growing complexities of technologies and user needs would in these 'pure markets' result in small numbers of product innovations. Empirical findings, however, showed a larger than expected number of these product innovations. This led Lundvall to introduce the concept of 'organised markets' in which users and producers interact and exchange more than just quantitative information. This new focus on organised instead of pure markets is needed because of the complexity of innovation activities: innovation occurs at the collusion of needs and opportunities, both of which show a large degree of variability and unpredictability. This requires not only exchange of information on quantities and prices of innovations, but also of information on the (technological and user-related) contents of these innovations. This content needs to be communicated.

The major role of knowledge in user-producer interactions calls for an emphasis on *interactive learning*; to innovate successfully, producers constantly need to learn about the technological possibilities as well as about user needs. This focus on learning has been followed up by scholars in organisational studies that explained interactive learning in dyadic company relationships using complexity, resources and structuring of innovative activities as variables (Meeus et al., 2001).

Lundvall's interactive learning and the evolutionary theory of economic change, as introduced above, constitute the two theoretical backbones of the systems of innovation approach: "interactivity paves the way for a systemic approach" (Edquist, 1997). Systems of innovation are mostly defined through geographical, technological or sector dimensions. One of the most well-known geographical types is the national systems of innovations: "the network of institutions in the public and private sectors whose activities and interactions initiate, modify and diffuse new technologies" (Freeman, 1987).

The performance of innovation systems is dependent on the quality of that system, in particularly on the quality of the subsystems (R&D, users, intermediary and supportive infrastructure), and on the mutual tuning of these subsystems (Freeman, 1997; Smits, 2002). Another consequence of the systems approach is that more heterogeneous actors, often at different levels and operating in various arenas, are involved in (the management of) innovation processes (Kuhlmann, 2002). This far more interactive model resembles the open innovation concept (Chesbrough, 2003) in which the sources of innovation are widely distributed, and learning through collaboration (R&D outsourcing, takeovers, alliances, etc.) is crucial. In a way 'open innovation' is not new, although this concept stresses the participation of non-traditional actors in innovation processes. Innovation always took place in a multi-actor context. Another recent addition is the attempt to move from a structural

to a more dynamic approach to innovation systems through the introduction of (system) functions of innovation systems (Hekkert et al., 2007).

Innovation systems and open innovation literature clearly shows the importance of including a diverse set of actors while studying technological innovations, ranging from the 'usual suspects', such as the government, universities and companies, to unaccustomed ones like intermediary organisations and users. Demand articulation plays a crucial role here (Galli and Teubal, 1997; Smits and Kuhlmann, 2004). Moreover, these literature strands show that interactive learning between different stakeholders in these systems is supportive to successful technology development and stimulation of innovations.

Summing up, this section presents three strands of literature within innovation studies that deal with user involvement in innovation processes. These strands have mutually influenced and reinforced each other. In the light of this thesis they illustrate that 1) users can be the 'locus' of innovative ideas (or at least needs), and in this way, have an important role in innovation processes and technology development; 2) demand articulation is a process in which users are engaged and lead to concretisation of demands; 3) demand articulation is also an interactive learning process between stakeholders in innovation systems; and 4) intermediary user organisations are a category of users in innovation systems occupied with interactive learning. In the next section we focus on intermediary organisations, whereas from section 2.3 onwards demand articulation and learning processes are explicated.

2.2 Role of users and intermediary organisations in innovation processes[13]

This section delves deeper into pharmaceutical and health care innovation processes and the degree to which users are involved. First, the term 'user' is defined and the choice for focusing on intermediary organisations is clarified. Then pharmaceutical innovation processes and the roles users might have in these processes are elucidated. Finally, we focus on the intermediary user organisation.

2.2.1 The user concept in pharmaceutical innovations

As the introduction and the previous theoretical section showed, users potentially play an influential role in technology development and innovation. However, the term 'user' should be made subject of reflection because it constitutes a rather *heterogeneous* set of actors. In many disciplines, users are equated with consumers but in business studies users and producers can be found in every stage of the value chain. To add to this complexity, some science and technology studies (STS) scholars (Wyatt, 2003) emphasise the role of non-users. This heterogeneity links to the fact that in STS users are regarded as much more than just economic entities that engage in buying decisions for certain products. Interactions with users convey much more information, and the identity of an actor as being a 'user' should always be contested because in some cases users can take on the role of producers as well.

One characteristic of the health care sector is that users are not as homogenously defined as, for example, in consumer markets (Oudshoorn and Pinch, 2003). 'Use' is not only seen as consumption or taking in (in the sense of swallowing a pill), but also includes the

13 Section 2.2.2 and 2.2.3 are based on Smits and Boon (2008).

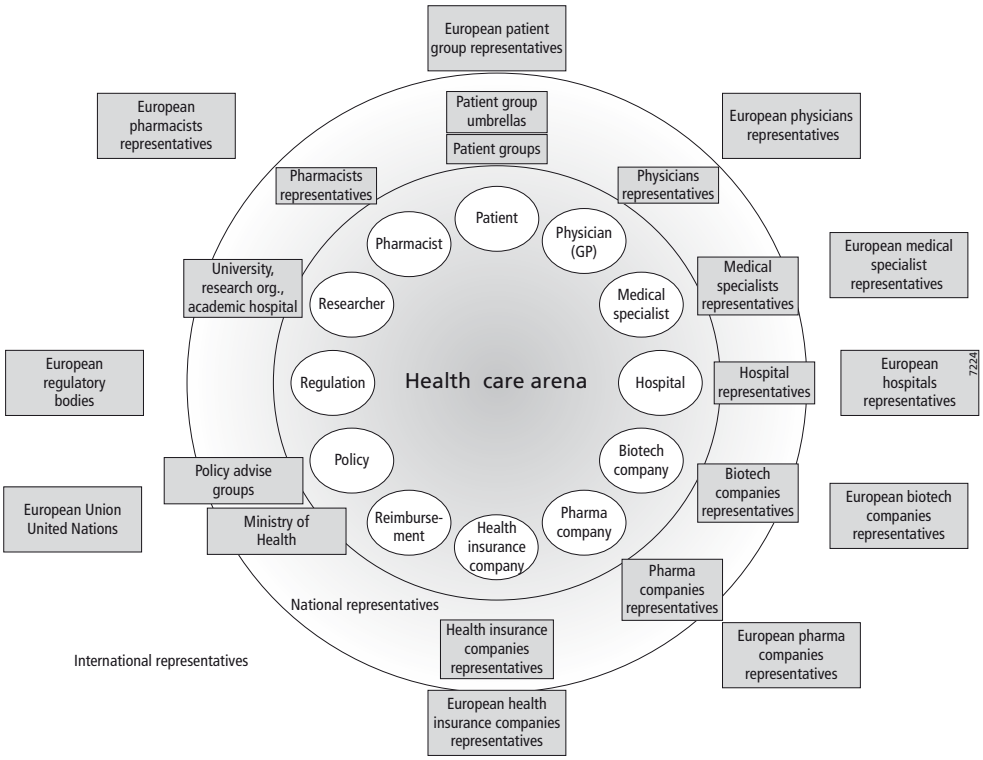

Figure 5 - social map of relevant actors in the field of medical applications of prevention, diagnosis and therapy in the Netherlands. Interactions between actors are not shown. The grey boxes are intermediary organisations.

decision to exploit the possibilities of the innovation. In the case of pharmacogenomics, pharmacists and physicians both play a role in deciding whether patients take a pill. Although they do not take this pill themselves, by prescribing and making it available they exploit the opportunities of the pill, e.g. ensuring a safer and more efficient therapy. Moreover, health insurance companies and governmental bodies in their role of public health insurers, also have demands and buying power, and could therefore be regarded as users.

In order to illustrate the heterogeneity of the user category, a series of explorative interviews was conducted with 24 representatives of actors in the Dutch health care sector[14]. A social map of the Dutch health care sector, included as Figure 5, illustrates this variety of users. It not only shows the presence of companies, governmental bodies, hospitals, but

14 They include a diverse range of individuals representing the medical profession (3), academic researchers (2), patient groups (4), advisory (1), regulatory (1) and reimbursement bodies (3), pharmaceutical and biotechnology companies (3), health insurance companies (1), parliament (1) and the government (5). The interviews were conducted following a semi-structured format that included questions on interactions with other actors in the health care arena in the Netherlands and internationally; especially in relation to innovations in the pharmaceutical and diagnostic industry. The transcripts of these interviews were subsequently fed back to the respondents for authorisation.

also of agents that mediate between two or more different actors, mostly on behalf of other actors. Examples include patients' or physicians' representative organisations, and umbrella organisations of insurance companies.

At least in the Dutch health care sector intermediary organisations, depicted as the grey boxes in Figure 5, take central stage as users in the innovation system. Before these intermediaries are conceptualised, we first delve deeper into pharmaceutical innovation processes and the increasing influence external stakeholders, such as users, have on these processes.

2.2.2 Pharmaceutical innovations: the linear model under pressure

In the pharmaceutical sector the adoption of the linear model is clearly demonstrated by the 'drug research and development pipeline'. This is a model that describes the development of new drugs in a rather linear way based on different phases. The reason for this R&D dependency lies in the industry's emphasis on product innovation. The urgency and strictness of the model and its phases is created and emphasised in interaction with regulatory requirements and its accompanying milestones, and technological conditions that bear a more process-like character. Figure 6 illustrates this model, in which also the regulatory requirements and technological process conditions are sketched.

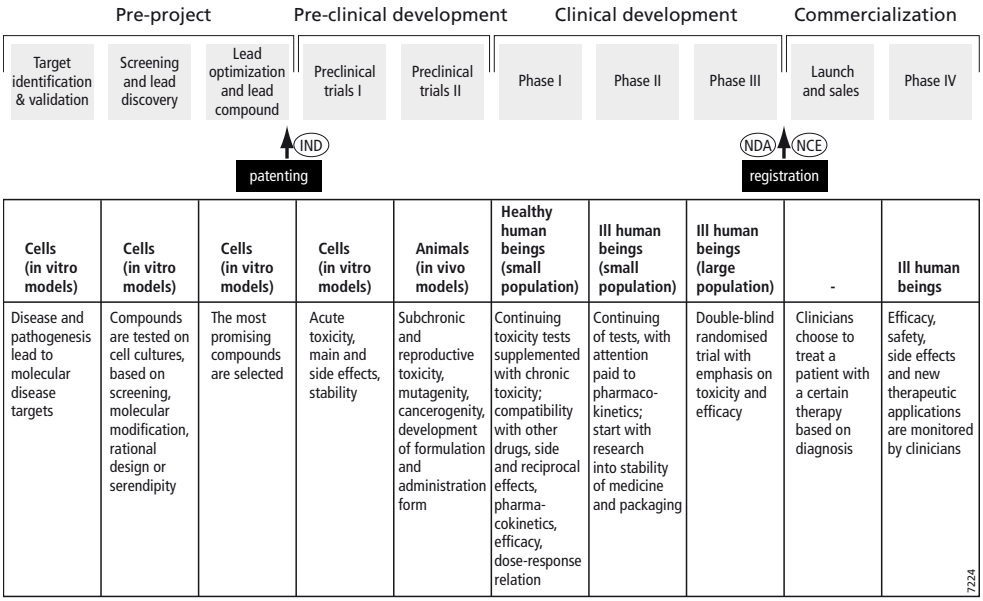

Figure 6 - a model of the drug R&D pipeline of pharmaceutical companies. In the first row of the table the test subjects are denoted, while in the second row objectives of every phase are mentioned (Jungmittag et al., 2000; Schellekens et al., 2001; Gassmann et al., 2004; Buurma et al., 2005)[a]. This picture has a linear layout just for presentation purposes.

a IND (investigational new drug), NDA (new drug application) and NCE (new chemical entity) are names for the compound related to the stage they are in.

Since the 1980s several authors (Vos, 1989; Schmid and Smith, 2004; Buurma et al., 2005) have begun to claim that the linear layout of pharmaceutical innovation processes could be enhanced by feedback and feedforward steps, and even cyclic interactions within the companies, and with basic and clinical research partners. These interactions occur between different stages in which also other stakeholders, such as small high-tech companies and university hospitals are involved. Examples include interactions between:

- Universities and companies within the pre-project stage (Maxwell, 1984): industrial research reveals working mechanisms of diseases or drug targets. University researchers use these findings to delve into the underlying working mechanisms. Companies can in turn, use these results.
- The preclinical and clinical development stage: research results of clinical trials can be used as starting points for new preclinical, and even basic research. Also by investigating the viability of targets early on through the use of animal or organ models, *in silico* ADME models, and computational drug-target interaction modelling (Schmid and Smith, 2004).
- Within the clinical trial phases themselves (Vastag, 2006): in what is called 'adaptive trials', dosages, patient pool sizes, etc., change under the influence of incoming data. Also in traditional clinical trials interactions occur revealing unexpected fields of indication and even subsequent information on underlying working mechanisms of drugs or diseases. A well-known example is the case of sildenafil (Viagra), a drug that was intended for angina, but appeared to have the side effect of strong and persistent erections. The traditional clinical trials that followed proved this and after market introduction sildenafil appeared to be a success. It is now also marketed for pulmonary hypertension patients as Revatio (Ghofrani et al., 2006).
- The commercialisation and development stage: post-marketing research is done in Phase IV. This means that a drug is approved and used on the market while pharmaceutical companies together with the medical profession conduct "in-life testing" and monitor the impacts in terms of efficacy and especially safety (Arlington, 2007). If drawbacks occur on these indicators, e.g. if adverse side effects arise, then the company or regulatory body will take appropriate action. This is all the more poignant in classes of people that were not included in clinical trials (children, the elderly), in fast-track approval cases, and with orphan drugs, where only small groups of people were tested. This monitoring can yield unexpected fields of indication as well. An example is thalidomide: at first it was intended as a sedative for pregnant women, but it turned out to cause skeletal birth defects. Later, a physician successfully applied it as a last resort to treat an inflammatory condition called erythema nodosum laprosum (ENL). Recently, pharmaceutical companies look at new uses of existing drugs in a more systematic way under the term of 'drug repositioning' (Ashburn and Thor, 2004).

These illustrations show that interactions can be beneficial for the success rates and effectiveness of pharmaceutical innovation processes. Nevertheless, interactions have hardly been structurally embedded in most organisations. Therefore, some authors (Schmid and Smith, 2004) advocate the solidification of these interactions between different phases of the drug R&D pipeline by pursuing a strategy that aims at faster feedback loops, e.g. by forming small, decentralised task groups that are able to accelerate internal decision-making.

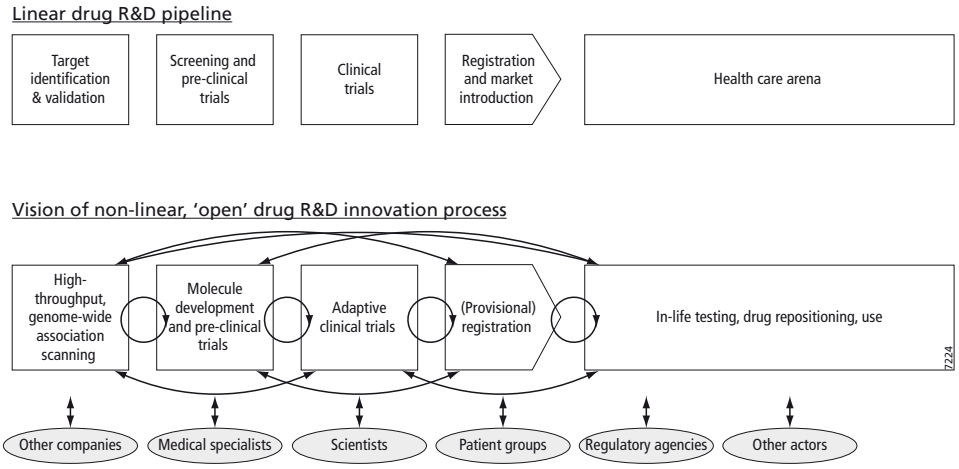

Figure 7 - linear model of the drug innovation process as compared to a more interactive representation (based on the above and partially on PriceWaterhouseCoopers, 2007).

The major conclusion of the foregoing is that in various phases of the innovation process a large role is, or could be played by actors external to the pharmaceutical company and their close companions, such as universities and specialised suppliers. Hara (2003) advanced this point as well: after claiming that the linear model cannot be upheld even in the case of the drug R&D pipeline, he emphasised that heterogeneous, interactive networking is important in the drug-shaping process. A diverse set of actors can influence the level of success of an innovation (process) and the pharmaceutical industry should therefore build communicative channels with these external parties through which learning and proper evaluating is possible. A more interactive picture of the drug innovation process, both inside the company and in relation to external actors, is portrayed in Figure 7 as a vision of the non-linear, 'open' drug innovation process.

Obvious examples of external actors influencing drug innovation processes are situated in the later stages of the pipeline, such as the involvement of medical specialists in clinical trials. Anxieties over ethical, legal and social impacts of medical and pharmaceutical R&D often also cause external parties to react. Examples include animal rights and pro-life activists, but also governments in developing countries that do not subscribe to international patent law (Ford et al., 2007). A simple denial of these institutions does not work and can even turn out to be counterproductive. It is often better to involve these stakeholders in the innovation processes and incorporate the viewpoints of these external actors. However, given the already stated heterogeneous character of this set of actors it is not easy to involve them in the management of innovation processes effectively and efficiently. At the same time they remain relatively independent of pharmaceutical companies. The next sections focus on one important actor that up to now has often been neglected in pharmaceutical innovation studies: the user. First, the reasons to involve users are discussed (2.2.3); then the users in the pharmaceutical sector are scrutinised, focusing on one category in particular: the intermediary user organisation (2.2.4).

2.2.3 Five reasons to involve users in the pharmaceutical industry

In recent years scholars from many disciplines have emphasised the role of users in innovation processes. In the previous chapter three reasons to involve users were given, namely instrumental, political and moral ones. Smits and Den Hertog (2007) discerned five reasons to involve users as well. They are illustrated with examples coming from the health care sector:

First, the market does not adequately meet all societal problems and companies do not develop products that are commercially unattractive. This leads to market failure. For example, companies are not keen to develop drugs for rare disorders or neglected diseases (conditions prevalent in developing countries) because the related markets do not provide enough economic incentives. Therefore, users can try to put appropriate measures for stimulating R&D for these diseases on the agenda of governmental agencies and companies. In relation to this, a WHO project called 'Priority medicines for Europe and the world' (WHO, 2004) aimed to construct, in consultation with scientists, the industry and patient groups, a list of diseases that should be the cornerstone of public investment in drug R&D.

Second, also in market-oriented sectors it is beneficial for companies to keep track of the wishes of users because knowledge on them will improve the adoption rate of their products. Medical professional organisations and authoritative medical specialists can play the role of so-called 'lead users' whom other physicians look at while deciding whether to adopt a therapy or diagnostic tool (Nelis, 1998; Hara, 2003). To go one step further, producers can enhance their products by mobilising the creative potential of users by making use of their 'experiential knowledge'. Examples are patients who have ideas on drug toxicology (Caron-Flinterman et al., 2005).

Third, public and patient involvement can also enhance the (cost)effectiveness of companies' R&D processes. Often patient groups stimulate research through charity funds or by stimulating the government to invest money. As was mentioned at the start of the previous chapter, disease advocacy groups largely attributed to convince people to back the California $3 billion stem cell research initiative that was approved in 2004 (Wadman and Abbott, 2006). For some patient groups, such as the UK Alzheimer's Society and the French Muscular Dystrophy Association, these financial contributions are linked to steering the direction of the R&D agenda (Rabeharisoa, 2003). Moreover, some patient groups try to influence the set-up and assist in the organisation of clinical trials; notably the HIV/AIDS (Epstein, 1995) and breast cancer trials (Bazell, 1998) in the US. Also other organisations such as the Cochrane Collaboration (www.cochrane.org) could be mentioned in this respect. It can even be the case that patient groups take a 'producer turn'. Sharon and Patrick Terry, parents of two children with the rare inherited disorder pseudoxanthoma elasticum (PXE), stimulated research, own the resulting patents and exploit them through a company (Terry et al., 2007). Increasing the (cost)effectiveness of innovation processes is all the more needed in cases of rare and neglected diseases, because R&D costs should be transferred to a small or low-income group of patients. There are indications that user involvement for these rare diseases is stronger (RGO, 1998).

Fourth, the introduction of new technologies might have considerable repercussions on society. To make sure that this does not result in societal resistance, different stakeholders, such as animal rights groups and pro-life organisations, can and should have their demands heard. Moreover, it is important for technology acceptance to have 'champions' among public groups who stress the benefits of new innovations (Bower, 2005). In the medical

sector patient advocacy and medical professional groups often claim this role, as we have seen in the genetically-modified animals debate at the start of the introductory chapter.

The *last* reason concerns the democratic value of innovation processes. Not only is much of the basic research publicly financed, but also innovation strongly influences people's lives. Therefore, they have a moral right to influence decision-making on these innovation processes.

As we have seen in this section there are several reasons for involving users in pharmaceutical and health care innovation processes. One category of users is the intermediary user organisations. The next section explains the role these organisations play in user-producer interactions within these sectors and underpins these organisations theoretically.

2.2.4 Intermediary user organisations

An *intermediary organisation* is defined by Howells (2006) as "an organisation or body that acts [as] an agent or broker in any aspect of the innovation process between two or more parties." He also states that there is much research going on with regard to this topic but theoretical focus is lacking. In the context of the innovation systems literature, these organisations mediate or bridge between firms, research and educational institutes, the demand side and the infrastructure of the innovation system (Lundvall, 1992; Edquist, 1997)[15].

In recent decades intermediary organisations have become increasingly important because of an increase in different sorts of actors involved in the innovation process and the related need for translating and transferring knowledge (Van Lente et al., 2003). Examples include strategic alliances, spin-offs, joint ventures, innovation centres, incubators, and science parks. Empirical research shows that the number and variety of intermediaries is growing as well (Van der Meulen et al., 2005). The initial focus was on the science-policy boundary, e.g. research councils (Bal et al., 2004), but soon broadened with the inclusion of small and medium-sized enterprises, knowledge intensive business services (Bessant and Rush, 1995; Den Hertog, 2000; Kaufmann and Tödtling, 2001), and the emphasis on the increasing role of users (Bunders et al., 1999; Davenport et al., 2003; Moors et al., 2003).

Users and producers come from different backgrounds and their interactions can be facilitated by what we call *intermediary user organisations*. We define these as ...stakeholders that facilitate interactions between users and one or more other actors.

This definition in some places remains rather indefinite because intermediary organisations can have different roles and functions at once (Galli and Teubal, 1997). The facilitation mentioned in the definition can take many forms including: delegate, steer,

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15 Intermediary organisations are also conceptualised in:
- Social network theory (Burt, 1992): intermediaries need 'social capital' (trust, impartiality) to bridge 'structural holes' between actors.
- Principal-agent theory: Braun, Van der Meulen and colleagues (Van der Meulen and Rip, 1998; Braun and Guston, 2003) use this theory as a way to analyse 'boundary organisations' between science and policy.
- Theory on market brokerage (Khurana, 2002): when there exist 'institutionalised gaps' between actors, these kinds of organisations could function as enhancers of interactions.

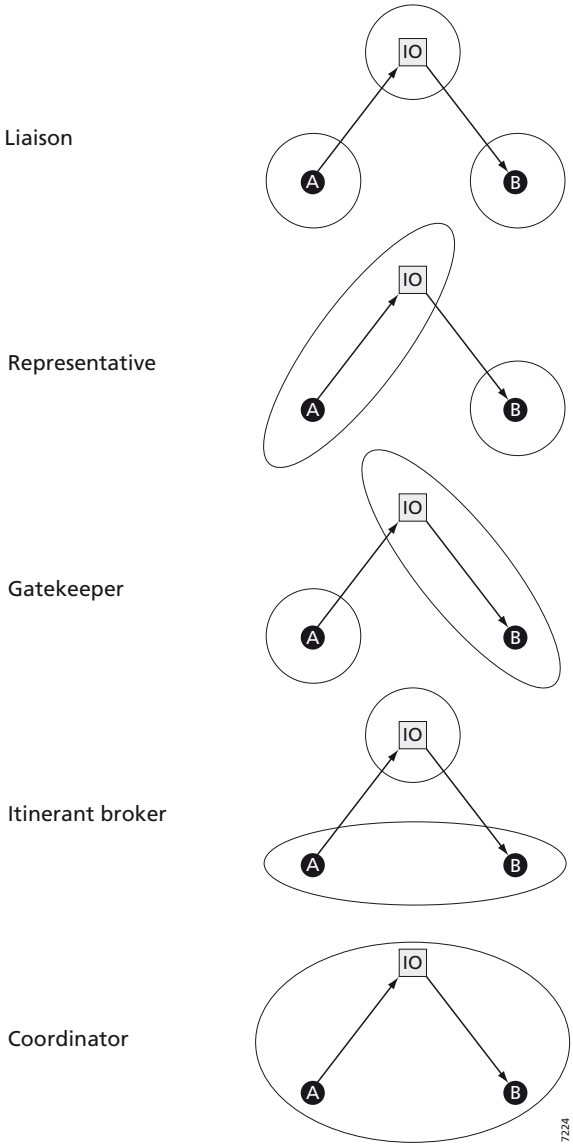

Figure 8 - types of intermediary organisations discerned by structural characteristics; the actor's positioning towards each other and the different social worlds is represented as ellipses (adapted from Fernandez and Gould, 1994)[a].

a The arrows in Figure 8 depict an interaction that goes in one direction, while this is not realistic. However, if a two-directional arrow is inserted, the differences between a representative and a gatekeeper might become unclear.

inform, coordinate, support, legitimate, aggregate, be a platform, be a broker, translate, and advise[16] (Fernandez and Gould, 1994; Van Lente, 2005).

A shift in focus of these intermediaries has been observed in recent years from short-term activities such as knowledge translation and brokerage to more upstream activities in the innovation process, such as scoping and the provision of strategic intelligence (Howells, 2006). When dealing with emerging technologies and their related uncertainties, intermediaries need to learn about using strategic intelligence, i.e. ways of obtaining information about prospective technologies that can be used to direct actions and decisions, and organising their demand articulation processes. This means that *demand articulation* has become an integral part of intermediary user organisations (Smits and Kuhlmann, 2004; Klerkx, 2007).

In order to study intermediary user organisations it would be interesting to construct a typology or classification of these organisations. However, an unequivocal *typology of intermediary organisations* has so far not been proposed (Khurana, 2002; Van der Meulen et al., 2005).

An interesting example of a typology of intermediaries is found in Fernandez and Gould (1994), based on differences in structural fixtures and the notion of belonging to different 'social worlds' or subgroups. Figure 8 illustrates this: the 'IO' dots are the intermediaries; the A and B are other actors between which the intermediary interacts, while the ellipses correspond to subgroup membership. For example, the 'representative' organisation belongs to the same subgroup as the entities it represents towards the actors outside the subgroup. In this context, the subgroup can be called the 'patient world'. Other types include liaison, gatekeeper, itinerant broker and coordinator. Because of the focus on organised users (see introductory chapter) this thesis concentrates on those intermediaries that are part of the same social world as the users (actors A), i.e. the representative and coordination types.

These types of intermediaries will be revisited when describing the structure of these organisations (Figure 9) and the selection of organisations to be studied.

Position of intermediaries

Intermediary organisations constantly need to position themselves vis-à-vis other stakeholders, because that is one major way in which they legitimise their existence (Van Lente, 2003). As was mentioned in the previous chapter, an *innovation arena* is defined here as a functional area of action in which stakeholders articulate their demands about (certain aspects of) new technologies (Benz, 2007). If a patient organisation presents itself as a representing agent of patients with a certain disease, it will only be able to fulfil accompanying roles and functions when other actors, such as the government and pharmaceutical companies, see the organisation that way. This necessarily imposes a focus on external parties. Therefore, processes within these organisations are mostly involving other stakeholders in the arena.

Intermediary organisations are always under pressure of their environment. Doorewaard (1990) even speaks of the "paradox of (representative) intermediaries": internally their

16 Types, roles and functions of intermediaries are not necessarily the same: for example, a patient group can perform functions like translation of knowledge, and advocate interests. There is not a one-to-one connection between types and roles, and one could claim that such a link is not informative either.

members push them, while externally other actors, such as the government, try to steer them. Often expectations about their tasks, mandate, their image and visibility are contradictory. Klerkx (2007) called this the 'function ambiguity'.

The focus of this thesis will be on demand articulation in intermediary user organisations in the health care sector. Following our focus on intermediary *user* organisations, the emphasis lies on two types of intermediaries, i.e. the representative and coordinating type (Figure 8), because in both cases the intermediary is part of the same social world as the users it represents (the As in Figure 8). Moreover, the representative and coordinating types are chosen because these categories are omnipresent in this sector in the form of patient associations, medical professional groups and steering committees. Based on the representative type of Figure 8, Figure 9 presents an intermediary user organisation that encompasses internal demand articulation processes (D_{in}). The organisation is engaged with 'interacting partners' inside its own social world (the 'represented actors' A inside the discontinuous lines), and outside this world (the 'other relevant actors' B); all inside the multi-actor innovation arena. Figure 9 illustrates this focus on representative intermediary user organisations as a first step towards a central conceptual model for this thesis. If one changes the discontinuous line around actors A and the intermediary, to include actors B as well, the figure would resemble the coordinating type.

To sum up, this section shows that the linear pharmaceutical innovation model is under pressure and that there are several reasons to increase user involvement. Furthermore, the emphasis of this thesis on intermediary user organisations is explained, leading to an overview of the heterogeneity and structure of these intermediaries (Figure 9), which will be used in the next section when we proceed with conceptualising demand articulation processes in the context of the intermediaries. The focus in this thesis is on the representative and coordinating intermediary user organisations. The representative

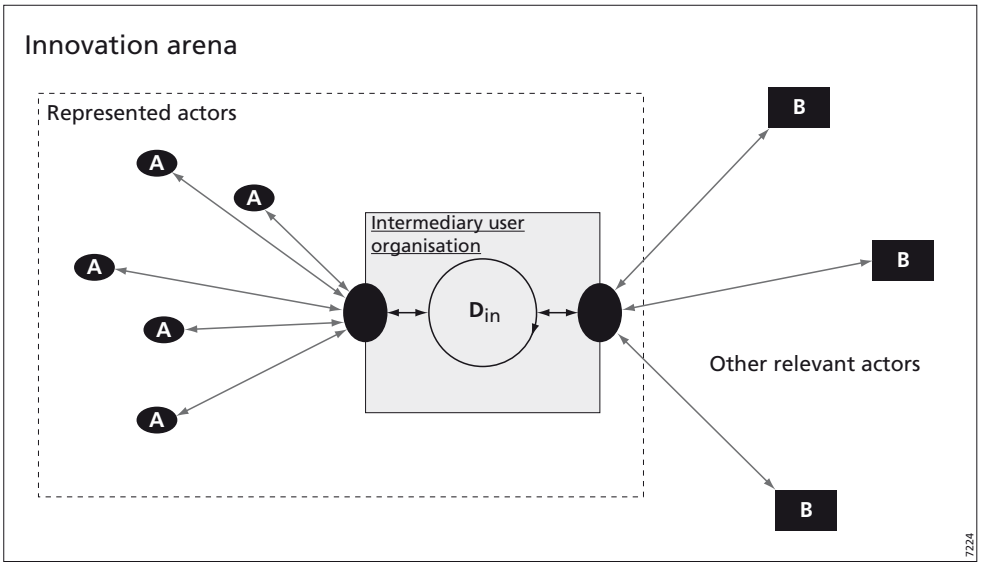

Figure 9 - step 1 in building a central conceptual model.

intermediaries embody the interests of the users towards other actors while being part of the same world as the users. The coordinating type of intermediaries organise (part of) the interactions between actors who, just as the intermediary, belong to the same social world.

2.3 Emerging technologies and demand articulation

This section deals with demand articulation processes in the context of emerging technologies and also defines both demand articulation and demand itself. First of all, *emerging technologies* are technologies in their early phase of development, which have not resulted in concrete products yet (Van Merkerk and Van Lente, 2005). This implies that several aspects, such as the characteristics of the technology and its context of use (demands), the configuration of the social network and their related roles are still uncertain and little specific. For certain technologies, especially those with a disruptive character and a significant influence on society, it is advisable to be aware in an early phase of development of the quality of potential (negative and positive) impacts.

This relates to the control dilemma of Collingridge (1981). In the emergent phase it is difficult for stakeholders to specify what they want from the technology, while owing to the fluidity of the technology, the direction of development can be steered more easily. In contrast, in the later phases demands are clearer but potential options to influence the direction decrease. Learning how to deal with this dilemma would be beneficial in the context of decision-making on emerging technologies. It would decrease the uncertainties regarding both the outcomes and the track that leads towards this ultimate end stage, the so-called emerging paths (Van Merkerk, 2007). Nevertheless, despite these insights innovation scientists still struggle to provide concrete instruments to tackle the Collingridge dilemma.

These uncertainties and 'fluidities' of technologies are associated with a large amount of attention from a diverse set of actors, ranging from scientists and companies to journalists and the general public. Sometimes this even leads to inflated ideas about the technology, and the forming of a hype. They are presented as 'eye-catching' or 'breakthroughs' (Brown, 2000). These actors convey their thoughts about the new technology through the use of future projections, expectations and visions.

As was introduced in section 2.1.1 in the context of the co-evolution of technology and society, 'societal entrenchment of a technology' is carried by different processes in which several aspects of the technology become articulated over time. Rip (1995) introduced these *articulation processes* in the early 1990s. Later, he and his colleagues studied them more elaborately. Examples of these processes include the articulation of technology specifications itself, product and maintenance networks, cultural and political acceptability, and demands.

Grounding *demand articulation* processes, Rip referred to the work of Teubal (1976; 1979). He emphasised that when bridging supply and demand in existing markets users have defined their needs quite precisely, and prices (also of competitors) play a major role in sales decisions. Breakthrough, radical, emerging technologies do not have predefined markets and the needs are less apparent. Producers can only offer blueprints, users might not have thought of the direction of solutions the new product offers, and the regime as a whole might even change as a result of the innovation (leading to different preferences of users).

In this context, Teubal (1976) introduced the term market determinateness as "the degree of specificity of the market signals received by the innovating firm and consequently to the extent to which it anticipates demand. In order to explain the concept we introduce four types of market signals, in ascending order of specificity: (1) signals about a need; (2) signals about a product class; (3) signals about basic functions; (4) signals about product specifications." Ideally, as a technology emerges and several of its aspects become clear, users are also becoming specific about their 'market signals' or demands.

Kodama (1995) later picked up market determinateness or demand articulation, which he defined as "a dynamic interaction of technological activities that involves integrating potential demands into a product concept and decomposing this product concept into development agendas for its individual component technologies". Building on this, the term 'latent demand' was introduced, which means that most stakeholders will not have an evident idea of what they want from the start (Orihata and Watanabe, 2000). An actor might have a certain need that is ill-defined or latent, but which, in a sense, cannot be denied. The demand articulation process, therefore, is the start of a consciousness-raising exercise in which demands become increasingly concrete.

Demand articulation is defined in this thesis as: *...an iterative, inherently creative process in which stakeholders attempt to unravel preferences for, and address what they perceive as important characteristics of an emerging innovation*. Demand articulation takes place when thoughts of stakeholders, in terms of content and position (in favour or against), are made explicit. Articulation of demand is a *learning process* that takes place inside organisations, and in interaction with other organisations. In the early phases of technology development stakeholders only have 'vague' ideas, which become more concrete and sharpened during the course of the demand articulation process.

The term *demand* merits some attention as well. Following some scholars (Mowery and Rosenberg, 1979; Teubal, 1979; Klerkx et al., 2006), a clear distinction should be made between economic or market demand (actor X wants a product and is prepared to pay a certain price), and substantive demand (e.g. actor X has ideas about how to develop a new technology). Moreover, Mowery and Rosenberg (1979) criticise the use of "the rather shapeless and elusive notion of 'needs'".

In this thesis we are interested in demands in early and fluid phases of technology development. This means that the demand concept should not be restricted to market or economic demands, but also include more substantive demands. Given this emergent character and the focus on articulation, we are also interested in demands that are ranging from being less (e.g. visions) to more defined (e.g. needs). Moreover, we consider demands broadly varying on content, including cultural, political, ethical, social issues, because in early stages of technology development it is unclear which issues would become important in steering, and because user preferences are diverse and partially dependent on these issues.

Demands are defined in this thesis as: *...explicit, univocal statements of actors on how they regard (the future concerning) a technology and which issues regarding this technology should be included or addressed by other stakeholders*. Demands include:

- Science fictions, (guiding) visions, 'Leitbilder', expectations or promises[17], being real-time representations of future technological situations and capabilities (Borup et al.,

17 The distinction between expectations and visions is not clear. Therefore, we treat these two categories as partially overlapping.

2006). They include statements on the future ('we expect...', 'we anticipate...', etc.). Visions are "mental images of an attainable future shared by a collection of actors; they guide the actions of and interactions between those actors" (Grin et al., 1999).
- Perceptions of problems and obstacles with existing products or situations.
- Ideas and solutions: the actor acknowledges a problem, knows a direction for solutions, and has some concrete ideas about how this end state should be reached.
- Concrete and latent needs for existing and non-existing products: "user needs in general are the preferences of the user for the properties of the service or alternatively for the performance dimensions of the product" (Teubal, 1979).
- Concerns about ethical, legal and social implications (ELSI) regarding new technologies.

In this section demand articulation processes are introduced as part of co-evolution dynamics of technology and society. Demand articulation refers to the development of a sharpened conception of a new technology by an actor (see next section). Moreover, demand articulation between different actors is also a subject of study, pertaining to the extent to which shared demands are developed within a coalition of actors or the innovation arena as a whole (section 2.5).

2.4 Demand articulation processes inside intermediaries

Section 2.3 introduced demand articulation as a learning process both inside an organisation and in relation to other actors. This section focuses on demand articulation processes inside intermediaries in connection with the first research question: *'how to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?'* In this section the two learning loops – first-order and second-order learning – are explained (Figure 4). Moreover, it is taken into account that they are interconnected, and that demand articulation mechanisms can be discerned.

2.4.1 Demand articulation as a learning process

Learning processes are extensively studied in organisational and policy sciences. Schön (1983) looked at activities of professionals, especially in unique and complex cases of high uncertainty and instability. He concluded that they shifted back and forth between problem definitions and solutions, using professional codes of conduct, earlier experiences and other generic notions as guidance. He called these assumptions that steered professional's behaviour 'frames of meaning'.

Following Schön, Van de Ven et al. (1999) proposed a learning process model that is primarily intended to conceptualise processes in innovation project teams within an organisation (Figure 10). They define the trial-and-error learning process as a mutual dependent process of actions taken by a project team and (perceived) outcomes. For example, an innovation project team introduces a new component to a technological artefact (action). This leads to an increase in the performance of this artefact (outcome), which leads to positive feedback: the innovator will continue with this action. Learning can also occur on another level, i.e. through shifting the goals and outcome criteria of an innovation project. For example, if an outcome is negative, besides adjusting its actions, the project team can

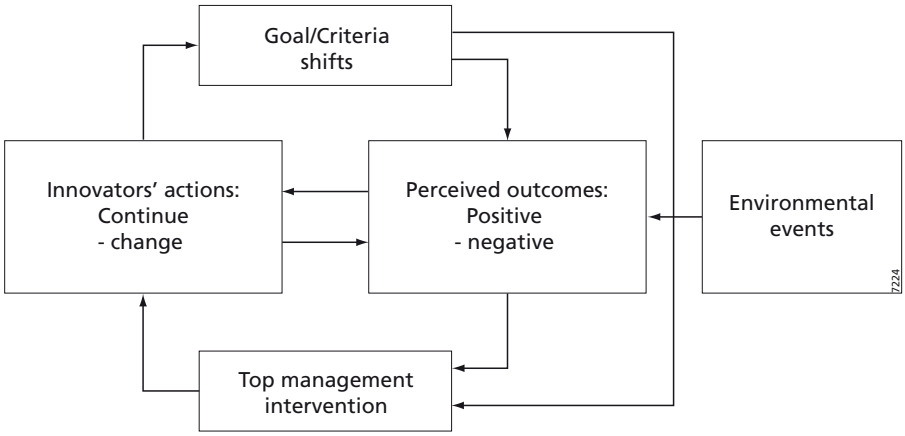

Figure 10 - learning model to guide the innovation journey (taken from: Van de Ven et al, 1999).

alter its goals and performance (outcome) criteria. Other influences on the trial-and-error learning process are external events and top management interventions.

Argyris and Schön (1978) describe the learning on these two levels as first-order (single loop) versus second-order (double loop) learning. The first-order loop "connects detected outcomes of action to organisational strategies and assumptions which are modified so as to keep organisational performance within the range set by organisational norms. The norms themselves [...] remain unchanged". Second-order learning concerns "those sorts of inquiry which resolve incompatible organisational norms by setting new priorities and weightings of norms, or by restructuring the norms themselves together with associated strategies and assumptions" or as Leeuwis et al. (2005) put it: "we speak of double loop learning when actors change their goals and/or the norms and values on the basis of which they evaluate problems and situations." In technology and innovation studies these first-order and second-order learning concepts are also frequently applied (Hoogma, 2000; Kerkhof and Wieczorek, 2005).

Following the work of Argyris and Schön, Grin et al. (1996a; 1997; 1999), refer to these as frames of meaning or action theories. An action theory is a set of beliefs of an actor that attempts to explain its actions. Frames of meaning or action theories consist of four elements that can be found at two different levels. These are summarised in Table 1. These two levels of learning have not been restricted to so-called professionals, but are also applicable to policy-makers (Fischer and Sabatier, cited in Grin and Van de Graaf, 1996a), managers and technology developers (Grin and Van de Graaf, 1996a; Grin and Van de Graaf, 1996b).

As is shown in Table 1, first-order beliefs concern the assessment of solutions and the definition of problems, while second-order beliefs include (normative) background theories and ultimate preferences. In the context of shaping future technologies it is assumed to be important to match short-term flexibility and incremental steps with long-term considerations. This is called 'directed incrementalism' (Grin et al., 1999). In this thesis we perceive changes in demands, as defined above, as *first-order learning* (see 2.4.2). *Second-order learning* occurs when organisations reflect on their and other organisation's strategies,

Table 1 - elements of frames of meanings; based on Grin and Van de Graaf, 1996a; Grin and Van de Graaf, 1996b.

Levels	Elements of frames of meaning	Definition	Related concepts and synonyms
First-order beliefs	Evaluate solutions	Evaluation based on efficiency criteria and causal relations between means and ends	Technical verification
	Problem definitions	Meanings are attributed to objectives, aims, solutions related to problems	Situational verification
Second-order beliefs	Appreciative (value) systems and overarching theories	The former is the normative framework in which an actor appraises the problem; the latter concerns the language and repertoire that helps to look at the problem	System vindication: systems of values and perceptions, world views and background theories
	Ultimate preferences	Amongst others preferences about the social order	Rational social choice

objectives and norms (see 2.4.3). Moreover, it is hypothesised that first-order and second-order learning influence each other (see 2.4.2). Figure 11 illustrates this, forming a second step towards the central conceptual model.

2.4.2 First-order learning loop

In the context of demand articulation we regard the acquisition and development of demands as part of the first-order learning loop. Building upon the Van de Ven model (Figure 10), in which a constant confrontation between actions and outcomes leads to learning, a similar model is used to conceptualise the first-order learning loop inside intermediaries (Figure 12).

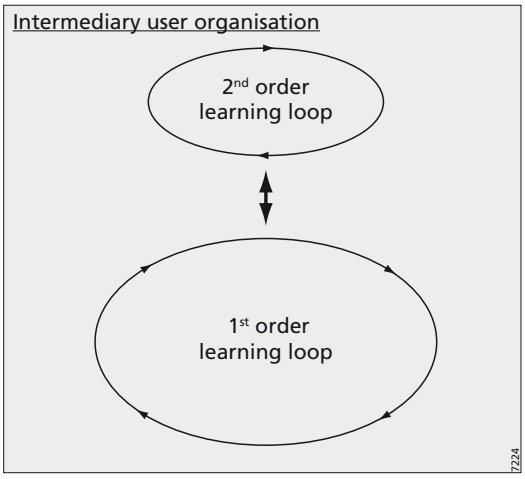

Figure 11 - step 2 in building a central conceptual model.

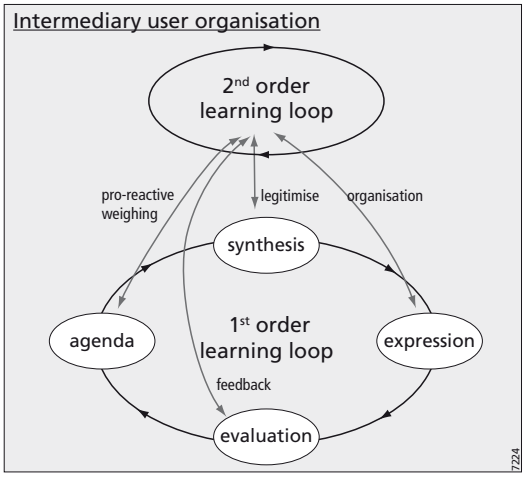

Figure 12 - step 3 in building a central conceptual model.

The first step of this loop consists of the *agenda*[18], which indicates priorities and directions. It can have a 'shared' (external) character, which means that actors within a certain field have the same ideas about priorities and directions. But it can also take the form of a 'local' (internal) agenda (Van Lente, 1993), as it does in this thesis. Issues enter the agenda because interacting partners introduce them to the organisation or because people internal to the organisation react to signals, such as media coverage of a topic. Decisions on agenda entrance can be made proactively and reactively. These decisions and the subsequent weighing of the issues once they are part of the agenda, are heavily influenced by the organisation's underlying assumptions.

Once a topic is viewed as being important to follow up, the second step in the loop concerns the *synthesis* of demand by the organisation. Again, internal and external pressures influence this. They can even be provoked by, for example, consulting actors. Underlying assumptions also influence this synthesis while during the formation of demands constant legitimisation is sought.

The issuing or *expression* of the demand to interacting partners forms a third step. Underlying assumptions partially determine the way in which the expression of the demands is organised and set-up.

The *evaluation* of the demand articulation forms the last step of the loop, in which the organisation reflects on the expressed demand, the way it corresponds to its own underlying assumptions, and how other actors react on it. This reinforces or tones down demand articulation efforts on this issue, and largely influences whether these activities are continued and put on the organisation's agenda once again.

This section concerns the first-order learning loop inside an intermediary, and also shows how the different steps in this loop are influenced by its second-order underlying assumptions (Figure 12).

18 The agenda-building process also features considerably within policy sciences. It is defined as the "process by which demands of various groups in the population are translated into items vying for the serious attention of public officials" (Cobb et al, 1976) or the public.

Different intermediary user organisations run through these loops in a different way, also depending on the characteristics of the issues that are at stake. These differently-characterised, situation-dependent and issue-dependent learning loops are called *demand articulation mechanisms*. One objective of this thesis is to determine several of these demand articulation mechanisms.

2.4.3 Second-order learning loop

In terms of the elements of demands cited in section 2.3, we should not only focus on short-term needs and ethical aspects, but also on visions and expectations of actors in the long run. Visions of actors, especially shared visions of relevant stakeholders, can contribute to the (long-term) shaping of future technologies. Actors can learn from each other's visions, but in order to create shared visions it is necessary to learn about the underlying assumptions of the actors as well (Grin et al., 1999). Grin and colleagues (2000) proposed the so-called 'vision assessment' in which visions can be analysed, evaluated and managed. Four important steps in this assessment are (Grunwald, 2004):

- assessing the future visions of different stakeholders
- assessing underlying assumptions
- constructive dialogue about the visions
- shape visions that guide in desirable directions

The point we want to make here is that besides first-order learning, second-order learning is a crucial addition to the demand articulation process. Second-order learning involves changes in the values that are underlying first-order statements. These underlying assumptions are a complex of organisational norms and values that frame the day-to-day decisions on strategies, operations and demands. As Table 1 introduced, they consist of two aspects (Grin and Van de Graaf, 1996a). Firstly, appreciative systems and overarching theories that form the reasoning behind operations, strategy, demands and problem solving ('how to get from the current to the perfect end situation'). They resemble the paradigms (Kuhn, 1962) or evaluation routines (Garud and Rappa, 1994) that shape scientific or professional practice, but also include objectives and starting points for organisations. Secondly, ultimate preferences, being the desired identity, attitude, social order or position in the field ('perfect end situation').

There are two reasons for studying second-order learning in intermediaries. Firstly, (changes in) underlying assumptions can change the process of demand articulation, as is made clear in the context of the Van de Ven-model: outcomes change not only because of a change in actions, but also due to shifts in goals and criteria (Figure 10). Secondly, as has been stated in section 2.2.4 ('position of intermediaries'), intermediaries have a constant need to position themselves towards others, (maybe) even more than other actors. Therefore, it could be hypothesised that explicating underlying assumptions is (more) crucial for such organisations.

With regard to second-order learning we refer to *positioning theory*. This theory originated from social psychology, in particular role theory, and sheds light on understanding and typifying social roles in relationships. A dynamic shade is added: social actors are constantly changing their relationships with others in the context of a certain development or 'bigger picture'. This theory implies that positioning occurs in a triadic relationship between this 'bigger picture' or *storyline*, *speech-acts* that actors make related to this storyline, and the *positions* they thereby take (Searle, 1969; Howie and Peters, 1996; Harré and Van

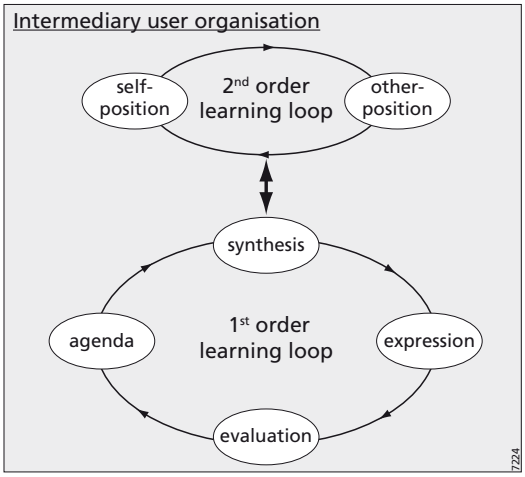

Figure 13 - step 4 in building a central conceptual model.

Langenhove, 1999). Speech-acts are statements made by actors that are at the same time binding: 'when you say something, you do it'[19].

The theory was primarily developed for interactions on the interindividual level. Van Lente (1993) made some suggestions to augment positioning theory to use it in the context of technological dynamics, and more precisely, in the light of emerging technologies. Following these propositions, Boon and Van Merkerk (2008) applied positioning theory while looking at the storyline of theranostics and individualised therapy[20]. They used the distinction that was introduced by Harré and Van Langenhove (1999), namely self-positioning vs. other-positioning. An actor's position is formed and stabilised when his or her own role agrees and is accepted by other actors. "Actors can [...] not position themselves freely, because in gaining a position you need support from others" (Van Merkerk, 2007).

As was stated already in section 2.4.1, organisations learn on a second-order level when they reflect on their strategies, objectives and norms and those of other organisations. In this regard, we envisage constant interaction between changing organisations' self-position (its underlying assumptions) versus changing the positions that other actors attribute to them. Section 2.2.4 illustrated the importance for intermediary organisations to position themselves clearly, as well as the omnipresent ascription of positions by other organisations.

19 For example, when A promises to cook dinner for B (a speech-act), it is assumed that A is in the position to invite B to join him/her. This happens in a storyline or moral universe that can change if B indignantly declines the offer.

20 Theranostics is an emerging technological concept based on genomics knowledge in which therapy and diagnostics are inextricably bounded. Diagnostics companies may want to connect with pharmaceutical companies, and vice versa. Different strategies, related to the different positioning of companies, were investigated in the light of this storyline, using speech-acts extracted from the annual reports of these companies.

Both the first-order loop (agenda – synthesis – expression – evaluation) and second-order loop (self-position – other-position) are now introduced in the model that eventually leads to the central conceptual model (Figure 13).

2.5 Demand articulation processes in interaction with other actors

Figure 4 already illustrated that demand articulation processes inside organisations are complemented and influenced by articulation processes with other organisations. This section deals with demand articulation processes of intermediaries in interaction with others in line with the second research question: *'how to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies?'*

Innovation studies focusing on the democratic quality of innovation processes and constructive intervention of technological development emphasise the importance of including all relevant stakeholders, thereby broadening and enriching their perspectives (Nahuis, 2007; Van Merkerk, 2007). However, a converging 'force' is needed to counterbalance the diversity of actors involved and the diverging of heterogeneous demand statements. Involving more actors is not always better because it can even have a counterproductive impact on the innovation process: resistance might arise and complexity might increase.

Converging is an important feature of the demand articulation process as part of interactions between different actors: the variety of demand statements becomes increasingly focused and concrete through time. This means that an important role of intermediaries is to use the available information to effectively narrow-down demand options. The harmonisation or orchestration of demands by the intermediary and its interacting partners is subject of the second part of the research questions of this thesis. Connecting with the interactive technology assessment, Grin et al. (1997) call these processes a "joint construction: a synthesis between the participants' different beliefs".

Nevertheless, the joint construction of demands is not restricted to convergence. It applies to a lesser extent to the early phases, which are often more divergent so as to not risk the exclusion or absence of options. At the same time, the increase in information and number of actors involved may result in more uncertainty and in different coalitions of ideas. Ultimately, these coalitions might also show convergence and closure in the form of a dominant design or, in contrast, result in stalemate, i.e. a situation in which demand articulation leads to the intensification of contrasts.

While this thesis is taking a more descriptive and evaluative stance on studying demand articulation processes, instead of interventionist or constructive, and is studying these processes retrospectively, we do not aim at broadening, enriching or building consensus in the debate. Consensus, i.e. general agreement on an issue, is not the predestined end goal of demand articulation processes involving several actors. Here we describe and explore the divergent and convergent development of demands of different (groups of) actors as part of studying demand articulation in interaction in innovation arenas.

This section deals with demand articulation processes of intermediary user organisations as they interact with other relevant actors in the innovation arena. A distinction should be made with regard to the demand articulation processes inside intermediaries as dealt with in the previous section. There, the focus is not so much on convergence but on the

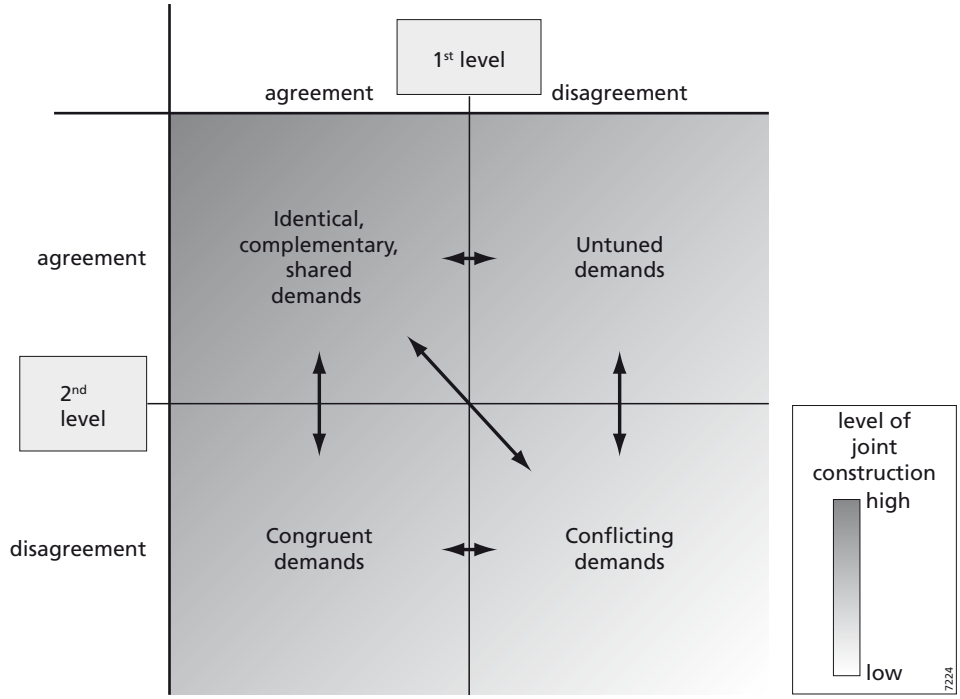

Figure 14 - four states of demand and the related level of joint construction.

sharpening and concretisation of demands. Demand articulation in interaction with other actors is occurring through first-order and second-order learning processes, which occur in interaction with other actors. In this way, learning takes into account the reactions of other actors, which can take the form of statements on demands for a technology. Demand articulation in interaction is influenced by agreement or disagreement between intermediaries and their 'interacting partners' regarding demands, or related to underlying assumptions.

This results in four different combinations of agreement and disagreement, which relate to four different situations of joint construction of demand, so-called '*construction states*' (Figure 14). If actors agree on both first-order and second-order elements they agree on the contents of the demand statements as well as on the values underlying them. The demand is 'complementary, shared or even identical'. At the other end of the scale, if actors do not agree on both levels, they have clearly 'conflicting' demands. The two states in between encompass one in which actors agree on their underlying assumptions but nevertheless disagree on the first-order demands: the 'untuned' demands. And a state in which actors have different values, but can still work together on the first-order level ('congruent' demands).

During the demand articulation or learning processes, actors can change their first-order or second-order levels, i.e. their problem definitions, solutions, and their underlying assumptions. If they do this, they will shift from one state to another.

As was explained in section 2.2.4, the intermediary is engaged with two types of interacting partners: the 'represented actors' (actors A) and the 'other relevant actors'

(B). This asks a great deal with regard to the information collection and dissemination capabilities of an organisation. Intermediary organisations collect and disseminate information through so-called *interfaces*. These are defined in this thesis as media of interaction or foci of communication between an intermediary user organisation and its interacting partners. These interfaces are studied focusing on the strategies and organisation involved.

The intermediaries use their interfaces in a strategic way in order to reach optimal demand articulation processes. In order to obtain effective demand articulation three major *interface strategies* can be put to the fore (based on Nahuis, 2007):

- Access strategies to involve all relevant actors.
- Empowerment strategies to supply them with sufficient (knowledge) resources to make contributions to the debate.
- Impact strategies to make sure that statements are taken seriously and are even appropriated.

We presuppose that the employment of these strategies differs with regard to the type of interacting partner, i.e. different strategies are necessary while interacting with represented actors as compared to interacting with other relevant actors. For example, members need to be well-informed by their representative organisation in order to be able to put their demands on the intermediary's agenda. On the other hand, the intermediary organisation itself probably needs to fight for access to debates in which they interact with other relevant actors.

Besides the strategic directions that are taken through these interfaces it is also important to note that the *organisation* of communication within these interfaces differs. The characteristics and dynamics of these interfaces will be analysed by using the following typology based on Mayer (1997):

- Consultation: relevant information is generated and clarified;
- Education: understanding is raised and knowledge is shared;
- Presenting, advocating: points of view are brought forward;
- Mediation: conflicting ideas are aligned (also: negotiating);
- Coordination: different interests and opinions are tuned;
- Deliberation: same as coordination but without having a predefined topic or agenda from the start;
- Anticipation: different future options are explored and assessed (if it is about current options, it can be called prioritisation);
- Co-production: activities or projects are taken up together with other actors.

Thus, interfaces are loci of communication between intermediaries and the actors with which they interact. In this thesis we focus on both the practical organisation of these interfaces and the strategies deployed while making use of them. These interface strategies might take different forms in distinct situations, issues and organisations. An objective of this thesis is to characterise several of these interface strategies.

2.6 Central conceptual model

Taking into account the concepts that were introduced in the last section and building on the previous step in the construction of the central conceptual model (Figure 13), Figure 15 illustrates the final version of the central conceptual model.

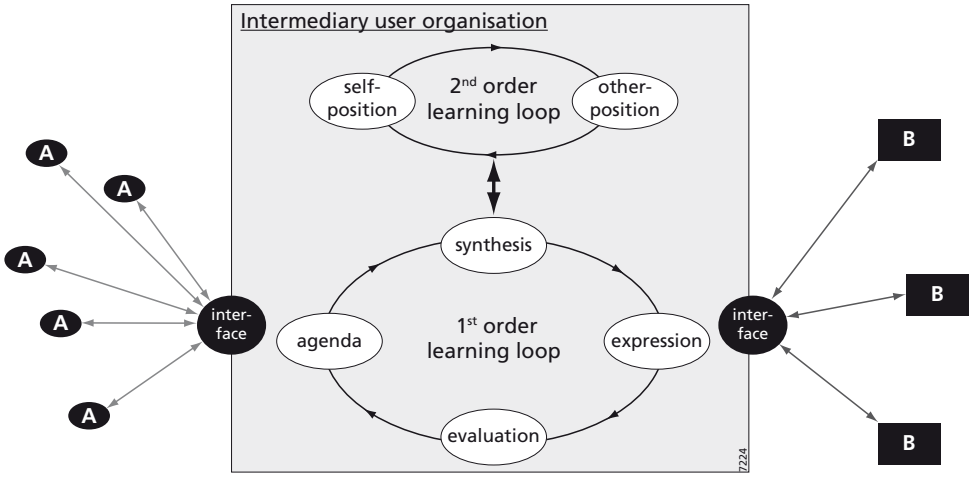

Figure 15 - the central conceptual model (last step or step 5 in building this model).

This central conceptual model clearly explicates the two parts of this thesis, i.e. concerning demand articulation processes ***inside*** intermediary user organisations (inside the grey box), and concerning demand articulation processes of these organisations in ***interaction with other actors*** in an innovation arena. The model reflects the perspective of this thesis on demand articulation processes in intermediary user organisations. Two major outcomes of this research would be in exploring whether the central conceptual model holds for the processes we discern in intermediary user organisations; and on a more abstract level, in discerning demand articulation mechanisms and interface strategies.

The model is used when studying demand articulation processes in three intermediary user organisations. Before turning to these cases, we delve deeper into an emerging technology (pharmacogenomics), and try to lay the groundwork for the case selection by providing clues on how to decide whether and which intermediaries are working on this emerging technology.

Chapter 3

Emerging pharmaceutical innovations: pharmacogenomics

Emerging technologies are technologies that gradually come into existence and through their systemic character can become disruptive to many aspects of society. At the moment several technologies are prominently emerging in the health care sector. Examples include stem cell therapy, gene therapy, xenotransplantation, cloning, telemedicine, biobanks, nanomedicine, anti-sense technologies, RNA interference technologies, and genomics. As was stated in the introductory chapter, this thesis focuses primarily on genomics.

Two general points can be made about these emerging health technologies. Firstly, some of them are interlinked, such as stem cell therapy and cloning, or biobanks and genomics. Secondly, the emerging or novel character of technologies can be contested. The degree of novelty of a technology can be an intrinsic part of the technology itself or a result of rhetorics, taking the form of promises, expectations, or debates about definitions (Brown and Webster, 2004). Discussions about the definitions of medical biotechnology and genomics are part of this contestation.

After the period in which plant extracts, physiological and organic chemistry had led to the Golden Age of drug discovery in the 1950s, the age of modern medical biotechnology started with the discovery of the DNA structure by Watson and Crick in 1953. Brink and colleagues (2004) discerned three generations in the evolution of biotechnology. The first generation or traditional biotechnology concerns non-industrial techniques that use living things (cells) for making products beneficial to man. These techniques have been around for centuries and were more the result of empirical observation rather than of scientific research. Examples include using yeast and bacteria for food production (fermentation), or improving animal or plant qualities by cross-fertilisation. The second generation refers to the application of these techniques in more industrialised ways, also making use of scientific knowledge spurred by chemistry, and biology.

The third generation or modern biotechnology started with the discovery by Watson and Crick and two other important discoveries in the 1970s. These were the recombinant DNA technique by Boyer and Cohen in 1973 and the monoclonal antibody technique by Milstein and Kohler in 1975. Genetic engineering forms recombinant DNA by combining or inserting DNA strands. The goal is to make numerous copies of a gene for analytical purposes or to gain a large amount of protein product. The first of these products appeared in the early 1980s, such as insulin, erythropoietin (EPO), and interferon. Monoclonal antibodies, which could also be produced by using recombinant DNA technology, are antibodies that are made in large quantities, and are aimed at triggering the immune system by attacking tumour cells or blocking cell receptors.

Genetic engineering techniques such as DNA sequencing made it possible to start the Human Genome Project, formally initiated in 1990 by the US National Institutes of Health, the Department of Energy and scientists from other countries. The project aimed to unravel the human genome by identifying its base pairs. This publicly-funded project later faced a private competitor, Celera Genomics, founded by researcher Craig Venter in

1998. Despite this rivalry, the two efforts jointly announced the completion of the human genome during a press conference featuring Bill Clinton and Tony Blair in 2000. Nature and Science published this 'rough draft' in 2001 (The Celera Genomics Sequencing Team, 2001; The International Human Genome Mapping Consortium, 2001), whereas the final chromosome was finished only in 2006 (Gregory, 2006).

The sequencing of the human genome was the start of the genomics era that features the study of the genomes of organisms, such as humans. Subsequently, scientists proposed to use this structural knowledge to uncover the functions of genes (which genes do what, when and why) and the interactions between these genes. This is called functional genomics. The field of functional genomics related to pharmacology is called pharmacogenomics. This chapter focuses on this emerging technology, discussing its definition problems, trends, characteristics and finally how we use an analogy between another class of drugs (orphan drugs) and pharmacogenomics to learn more about the future of this emerging technology.

3.1 Definition of pharmacogenomics

The application of functional genomics in the field of health and medicine is usually referred to as pharmacogenomics. This term is at the moment under debate because of an eventual distinction with pharmacogenetics. Although some authors are convinced that there is a difference, no consensus has been reached and the terms are often used interchangeably (Van Delden et al., 2004; Webster et al., 2004). On an official level the European Agency for the Evaluation of Medicinal Products (EMEA, 2003) tried to define the two terms as follows: "pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response", while "pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level".

Hedgecoe (2003) performed a scientometric analysis with these two terms and found that pharmacogenomics was used for the first time in 1997, while pharmacogenetics has been around for more than 40 years. His data show that commercial authors introduced the term pharmacogenomics, i.e. writers linked to firms, and can thereby be seen as having a rhetorical role. Nevertheless, he discerns two schools of thought: one in which pharmacogenomics is the successor of pharmacogenetics, and another that presumes pharmacogenomics as the new pharmacogenetics. The former regards the pharmacogenomic developments as totally novel and thereby discernable from the 'old' pharmacogenetics. In other words, pharmacogenetics is outdated and replaced by a new technology group. The latter views the new developments not as basically different. Here, pharmacogenomics is just another term for the old pharmacogenetics.

In a large-scale EU/IPTS study on pharmacogenomics the following definition was used: "the science and technologies associated with dividing patients or populations into groups on the basis of their biological response to drug treatment using a genetic test" (Hopkins et al., 2006). They explicitly took a broader definition while they included tests that not only relied on DNA analysis but also on phenotypic and proteomic characteristics.

All in all, emerging technologies – like pharmacogenomics – are often described using 'umbrella terms' in order to include a large range of technologies. This can be the subject of contestation, just as the discussions prove about the extent to which genomics is fundamentally new compared to biotechnology, because some fear the detrimental

effects of hyping a technology (Brown and Webster, 2004). But it can also stimulate technological and scientific developments. Here, we adhere to a rather broad definition of pharmacogenomics.

3.2 Trends of pharmacogenomics[21]

To provide an idea of the importance of the pharmacogenomics developments in science and technology we used scientometric methods to reveal trends. When mapping an emerging technology field, some authors proposed a *hot spot analysis* (Rothman, 1997). To measure these hot spots, indicators based on patents and publications serve as proxies. Patents shed light on business activities concerning a topic, while publications do the same for science.

The advantages and disadvantages of using patent and publication data as indicators of innovation are well-known and thoroughly discussed by several authors (Kleinknecht et al., 2002). The advantages include the availability of historical time-series, the detailed classification by technological subfield, and easy access. Disadvantages feature differences in propensity to patent across countries, sectors and even over time, a disregard for other types of knowledge that cannot be patented or are not patented because of strategic reasons, differences in patent procedures across countries, and the inability to diversify between patents that are economically valuable and those that are not. For example, for the pharmaceutical industry the propensity to patent is notably high because this is one of the major ways to protect innovation (Jungmittag et al., 2000). But even here the relationship between patenting and product introduction and approval has become subject of debate: this relationship decreased in strength (Graham and Higgins, 2007).

Therefore, publications and patents are merely used as indicators. Nevertheless, the next three sections show the trends in pharmacogenomics patents (3.2.1) and publications (3.2.2), and draws conclusions on hot spots in this emerging technology field (3.2.3).

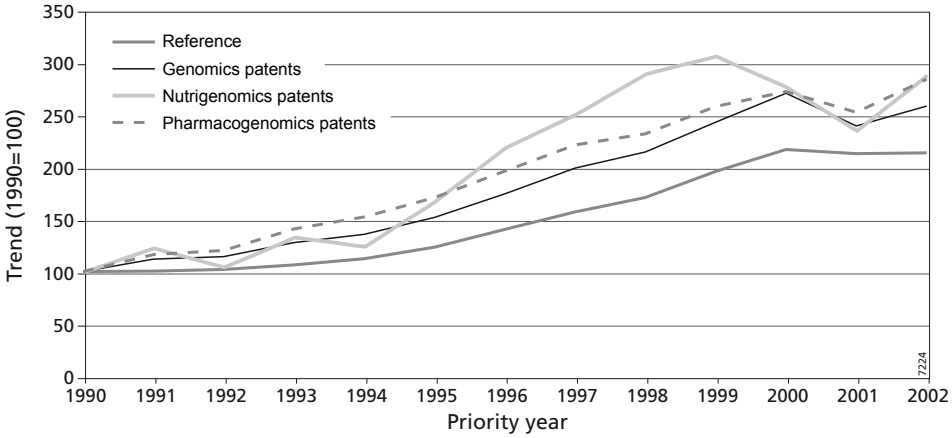

Figure 16 - trend of EP and WO patent applications in genomics, nutrigenomics and pharmacogenomics between 1990 and 2002.

21 This section is based on Boon and Vandeberg (forthcoming).

3.2.1 Trends in pharmacogenomics patents: methodology and results

The major challenge regarding statistical analysis of patent data lies in the proper definition of technology fields in order to retrieve statistically representative samples. The international patent classification (IPC) was used when defining these fields, despite the disadvantage of its inertia. Emerging technologies, e.g. gene therapy, are difficult to file under a class, because the class structure is only revised every seven years. One often-applied search strategy is to define fields by the cross-section of two different pools of IPC classes (Hinze and Schmoch, 2004): pharmacogenomics can then be seen as a crossing of pharmacology and genomics[22].

The patent search was conducted in the Questel database that incorporates patents from both the European Patent Office (EPAT; so-called EP applications) and the World Patents Index (WPI/L; so-called WO applications). The process from patent application to granted patent could take years. Using patent applications has the advantage that the newest entries are taken into account, which is of special interest when studying emerging technologies. The search is limited to European countries, the United States, and Japan, and to the time span of 1990 to 2002. Since the patent analyses were performed as part of a research in spring 2005, the database is only up-to-date until 2002[23]. Relevant patent documents were collected based on primary and secondary IPC classification. For this hot spot analysis we also looked at nutrigenomics[24].

To obtain an overview of the developments in genomics, the numbers of all patents, genomics patents, and pharmacogenomics and nutrigenomics patents per year were plotted as index figures in Figure 16 above.

Figure 16 shows an upward trend, which signifies pharmacogenomics and nutrigenomics innovations as fields that are steadily gaining momentum. Based on the pharmacogenomics and nutrigenomics patents, and the total number of genomics patents for each individual country, the revealed technology advantage index (RTA) was calculated, which represents the relative importance of nutrigenomics and pharmacogenomics patents compared to all genomics patents for each country. It is an index that shows the extent to which a

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22 For the selection of IPC classes an iterative process was used: i) drawing upon experience of previous patent research in the field of biotechnology (OECD, 2004; Reiss et al., 2004; Schmoch, 2007); ii) scanning the International Patent Classifications books; and iii) interviewing experts to discuss keywords that are used in the genomics context and subsequently checking in the Espacenet database whether all relevant IPC classes were included and whether those included were relevant. Two pools of IPC classes were intersected: Pharmacology (A61K038, A61K039, A61K048, A61K049, A61K051, A61P001, A61P003, A61P005, A61P007, A61P009, A61P011, A61P013, A61P015, A61P017, A61P019, A61P021, A61P023, A61P025, A61P027, A61P029, A61P031, A61P033, A61P035, A61P037, A61P039, A61P041, A61P043, C12Q001-68) and Genomics (A61K-031, A61K-033, A61K-035, A61K-038, A61K-039, A61K-041, A61K-047, A61K049-00, A61K-048, C12N-015, C07H-021/02, C07H-021/04, C07G, C07K-004, C07K-014, C07K-016, C07K-017, C07K-019, C12F-003/04, C12F-003/08, C12F-003/10, C12F-005, C12N-001, C12N-003, C12N-007, C12N-009, C12N-011, C12N-013, C12P NOT C12P-033, C12S, C13K).

23 It takes some time before all new patents are included in the databases.

24 Nutrigenomics concerns the application of functional genomics knowledge to the field of nutrition. More information on this is found in the PhD project of Rens Vandeberg MSc, which is part of the same programme as this project.

country I is specialised in a technology or sector J. This index is calculated by the national share of patenting in that particular sector divided by the national share of patenting in all sectors. Logically, a value above unity (1) means a relative specialisation of a country in that technological area, while a value below 1 reflects a relative under-specialisation.

$$RTA_{IJ} = \left(\frac{P_{IJ}}{\sum_{J} P_{IJ}} \right) \Bigg/ \left(\frac{\sum_{I} P_{IJ}}{\sum_{IJ} P_{IJ}} \right)$$

A standardised or normalised version of this formula is the NRTA = (RTA – 1)/(RTA + 1), which keeps the values between -1 and 1. Figure 17 illustrates this.

Comparison of genomics patents using the NRTA indicator shows that pharmacogenomics is mainly dominant in Italy and France. It seems that smaller countries with generally lower GDPs have higher RTAs than larger countries with generally larger GDPs. This might be due to the rather limited number of resources available for smaller countries, which force them to make more specialised decisions, i.e. focusing on one subfield, because they cannot afford to invest in a broad spectrum of technologies.

In order to scan for hotspots within pharmacogenomics, this technology was divided into subfields based on disease areas. These are present in IPC classes A61K ("medicinal preparations") and A61P ("therapeutic activity of chemical compounds or medicinal preparations"), such as drugs for disorders of the digestive system, the metabolism, and the endocrine system. In the pharmaceutical industry such a subdivision following disease areas is common. Moreover, the C12Q001-68 class about testing, which plays an important role in the context of pharmacogenomics (Hedgecoe and Martin, 2003; Boon

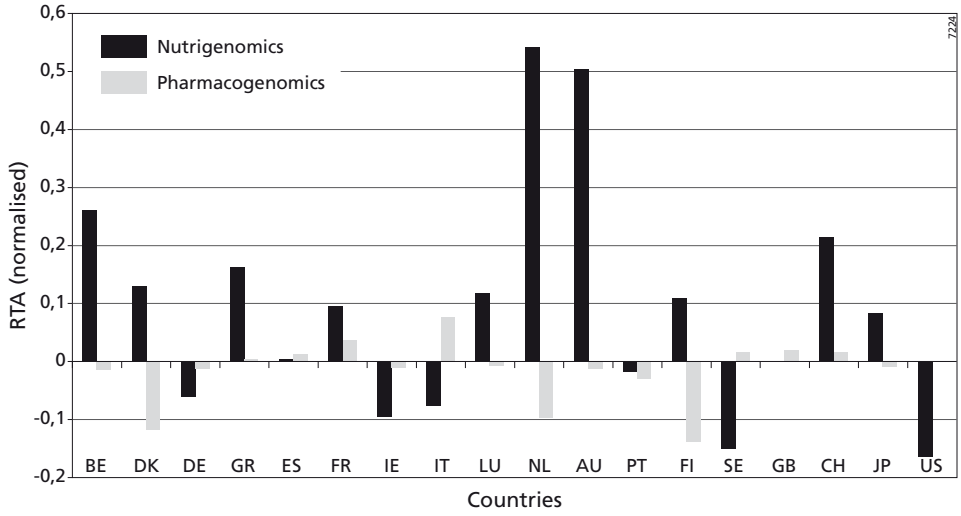

Figure 17 - the NRTA of nutrigenomics and pharmacogenomics EP and WO patents compared to genomics EP and WO patents (period 1990-2002).

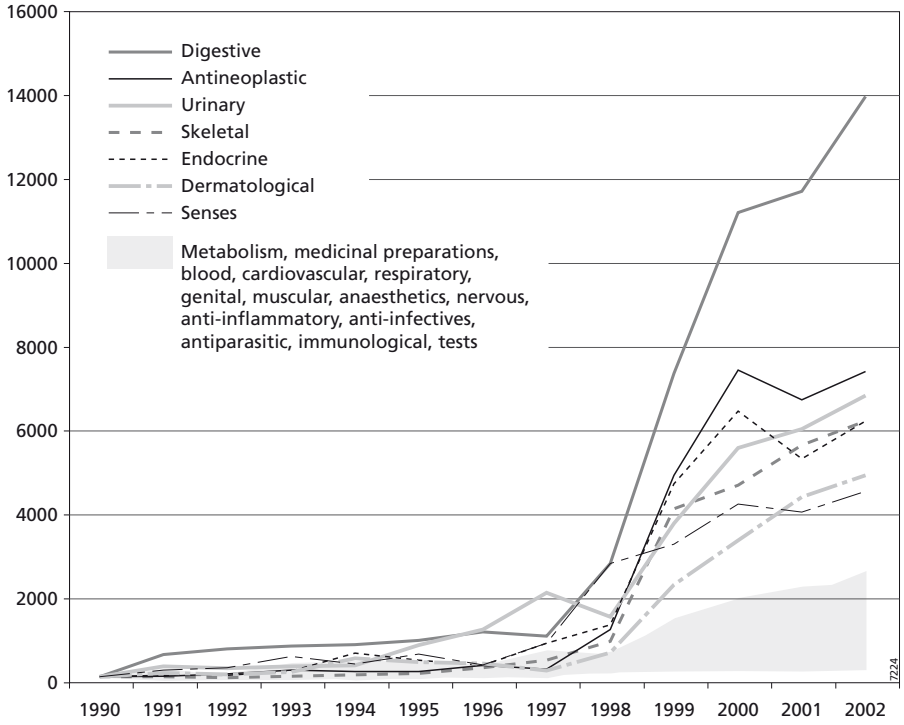

Figure 18 - interesting subfields in pharmacogenomics EP & WO patents based on patent analysis period 1990-2002 (only the fastest growing subfields are demarcated in lines).

and Merkerk, 2008), was also included. Figure 18 shows the results for the subfields within pharmacogenomics: especially patents intended for the digestive system and anti-cancer treatments predominate.

3.2.2 Trends in pharmacogenomics publications: methodology and results

Two publication and conference paper abstract databases were consulted: the Science Citation Index (via ISI Web of Science) and PubMed[25]. Generally, both databases were suitable for the analysis of medical-related topics as the SCI covers a large number of journals from the field of medical research, and PubMed focuses mainly on medical publications.

The search strategy focused mainly on using keywords, because an analogy of IPC classes did not exist in the two databases. The importance of the pharmacogenomics field was investigated by determining the relative growth of publications in these areas. The first strategy to construct this pool of publications was to use the term 'pharmacogenomics' literally as search words. The advantage was that the included data had a high probability of really belonging to that field. The second strategy was to use a group of keywords that together described or 'constructed' the pharmacogenomics field. These keywords were collected by scanning relevant literature and subsequently reviewed by interviewing experts in the field. The strategies are summarised in Boon and Vandeberg (forthcoming), which

25 All publications are abstracted from these databases in October 2005.

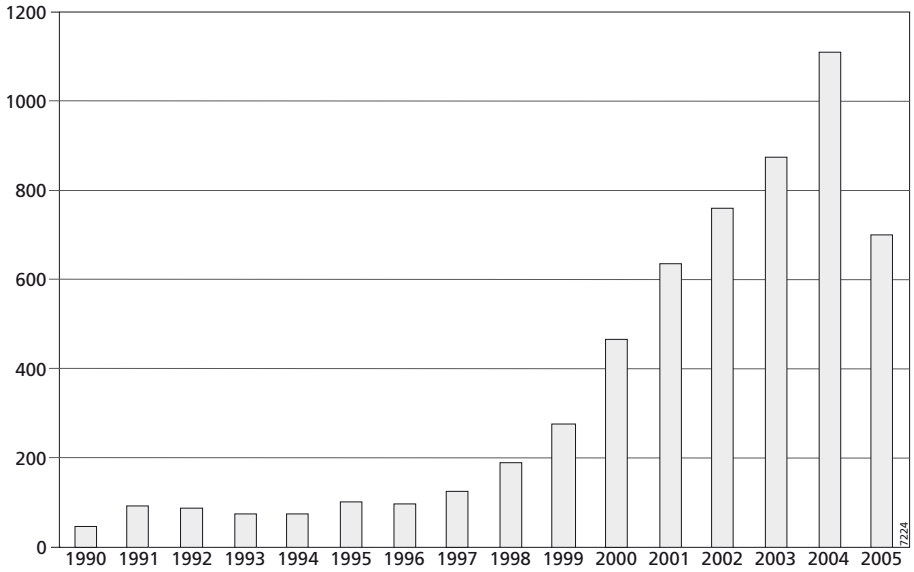

Figure 19 - number of pharmacogenomics articles over the period 1990-2005.

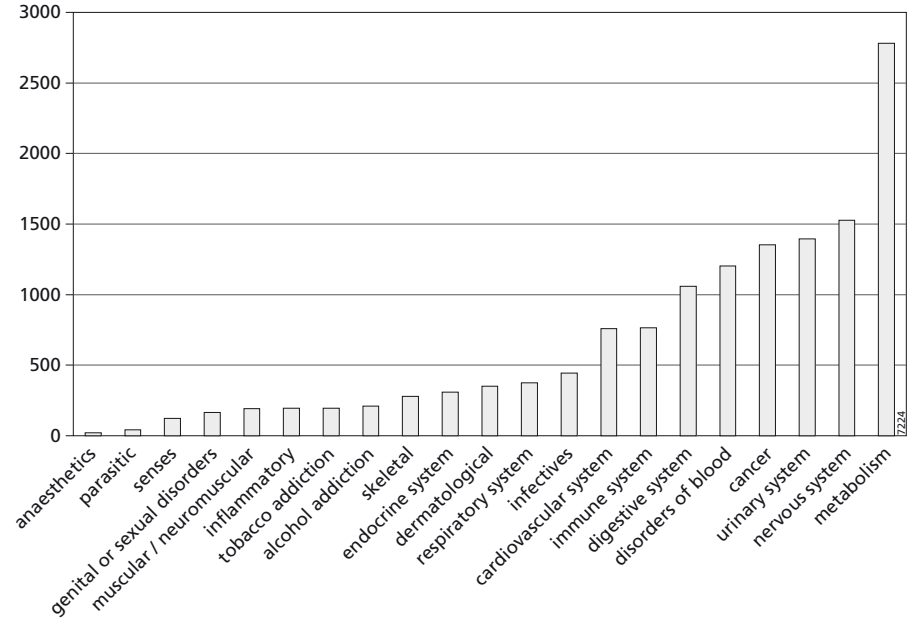

Figure 20 - pharmacogenomics articles on disease areas.

also explains in detail why the first strategy was ultimately chosen. Figure 19 shows a clear growth up to 2004 in publication numbers[26].

We also crossed the set of resulting publications with keywords based on expert interviews in order to obtain disease-specific subfields. This gave us insights into hot spots within the pharmacogenomics field (Figure 20). Here, publications about pharmacogenomics for the disease areas of metabolism and the nervous system prevail.

3.2.3 Conclusions

We observed a general upward trend in scientific articles and patent applications in pharmacogenomics, which indicates a growing interest in this field. There is a good start for patent applications in absolute numbers and we see a significant positive growth when compared to all patents. Pharmacogenomics and nutrigenomics are lighting up as hot spots, which are even brighter than the total field of genomics as can be concluded from Figure 16.

The most important subfields within pharmacogenomics are summarised in Table 2 for both publication and patent searches.

When the results of the patent and publication searches are compared it appears that some subfields are hot spots both in the patent and in the publication ranking. This is, for example, the case for anticancer drugs and medicines for disorders of the urinary system.

The hot spot analysis conducted in functional genomics fields needs some critical reflection as well. Firstly, there are some theoretical issues. The use of patent and publication data has some pros and cons, which were mentioned above. More fundamentally, one could ask whether it is possible to scan current technology fields for future promises, using these types of data. Identifying hot spots would inherently require some critical mass, while some promising developments may be 'hiding' behind just a single patent or publication or in unexpected fields of application. Starting from the thought that an emerging technology is something new, it might not yet be visible in publications and patents. Scientists working within an emerging field have not yet published on the topic because there are no findings as yet and they only engage in agenda-setting. Either that or they are still trying to define what it is they are studying. This might also be the case with regard to company R&D efforts that have not yet led to patent applications.

Secondly, when choosing for patent and publication searches two methodological questions arise: what is the quality of the data? And what is the search demarcation? To answer the first question, the data used came from high quality and widely used databases, e.g. Questel. Only for the most recent years might problems arise due to the update frequency of the patent databases and the latency time between patent application and publication. The search demarcation is rather more difficult. The best way to test this is to take a sample from the resultant search and study its contents for relevance. This was done for the publication searches on pharmacogenomics and it showed some problems using keywords that define the field.

26 The start date of 1990 is based on Hedgecoe (2003). The 'drop' after 2004 is due to the fact that the publication analyses were performed as part of a research carried out in Spring 2005 and therefore only publications in the first quarter of 2005 were taken into account.

Table 2 - most important pharmacogenomics subfields based on (relative growth of) patents and (absolute number of) publications.

	Pharmacogenomics patents	Pharmacogenomics publications
1	Drugs for disorders of the digestive system	Drugs for metabolism disorders
2	Antineoplastics (drugs for cancer)	Drugs for nervous system disorders
3	Drugs for disorders of the urinary system	Drugs for disorders of the urinary system
4	Drugs for disorders in the endocrine system	Antineoplastics (drugs for cancer)

Another route could be to compare the results with findings and expectations coming from other sources that aimed to search hot spots. For example, many review articles and reports on pharmacogenomics expect a golden future for cancer genomics (PriceWaterhouseCoopers, 2005; Royal Society, 2005). This triangulation of sources supports the arguments and results presented in this section. In this light, it might be worthwhile to fine-tune the resulting searches by scrutinising their contents and iteratively adjust the keywords used.

Notwithstanding these trends, some authors tone down these songs of praise for pharmacogenomics. They are highly critical of the "myth of the biotech revolution" (Nightingale and Martin, 2004), they are not convinced that pharmaceutical companies want to give up on 'blockbuster' medicines in favour of small-market ones, and they claim that there are significant ethical, legal and social impacts to take into account (Technologiefolgen-Abschätzung, 2004; Van Delden et al., 2004). These arguments come to the fore when discussing the characteristics of pharmacogenomics in the next section.

3.3 Characteristics of pharmacogenomics

The EMEA definition of pharmacogenomics focuses on the variability of gene expression relevant to disease susceptibility and drug response. Several factors influence the latter, namely drug dose, compliance to medicines use, drug-drug interactions, ailments of kidneys and liver, environmental factors (smoking, diet, alcohol use), and genetic polymorphisms. Besides mutations to chromosomes (translocations, insertions, deletions), mutations to single nucleotide bases of DNA occur, which are called single nucleotide polymorphisms (SNPs). These mutations can have an impact on drug response and disease susceptibility when they are expressed, i.e. when they are responsible for conversion to proteins. Drug response is influenced through three routes (Sitsen et al., 1996; Maitland-van der Zee et al., 2000; Van Delden et al., 2004).

Firstly, pharmacokinetics concerns the process of drug absorption, distribution and elimination, including excretion, and determines the development of drug concentration in a patient's body. Individuals differ in terms of pharmacokinetic properties, which are partially influenced by genetic differences. Genetic polymorphisms that code for metabolising enzymes, such as CYP2D6 genes for cytochrome P450 enzymes in the liver, result in differences in drug metabolism and consequently in groups of patients classified as poor, intermediate, extensive and rapid metabolisers. Therefore, it is directly related to the safety of a drug, e.g. poor metabolising might result in a drug overdose. Roche

Box 3.1 TPMT

Thiopurine drugs, such as mercaptopurine en azathioprine, have been used for immunosuppressant conditions and leukaemia since the 1950s. Thiopurine S-methyltransferase is an enzyme that is associated with thiopurine metabolism. In 3% of all individuals mutations in the TPMT-coding gene cause low enzyme production and very poor metabolising of the drug: these patients show efficacy at 5-10% of a normal dose. National cancer centres in a large range of countries made sure that TPMT testing is available for patients with acute lymphoblastic leukaemia (ALL) (Woelderink et al., 2006). This is currently one of the only tests that has properly been integrated into clinical practice (Shastry, 2005), although the adaptation is slow because of a lack in commercial interest (Marshall, 2003).

Molecular Diagnostics developed a CYP2D6 test, the Amplichip CYP450, which the FDA approved in 2004. Additionally, Box 3.1 illustrates the prominent example of TPMT.

Secondly, pharmacodynamics deals with the question whether a drug produces the desired pharmacological results and shows efficacy. This is influenced by four different kinds of regulating proteins: receptors, ion channels, enzymes, and transport proteins. Genetic variation can influence the expression of these proteins, i.e. the structure or number of receptors. An example includes variation in the Gly16-genotype that codes for beta1- or beta2-adrenergic receptors, which beta2-agonists and beta1-antagonists target respectively. This category might lead to medicines for asthma, cardiovascular diseases (Evans and Relling, 2004), and breast cancer (see Box 3.2). Chapter 7 returns to the topic of Herceptin because it features in the case of breast cancer advocacy presented there.

Thirdly, genetic polymorphisms influence disease susceptibility. In some cases this influence is straightforward. This applies to monogenetic diseases, such as Huntington's disease and cystic fibrosis, in which a defect in one gene is responsible for a disease. Mostly these diseases have a high 'penetrance', i.e. the proportion of individuals who have a gene variation that also acquire the disease. On the other hand, polygenetic diseases are ailments that are caused by a combination of genetic mutations, also in interaction with environmental factors. Differences in the pathways that lead to a disease, initially expressed in one phenotype, might result in a new classification of disease on a molecular level. In the area of oncology and neurology, such as in schizophrenia, several different disease pathways have already been identified (Poste, 2001). Moreover, it is hypothesised that polymorphisms that relate to disease susceptibility also are a major determinant of drug response (safety and efficacy). A much cited example (Hedgecoe, 2004) concerns a mutation in the APOE gene (apoE4), which codes for apolipoprotein E. This gene correlates with increased risks for Alzheimer's disease, whereas patients with this mutation respond worse to the anti-Alzheimer drug Tacrine (Poirier et al., 1995).

A range of industry watchers, scholars and social scientists have studied how pharmacogenomics might influence society and vice versa (Hedgecoe and Martin, 2003; Hedgecoe, 2004; PriceWaterhouseCoopers, 2005; Royal Society, 2005; Hopkins et al., 2006). Here, we discuss the influence on the pharmaceutical innovation processes, because it serves as a starting point from which all other aspects can be viewed, such as regulation,

Box 3.2 Herceptin[1]

Herceptin® (trastuzumab) is a monoclonal antibody drug that treats metastatic breast cancer.

Biological and/or pharmacological background

HER2 is a gene situated on chromosome 17 that codes for a protein called HER2 cell membrane receptors, also called c-erbB-2/neu. This protein controls the growth, division and reparation of cells. A normal, 'healthy' cell contains two copies of the HER2 gene. But sometimes a cell has more copies, which leads to a 10-fold to 100-fold increase of HER2 receptors on the cell surface. This is called HER2 overexpression. This might result in more aggressive growth characteristics and eventually oncogenesis and metastasis. Although the presence of the genes in breast cells are of a somatic nature, pertaining to the body instead of to germ cells, diagnosing and treating overexpression of HER2 receptors is regarded as pharmacogenomics (Lindpaintner, 2002). How does Herceptin work? It is thought that Herceptin binds to the HER2 receptor sites and in this way blocks them. This disrupts growth signals and consequently prevents further cell division. 20-30% of all women have an overexpression of HER2 receptors. This means that only for these patients treatment with Herceptin is efficacious.

Development history

In 1986 Dennis Slamon, a UCLA oncologist, and Alex Ullrich, a molecular biologist working at the US biopharmaceutical company Genentech, discovered that the over-expression of a gene, HER2/neu, occurred in certain types of tumours related with breast and ovarian cancer. Once this correlation was established, researchers at Genentech looked for ways to treat these cancer types. They focused on monoclonal antibodies and developed a 'humanised' form of the mouse protein 4D5, trastuzumab. The company filed the drug as an Investigational New Drug (IND) in 1991. The compound entered clinical trials in 1992 as a monotreatment as well as in combination with chemotherapy. It was particularly centred on patients with metastatic breast cancer, because for this type of cancer there had not been a good medicine on the market. These trials were largely a success: the spread of the disease was less profound in certain types of patients. The only major side effects were related to cardio-toxicity.

Phase III trials were completed in March 1997 and showed no clear advantages over chemotherapy. These trials were followed by genetically-based post-evaluation studies, which showed that the compound was efficacious in a genetically-defined group of patients. Based on this evidence, the FDA assigned the FDA Fast-Track designation to the drug in March 1998. Genentech contracted Dako Diagnostics in Denmark to develop a diagnostic tool to determine the group of patients for which the drug showed high efficacy. They developed the Dako HerceptTest®, a test based

1 Based on Bazell (1998), Hedgecoe (2004), corporate websites of Roche, and information acquired in the context of the case study on the Dutch Breast Cancer Association (Chapter 7).

on immunohistochemistry that works by counting the number of HER2 proteins expressed on the tumour cell surface.

Only 4.5 months later the combination of drug and diagnostic tool received FDA approval (in September 1998). The EMEA approved the drug in August 2000 and the Swiss pharmaceutical company Roche obtained the marketing rights for Herceptin in Europe. Vysis developed a second type of tests based on fluorescence in situ hybridisation (FISH) technology, PathVysion®, which was approved in January 2002. This test measures gene alternations in a patient's tumour. Herceptin itself is currently approved for metastatic as well as early-onset breast cancer, in various forms of combination therapies (EMEA, 2007)[2].

2 Moreover, other diagnostic tests were developed and marketed as well, e.g. by Ventana Medical Systems and DakoCytomation.

ethical, legal and social impacts, and the impact on the clinical setting. These impacts are discussed in the next section.

The industry watchers and scientists expect that pharmacogenomics will have implications for every stage of the drug research and development process as represented in Figure 6 (Boulnois, 2000; Dean et al., 2001; Ginsburg and McCarthy, 2001; Pirmohamed and Lewis, 2004; Van Delden et al., 2004). Firstly, during the target and lead identification and validation phase genomics has already shown a shift in approaches. Family linkage-based discovery was successful in the context of monogenetic diseases, while the candidate gene-approach is centred on genes that are known or suspected as being related to diseases. These approaches have been supplemented by genome-wide association studies, which concern a comprehensive scan of the genome and offer an unbiased identification of novel susceptibility factors. Scientists do this by using information based on the human genome project, the SNPs databases, and DNA micro array tools. This might lead to lower 'attrition rates', improved quality and quantity of targets, and higher throughput.

Secondly, if hypotheses are available about drug response, then ideally this information can be used during the set-up of clinical trials. Stratification of the patient population is possible and leads to scientific robust results while making use of small test groups. This leads to larger probabilities of success, as well as cost and time reductions associated with clinical trials.

Thirdly, pharmacogenomics will also have an impact on drugs in the commercial phase. It is expected that better insight in drug response leads to the development of drugs for specific patient populations which show a particular genetic make-up. This leads to tailor-made therapy. There will be a shift from blockbusters or 'one size fits all' and the broad application of drugs to individualised medicines. This will not necessarily mean that every individual has his or her own therapy, though. Stratified patient populations could form a middle course, leading to drugs suitable for groups of patients that are identified by biomarker tests (Trusheim et al., 2007). Herceptin is an example of such a drug. In this light it is important that it is technically feasible to discern these patient populations using biomarkers. Along this line, several authors of review articles on pharmacogenomics (Ensom et al., 2001; Ginsburg and McCarthy, 2001; Webster et al., 2004; Weinshilboum

and Wong, 2004; PriceWaterhouseCoopers, 2005) envisage a strong relationship between diagnosis, treatment, and prevention. Fierz talks about a "diagnostic (Dx) – therapeutic (Rx) tandem combination" (Fierz, 2004), recently referred to as theranostics. This strong combination is necessary because when a drug is only applicable to one segment of the population it needs to be identified by means of diagnostics.

This section has given an overview of the main characteristics of pharmacogenomics, especially regarding three aspects of drug response (pharmacokinetics, pharmacodynamics and disease stratification) and in relation to the drug R&D pipeline. The discussion of the definition and characteristics of pharmacogenomics revealed many aspects of this technology. Although it differs in the extent to which pharmacogenomics entered the different stages of the pipeline, expectations are that the bulk of products will enter the market in five to 20 years (Roses, 2000; Technologiefolgen-Abschätzung, 2004, interview results). This has repercussions for studying how intermediary user organisations deal with pharmacogenomics. Besides the questions how they proactively prepare for this emerging technology, it is helpful to study an analogy or predecessor of pharmacogenomics because certain issues might be comparable.

The next section compares orphan drugs, medicines for rare diseases with a low prevalence, and pharmacogenomics on several aspects and analyses the (dis)similarities between these two fields. The objective is to investigate to what extent the field of orphan drugs can be seen as a metaphor for the emerging pharmacogenomics field. This metaphor analysis sheds light on the viability of using case studies centring on orphan drugs as an analogy for the pharmacogenomics future. Additionally, this comparative analysis highlights several characteristics of pharmacogenomics.

3.4 Pharmacogenomics and orphan drugs: an analogy?[27]

Emerging technologies are technologies in their early phase of development. This implies that several aspects, such as the characteristics of the technology and its context of use, the configuration of the actor network and their related roles are still uncertain and less specific. For certain technologies, especially those with a disruptive character and a significant influence on society, it is advisable to be aware in an early phase of development of the quality of potential (negative and positive) impacts. This relates to the control dilemma of Collingridge (1981): in the emergent phase it is difficult for stakeholders to specify what they want from the technology, while owing to the fluidity of the technology, the direction of development can be steered more easily. In contrast, in the later phases demands are clearer but potential options decrease. Learning how to deal with this dilemma can be beneficial in the context of decision-making on emerging technologies.

This section focuses on assessing *metaphors* representing the future of a technology and exploring possibilities to anticipate on future developments. Metaphors describe something in terms of something else. By subsequently bringing these aspects together, the central concept is clarified (Wyatt, 2000; Miller et al., 2006). A future technology, of which only a few characteristics are known today, can be compared with a more established technology. This helps engaged people in creating and discussing a vision about the future technology.

27 This chapter is based on Boon and Moors (2008).

Box 3.3 quotations on the similarities between pharmacogenomics and orphan drugs

From review articles:

"Pharmacogenomics technology might create an avalanche of new orphan drugs" (Loughnot, 2005)

"Testing based on pharmacogenomics could 'segregate the population into smaller and smaller pieces', resulting in an 'orphan drug syndrome'" (Larkin, 1998).

"It is anticipated that pharmacogenomics will result in the identification of more 'orphan diseases'" (Haffner et al., 2002)

From interview statements:

"There is a big chance that indications will be subdivided into smaller ones. The unravelling of the human genome accelerated this division process" (representative of innovative pharmaceutical companies, 2004)

"There are many similarities in research and application" (university researcher on rare diseases, 2005).

"There is a chance that we will go towards a future with more 'orphans'" (representative of biotechnology companies, 2005)

"Tailor-made medicine means that 'common diseases' will turn into 'orphan diseases'" (clinician, 2005)

"Everyone will have a rare disease in the future because of pharmacogenomic developments" (intermediary organisation working on orphan drugs stimulation, 2005)

"Rare diseases can be seen as a model for the future of more personalised medicines" (policy-maker at the Ministry of Health, 2006)

A foremost example of metaphors used in the context of (medical) technology is the gene envisaged as a "book of life" (Keller, 1995; Copland, 2005).

The emerging technology we focus on here is pharmacogenomics. The promise of pharmacogenomics features the use of stratifying the patient population, on the basis of genetic make-up, into smaller groups for which specific treatment can be developed (EMEA, 2003). This could mark the advent of individualised drugs. As was mentioned above, the Royal Society (2005) report stated that pharmacogenomics could be at least fifteen to twenty years away due to gaps in the understanding of how genetics relates to disease-working mechanisms. Currently, only a few pharmacogenomics products are on the market, and although there is a notion of the acceptability, ethical, legal and social expectations regarding the future of pharmacogenomics, their quality and impact remain uncertain.

A large range of technology watchers and peers in health care claim that (the future of) pharmacogenomics might resemble the currently more established orphan drugs. This is not only evident from review articles, but also from explorative interviews[28] conducted among a heterogeneous set of experts, ranging from members of the medical profession to scientists, industry representatives and patient advocates (see Box 3.3). Orphan drugs are defined as medicinal products developed for diagnosis, treatment or prevention of rare diseases. Rare diseases are a heterogeneous group of life-threatening or chronically-debilitating conditions, from which no more than 5 out of 10,000 inhabitants of the

28 See section 2.2.1 for more details on these interviews.

European Union suffer. Examples are Pompe disease, haemophilia, and phenylketonuria. Often, there is no access to effective medicines. Despite the urgent health needs of persons with a rare disease, the drugs are known as 'orphans' because companies are not interested in 'adopting' them.

The small number of patients makes the comparison between orphan drugs and the pharmacogenomics future instructive. It is claimed that orphan drugs can act as an analogous model with comparable characteristics, such as economic impacts on businesses and the health system in general, regulation, and the organisation of basic and clinical R&D. If we assume that this comparison between orphan drugs and pharmacogenomics is useful, it might be interesting to study orphan drugs to increase our understanding of pharmacogenomics. We perform this comparison by studying discourses of how actors view developments across the different 'domains' of the drug R&D and application pipeline, through the use of metaphors regarding pharmacogenomics and orphan drugs. First, metaphors are identified by systematically reviewing the literature, using these domains. Second, orphan drugs and pharmacogenomics are compared following these domains. This sheds light on similarities and dissimilarities between these drug classes. In other words, we want to answer the question whether orphan drugs can serve as *the* metaphor for pharmacogenomics. Next, this exploration of the comparison of two drug classes leads to visions of and lessons for future emerging technologies, such as pharmacogenomics.

Accordingly, the question we focus on in this section is: *what metaphors are used in pharmacogenomics and orphan drugs in the different drug R&D domains? What are the (d_{is}) similarities? Can orphan drugs be regarded as a metaphor for pharmacogenomics, and what can we learn from them in the context of the emerging pharmacogenomics future?*

This section starts from the assumption that learning about the (dis)similarities between the two drug classes might contribute to a better understanding of pharmacogenomics innovations among policymakers and managers by creating prospective images of emerging technologies, which in turn help them overcome the Collingridge dilemma. For example, policymakers can decide which characteristics of orphan drugs to include in their vision of pharmacogenomics, and they can learn more about both orphan drugs and pharmacogenomics because the metaphors accentuate their characteristics. More importantly, this analysis adds to the existing literature and methodology on technology future analysis and metaphor assessment (see next section), and might prove to be applicable to other emerging technologies as well.

Section 3.4.1 deals with the theory on metaphors and its use as a future analysis method. Section 3.4.2 presents the methodology used, while the subsequent sections deal with the results, the conclusions and discussion.

3.4.1 Theory on studying the future using metaphors

Assessing technologies in their "embryonic state" (Mambrey and Tepper, 1999) is the premise of a large array of technology futures studies (Porter et al., 2004). One way of analysing the future is through the prospective and desirable images shared by numerous actors, i.e. images that steer stakeholders' actions and interactions (Grin et al., 1999). They include visions, 'Leitbilder', expectations and promises. Methods investigating this type of futures include vision assessment, science fiction analysis and metaphor assessment.

A metaphor is described as "a conceptual system that allows us to understand and experience one type of thing in terms of another" (Miller et al., 2006). Several authors have

contributed to theories of metaphors ranging from Aristotle and his substitution theory to Lakoff and Johnson (1980) and their cognitive theory. In the latter, a metaphor is defined as "a cross-domain mapping between the source (secondary) and the target (primary) domains" (Hellsten, 2002). This mapping process treats these two domains as holistic, abstract concepts, in which some – but not all – features of the source are used to highlight some of the features of the target. An emerging technology, for example, will consist of a combination of known and new features.

Metaphors describe situations that people involved in the public debate are expected to be familiar with, and by doing this reduce the complexity of issues. In this way they function as communication devices. At the same time, metaphors have a normative and even political quality (Miller et al., 2006). The normative character of metaphors lies in the fact that people put their wishes, needs, values and assumptions in the metaphors they use: "different social groups use different metaphors to capture and promote their own interests and desires for the future" (Wyatt, 2004). Metaphors can therefore become shared and might have the same functions as visions and expectations in guiding technological development (Brown et al., 2000). The political use of metaphors ties in with the fact that they are mostly formed as a result of an interactive discourse in which different stakeholders – sometimes strategically (Berkhout, 2006) – use different metaphors or the same metaphor with different meanings. Meanings of metaphors are heterogeneous and sometimes ambiguous but as the debate goes on, closure is expected and the use and meaning becomes solidified.

Using metaphors in the context of science and technology has two functions (Hellsten, 2002). First, they help in elucidating science and technology for the general public, while facilitating science communication, knowledge transfer, and promoting science. Second, the use of metaphors has a stimulating effect on the scientific development itself, by making ideas more concrete, generating new ideas, helping to communicate complex matters or interests between scientists, and by legitimising the research projects to financial backers. Nevertheless, it can have detrimental effects on science as well, such as was the case with the metaphor 'Frankenfood' for genetically-modified food.

Accordingly, metaphors take shape in an interactive discourse, have a strong normative character, and while representing the desired state of a currently emerging technology, could drum up strong guidance for these technologies. Few authors have already contributed to such a technology future analysis based on metaphors, and nearly all of them focused on studying metaphors within a discourse around a technology. Examples include a so-called 'metaphor analysis' (Miller et al., 2006) in which scientific journal editorials are screened for opinions about and metaphorical imagery of the future of human genetics. Other authors use different classes of metaphors (hyperboles, analogy, contrast, etc.), dissecting metaphors in different elements or as members of a shared domain (Mambrey and Tepper, 1999). Additionally, Wyatt (2004) screened magazines to uncover metaphors that were used during the development of the Internet. The next section shows how metaphors can be used to study the discourses of orphan drugs and pharmacogenomics.

3.4.2 Methodology

To elucidate the metaphors used in the context of orphan and pharmacogenomics drugs we investigated characteristics of these two drug classes as found in literature. We restricted our search to international review articles and reports published in the period 1997 up to the beginning of 2006. The starting point of this period was marked by the arrival of

the term pharmacogenomics in scientific papers (Hedgecoe, 2003), which coincided with the growing interest for structural and functional genomics aspects in the context of the Human Genome Project.

The articles and reports on both pharmacogenomics [1-27; see Appendix B] and orphan drugs [28-53; see Appendix B] were collected by searching two publication and conference paper abstract databases, i.e. the Science Citation Index (via ISI Web of Science) and PubMed. We interviewed three genomics scientists and three Dutch scientists and policy-makers engaged in work on rare diseases. They provided keywords that cover the technological fields in a comprehensive way. The experts on pharmacogenomics and orphan drugs were identified through consulting the Netherlands Genomics Initiative and the Dutch Steering Committee on Orphan drugs respectively. These keywords were then used in structurally searching the databases; taking into account the time period (1997-early 2006) and whether the articles were classified as 'review articles'.

The resulting set contained 688 articles on pharmacogenomics and 63 on orphan drugs. From this database we selected those articles that were cited at least 10 times in other articles. This might have led to a bias towards older articles but this consideration was outweighed by the need for 'authoritative' publications, especially because the emergent, undefined character of pharmacogenomics calls for a deliberate set of views.

We also included reports on orphan drugs and pharmacogenomics, published by leading regulatory institutes such as the EMEA, FDA and NICE. These reports featured most often in the lists of references of these articles. After reading through the resulting 57 pharmacogenomics and 39 orphan drugs publications it appeared that only 27, respectively 25, would be of use for our analysis (some were too scientific/technical or contained duplications). The review articles are internationally-oriented although we acknowledge that the reports have a strong European focus. This bias is caused by the way we selected the reports, because during the time period under consideration the EU was trying to redress its lacking orphan drug regulation compared to the US (EU orphan drug regulation came in place in 2000). These reports still reflect a perspective that is not solely restricted to Europe because they constantly make comparisons with the situation in the US.

Subsequently, we undertook a literature review and metaphor analysis consisting of three stages. First of all we analysed the articles and reports using a so-called 'domains' heuristic consistent with Miller et al. (2006). We read the texts, extracting quotes and concepts that are important for an understanding of the orphan drugs context and the pharmacogenomics

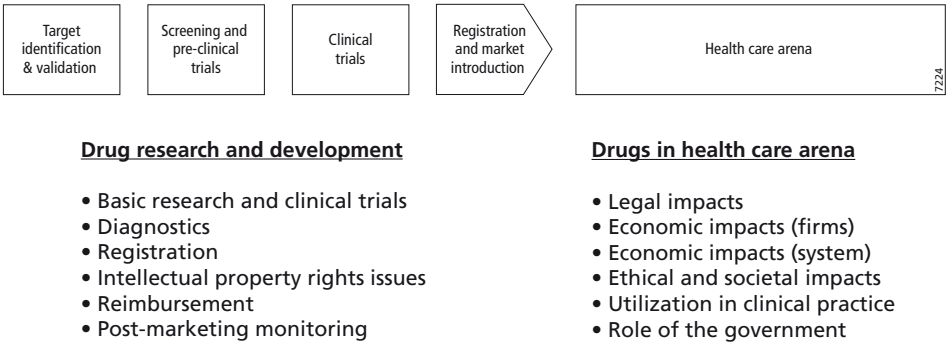

Figure 21 - domains used in the context of the drug R&D pipeline (this picture has a linear lay-out just for presentation purposes).

future. To structure the search results we labelled the texts into predefined domains that are derived from the important aspects of drug R&D, following the drug R&D pipeline, marketing, and utilisation (Gassmann et al., 2004). Figure 21 illustrates the different search domains used.

The second step dealt with constructing concise summaries and identifying eye-catching metaphors that were representative of the different domains in the two drugs classes. We took the texts with the same labels together, making sure that these summaries contained all different metaphors, especially the ones that were mentioned most often, in this way reflecting relevant issues of all topics. Both steps, i.e. extracting texts from the articles and reports, and summarising, were done taking into account interrater reliability. Two researchers rated all the publications and made summaries independently, which were then discussed. Especially the question of what could be regarded as a metaphor was discussed thoroughly. For a start, a phrase should comply with the definition of a metaphor as presented in the previous section. When uncertainties remained, we searched the aforementioned literature databases and investigated in which context these phrases were used in other articles. The uniform list of summaries and notable metaphors is presented in the next section.

The final step was to compare the most important issues per domain. This implied focusing on the metaphors used in the discourses of orphan drugs and pharmacogenomics to obtain a better understanding of the problems and solutions, as well as their underlying assumptions and values. The level of importance of the metaphors found could not be quantified. This would suggest that metaphors and their meanings could be added up, which proved difficult because of nuances in the metaphors used. Therefore, we used a qualitative analysis in which both raters discussed which metaphors were comparable and would form a major discourse within one domain. Analogously, the analysis of similarities and dissimilarities between the different drug classes on each domain was done based on discussions between the raters. Table 3 in section 3.4.5 illustrates this comparison.

3.4.3 Results

This section outlines the findings following the presented domains structure (Figure 21).

Basic research and clinical trials

The orphan drug publications emphasise the lack of understanding of the pathogenesis of rare diseases ("health orphans" [30, 33]), available animal models, and current treatments: "the absence of treatment for many rare diseases constitutes a 'clear pharmacological gap'" [52]. The barrier to prevention, diagnosis, and treatment is a 'lack of mechanistic knowledge about the disease' [50]. On the other hand, orphan drugs act as "model systems" [52] for research on more prevalent diseases. The clinical trials prove difficult to organise because of the low number of patients with a specific rare disease. Therefore, complying with clinical trial standards as used for more prevalent diseases is complex: "It is next to impossible to gather enough patients to achieve sufficient statistical power to demonstrate significant clinical benefits of a therapy" [34]. The same goes for the "uncontrolled" phase II studies [38]: there are no markers to follow the treatment, and the natural history of the genetic orphan disease is often unknown [41].

The pharmacogenomics documents focus on the subdivision of patient groups providing opportunities for adequate data on efficacy and safety. This might increase efficiency and chances of success for the innovation process with efficacy and safety data resulting

in "early decisions" [13] and "a paradigm shift from a linear process to an integrated and heuristic one" [9]. Also the imminence of a rescue strategy is put forward. Drugs that have shown insufficient efficacy or safety levels in the general population can now be approved for smaller subgroups of patients. Basic research might benefit from the discovery of similar underlying patterns or pathways between diseases.

To conclude, in the domain of basic and clinical research we see a difference in perspective between the two classes of drugs. Patients see orphan drugs as a gift, whereas searching for new orphan drugs is seen as a 'problem'. Conversely, companies and others see pharmacogenomics as a 'chance' or opportunity, while it is stressed that developments should be kept under control because of the fear that such drugs might turn into a poison. Moreover, the problems stated in the orphan drugs articles are more specific, while those in pharmacogenomics articles are not.

Diagnostics

The major concern in orphan drugs articles is the lack of appropriate diagnostic tools, which leads to limitations on orphan drug development and recognition of rare diseases. Regarding pharmacogenomics, advantages include facilitating market definition for businesses and the fact that genetic test results are valid for a lifetime, while disadvantages concern fears about test accuracy, genetic determinism and consumers using these tools without medical supervision. Many authors see diagnostics as an essential part of pharmacogenomics because it concerns the combination of diagnostics and therapy or the "personalised diagnostic-therapeutic tandem combination" [8]. This goes for drugs that are on the market, and also for those that are still part of clinical trials. After all, patient populations will have to be stratified by conducting genetic tests. Businesses can choose to follow three strategies: 1) co-development of therapy and diagnostic testing, 2) first developing diagnostics then therapy, or 3) first therapy then diagnostics. As it is not in the interest of pharmaceutical companies to stratify or reduce their "one-dose-fits-all" market [13], they will hesitate to follow these strategies, whereas diagnostic companies might be less irresolute.

Registration

Similarities are observed within the registration domain. Both classes pertain to small populations in clinical development and in the market phase. "The lack of reliable methods for evaluating the effect of drugs on small numbers of patients is partly responsible for the generally poor quality of the dossiers" [38]. Both classes mention phrases like "stratification" [37], "salami slicing" [42] and "genotypically enriched populations" [2, 20]. Second, a speeding up of the drug development process is expected in both instances, leading to faster registration, because these small populations are genetically characterised in the case of pharmacogenomics. For rare diseases new drugs are often "first-in-class" [36] and thus obtain "fast-track" approval [48] more easily. "Less stringent criteria are acceptable for orphan drugs" [38], also in the light of the novel and lifesaving aspects of these drugs. Third, pharmacogenomics and orphan drugs change the way the drug development process is organised. Interaction with pharmaceutical companies is induced through "voluntary submission of pharmacogenetic analyses" [13]. These data are then discussed in so-called "safe harbours" [21], i.e. results of the discussions will not influence the FDA's approval decision. It is simply a way of experimenting and learning in a niche. Moreover, for orphan drugs a "collegial relationship" [16] exists between the FDA and drug sponsors.

Thus orphan drugs are "fast-tracked" to approval due to the life-threatening nature of the disease, the lack of alternative effective treatments and a reduced clinical trial size required to license a drug. For pharmacogenomics, a drug shown to be more effective for a serious disease in a defined subpopulation has many characteristics in common with traditional orphan drugs.

Intellectual property right issues
Patents are deemed to add time to market exclusivity, and attempts to appropriate genes and gene manifestations are uncertain. Moreover, pharmacogenomics might lead to "new claims for old products" [5] ("recovering 'lost' drugs" [48]). This domain does not provide a clear view about the (dis)similarities between the two drug classes.

Reimbursement
In the context of orphan drugs, reimbursement is seen as a major hurdle to market introduction and a cause of inflated prices. This applies especially for Europe where companies have to cope with different reimbursement procedures in different member states. Nevertheless, organising reimbursement is important "because orphan products address considerable unmet needs for relatively small patient groups for which care would otherwise be extremely expensive" [43]. For pharmacogenomics the potential higher prices because of smaller markets were mentioned as well, alongside decreasing costs due the possibility of genetically downsizing the patient population for which the drug is efficacious and safe [48].

Post-marketing monitoring
For both drug classes an emphasis is put on the importance of post-marketing surveillance because of the fast-track procedures these drugs are supposed to be going through. This implies the obligation to produce safety and efficacy data after market introduction to show that the drugs have been approved with good reason.

Apart from this similarity, pharmacogenomics technology has the potential to improve post-marketing monitoring, while for orphan drugs the lack of epidemiologic, efficacy, and safety data is stressed, as also is knowledge on the natural course of the disease. Many authors claim that the setting up of a data monitoring system, centres of expertise, and better diagnostics should contribute to the collection of these data. Again, the contrast of 'chance' versus 'problem' is evident in this domain.

Legal impacts
Not many legal impacts are mentioned for pharmacogenomics. Only the issue of physicians' responsibilities associated with genetic tests were found as medico-legal implications. Legal issues surrounding orphan drugs focus on the Orphan Drug Act in the US (since 1983) and the EU Orphan Drug Regulation (since 2000). Drugs can obtain an Orphan Drug Designation that guarantees "appropriate incentives" [32, 50], such as market exclusivity and protocol assistance. Beneficial effects are discussed: "the [...] orphan regulation provides hope" [29, 34]. On the other hand, some authors stress the abuse of orphan drug regulation [e.g. 40,49]. "Had the Orphan Drug Act been co-opted as a Biotechnology Promotion Act?" [42]. Orphan drug regulation encourages businesses to "game the system" [37] by identifying subgroups of diseases as new diseases in order to qualify for orphan drug status, also called "balkanization" [37] or "stratification" [37], since common diseases

are split up into many rare diseases. Moreover, medicines that have already been approved under the Act can become blockbusters because of unintended proven effectiveness against common disorders, or because the indication area is suddenly expanding. Consequently, legitimacy questions are constantly asked about this so-called "unreasonable profitability" [42]. Concluding, for orphan drugs legal impacts are more concrete, but potential abuse in the case of pharmacogenomics could become a major issue.

Economic impacts for businesses

Statements made on economic impacts for businesses partially show similarities between both orphan and pharmacogenomics drugs. Both classes imply smaller markets ("ultra-orphans" [44]), which are not attractive for pharmaceutical companies: "the more personalised the medicine, the less interesting the business" [10]. Disease stratification would decrease the market size for an individual drug. At the same time, niche markets are still interesting for companies, mostly smaller ones. While stratifying the patient population a drug might position itself in an exclusive, monopolistic way within the market: "a particular drug could fully command 10% of the huge depression market and that would be a blockbuster [... in an] exclusive market without having to fear generic competition" [5]. Drugs can then turn into "minibusters" [11], "niche franchises"[18], or "best-in-segment" [18] medicines: promising drugs that work for a portion of the population, whereby patients are pre-selected based on their genetic profiles.

Accordingly, the economics of orphan drug development could be favourable: entry barriers are lower and markets, although smaller, are predictable and profitable, plus patients are chronically ill and thus for a long time dependent on a particular product. This could be a "therapeutic Gold Coast" [43]. Market exclusivity provides protection against 'me-too' competitors, and the small markets for orphan drugs dissuade generic competition. Furthermore, marketing costs are lower since knowledgeable medical specialists could be fast-reached.

Nevertheless, there is a difference in expected costs in drugs R&D. Thanks to more efficient clinical trials, target and lead discovery, it is foreseen that pharmacogenomics will lower development costs. This decrease in cost is not foreseen for orphan drugs because of the anticipated small markets.

Economic impacts for the health care system

The high prices cause problems for the financing and affordability of orphan drugs through (national) reimbursement schemes. The absence of competition adds to this problem, which is propagated by legislation that ensures market exclusivity for a drug treating a specific rare disease. The reasoning that it encourages pharmaceutical companies to back the development of drugs with small markets legitimises this measure [28]. The same goes for pharmacogenomics drugs: "sponsors likely demand a higher price for them" [18] as they are innovative, high-quality drugs on a monopolistic market. Nevertheless, it is uncertain how the overall balance of costs and benefits will turn out. Some authors claim that higher efficacy and safety results in cheaper clinical practice, e.g. through less adverse drug effects, less trial-and-error treatment, and reducing hospitalisation. Others emphasise the uncertainty regarding financing the accompanying diagnostics.

Ethical and social impacts

For pharmacogenomics, a large number of ethical and social impacts are suggested. They include public trust in general, as well as questions on privacy protection, equity, confidentially and discrimination [45]. The latter not only includes neglecting persons in their relation with health insurance companies and employers, but also includes concerns about the development of drugs only for certain subgroups ("dispossess subgroups of patients" [10], "splinter groups" [10], and "genetic exceptionalism" [21]), possibly excluding those that live in developing countries. Other risks include ignoring non-genetic aspects of drug response and disease susceptibility ("genetic reductionism" [5]), and risks concerning a whole country (developing "genocide weapon[s]" [2]). Lastly, the need for patient participation and education in clinical trials and genetic testing is stressed, mostly with respect to getting patient's "informed consent" before they participate [5, 8].

Orphan drugs do not share the genetics-specific ethical and social issues. One issue deals with the lack of interest of society in general, whereas rare disease patients are heavily engaged. As one patient said: "orphan diseases are not important unless you happen to have one" [33]. There is a societal "ignorance of the seriousness of rare diseases" [31]. Dissemination of information is important for patients and professionals in order to prevent misdiagnoses, but there is a lack of infrastructure and proper exchange of information. Especially regarding rare diseases, patient advocacy groups have shown to have a major influence on drug innovations because these patients are highly involved and there is much to be gained ("hope" for a new future [46]). The equity issue [31, 35] is also in agreement with the one presented in the pharmacogenomics context: there are fears of unequal access to therapy, e.g. because of registration and reimbursement, and unequal attention paid to certain diseases in drug R&D.

Utilisation in clinical practice

For both rare diseases and pharmacogenomics, the importance of medical professionals' awareness is mentioned. For pharmacogenomics there is a need for "genomic education" [5, 23]. Moreover, there will be changes in the role of information technology, the paradigm of trial-and-error prescription, and the distribution of workload and responsibility. Application of pharmacogenomics in the health care setting necessitates physicians and specialists to adjust to prescribing drugs based on molecular profiles. They could be resistant to disease (re)classification at a genetic or genomic level as they are trained to diagnose on the basis of symptoms and morphology. Additionally, what is the degree to which insurers will limit physicians' prescribing flexibility?

Furthermore, the expectations of patients are stressed, and the consequences of smaller patient populations ("'one size fits all' mentality" [5], "individualisation" [5, 8], "personalisation" [8], "customisation of drugs" [16]) are sketched in a far more abstract way than in the orphan drug context. The term personalised medicine is often used in the context of pharmacogenomics. It conveys the most extreme vision of what the pharmacogenomics future might bring, namely separate treatment for each person. At the same time this term caused debates about its use as a metaphor. Scientists think that pharmacogenomics first and foremost will lead to the stratification of the patient population into groups, instead of individuals, for which certain treatments work efficaciously or safe. In this way it leads to "tailor-made" rather than personalised medicine [12].

Role of government

For orphan drugs, ideas and needs for the role of the government are significantly apparent. They include tax credits, simplification of marketing authorisation procedures, extended market exclusivity, scientific research programmes, clinical trials set-up support, pan-European networks of excellence, and support for medical education and training for health professionals. Compared to pharmacogenomics there is a difference in the legitimisation and scope of public intervention. Research on orphan drugs should be supported because this is a problem that has its roots in failing markets, whereas the government should not necessarily sponsor research on pharmacogenomics while it is regarded as an opportunity that the market will and should take up itself. The government should only give more attention to those patient populations the pharmaceutical companies are unwilling to invest in, in order to avoid "an African-like development" [2]. Moreover, research on rare diseases can function as a scientific model system for other, more prevalent diseases. Studying these models then works like performing basic scientific research, for which public support is more common.

Box 3.4 convergence of orphan drugs and pharmacogenomics: the Glivec case

Glivec/Gleevec ® (imatinib) is a monoclonal antibody drug that was approved for chronic myeloid leukaemia (CML) in 2001 and gastrointestinal stromal tumour (GIST) in 2002. The drug was developed by the Swiss pharmaceutical company Novartis. Users were involved in the development as well: Novartis made use of the Internet to make potential buyers aware of the existence of Glivec. One patient in the USA became very enthusiastic and recruited 3000 other patients and medical professionals to sign a letter intended for Novartis to accelerate clinical testing (Gassmann et al., 2004).

Glivec is an example of a pharmacogenomic drug. 95% of CML patients have a chromosome translocation (Philadelphia chromosome) resulting in the formation of the bcr-abl gene that codes for a tyrosine kinase protein. This bcr-abl protein stimulates cell division. Imatinib acts as a competitive inhibitor. 85-90% of GIST patients have a mutated (c-kit) gene leading to continuous activation of the cell division steps. Imatinib inhibits the binding of the stem cell factor on the KIT receptor. These mutations are detected by immunohistochemistry[1]. If these mutations are present, then treatment with Glivec is efficacious.

Moreover, Glivec gained orphan drug status, because of small patient populations affected by CML. Later the indication area was expanded to GIST and other cancers, such as skin cancer. Sales jumped to 3.05 billion dollars in 2007. The question is then; can this drug still be seen as an orphan drug? Did the company know that it would be applicable to a wider range of diseases and patient groups? And did they invade

1 DakoCytomation developed a c-kit pharmDx cancer diagnostic test to identify GIST patients that are susceptible to Glivec. The FDA approved this test in June 2005. It had already been available in Europe and South-America since August 2004.

the Orphan Drug Act and their rights as a "Trojan horse"? Or is it a good example of making use of a niche market and the promises of knowledge on pharmacogenomics and the underlying mechanisms of diseases?

This is currently under discussion by the European Agency for the Evaluation of Medicinal Products (EMEA), the body that oversees orphan drug designations in the European context as well as on the national level. At least in the Netherlands, various parties are involved in a debate on 'real' versus 'unreal' orphan drugs, and how a distinction between these two classes can and should be measured objectively. The fact that no malicious intent existed in the Glivec case is illustrated by the fact that this drug was hardly seen as lucrative during its development: "Before the merger with Sandoz in 1999 the project was continuously in danger. Senior research management seriously considered putting the efforts into other potentially more profitable projects even though the laboratory results were highly promising. The new Novartis director, however, was fully behind the project" (researcher Novartis, 2003)

Summarising, the Glivec case presents many of the found characteristics in the comparisons between orphan drugs and pharmacogenomics on different domains.

3.4.4 Conclusions and discussion

The introduction to section 3.4 assumed to improve understanding of the emerging pharmacogenomics future by studying and comparing discourses of how actors look at developments across different domains of drug research, development and application in both orphan drugs and pharmacogenomics developments. This section therefore focused on *what metaphors are used in pharmacogenomics and orphan drugs in the different drug R&D domains? What are the (dis)similarities? Can orphan drugs be regarded as a metaphor for pharmacogenomics, and what can we learn from them in the context of the emerging pharmacogenomics future?*

Pharmacogenomics is an emerging technology with many uncertainties. Its premise is that patients can be stratified by diagnostic tests into smaller, genetically homogeneous groups that respond favourably to certain drugs or are susceptible to a certain disease. This subdivision of the patient population into smaller groups (see section 3.3) suggested the viability of comparing orphan drugs and pharmacogenomics, which subsequently led to the metaphor analysis in the previous sections. Table 3 summarises the most important similarities and dissimilarities between orphan drugs and pharmacogenomics in the various domains, including the major metaphors used.

Concerning the discourses within the different domains, we identified that the orphan drugs metaphors and statements used were more specific regarding concrete outcomes (e.g. 'ultra orphans', 'clear pharmacological gap'), whereas with pharmacogenomics the content remained more fluid, more an expectation or promise than something concrete (e.g. 'safe harbours', 'customisation', 'genetic reductionism'). This is a consequence of the emerging character of pharmacogenomics. Whereas orphan drug development is already quite specific, with more than 23 years of experience having been acquired since the introduction of the first Orphan Drug Act in 1983, pharmacogenomics only really took off after the completion of the Human Genome Project in 2000.

Table 3 - comparison of pharmacogenomics and orphan drugs per domain.

	Pharmacogenomics	**Orphan drugs**
Similarities		
Basic research and clinical trials	Uncovering underlying disease pathways	"Model systems" for more common diseases
Diagnostics	Diagnostics are essential to the pharmacogenomics concept ("tandem")	Diagnostic tools are important (but currently lacking)
Registration	Small populations ("genotypically enriched populations")	Small populations ("salami slicing")
	Speeding up process ("fast-tracked")	Speeding up process ("first-in-class", "fast-tracked")
	Change organisation of process ("safe harbours", "voluntary submission")	Change organisation of process ("collegial relationship")
Reimbursement	Higher costs due to smaller groups Lower costs due to increasing safety and efficacy	Higher costs due to smaller groups
Economic impacts (companies)	Stratification leads to smaller, uninteresting markets	Small markets are uninteresting ("ultra orphans")
	Niche markets beneficial through high market penetration ("minibusters", "niche franchises", "best-in-segment")	Niche markets beneficial ("therapeutic Gold Coast")
Economic impacts (system)	(Uncertainty about) increasing expenditure	(Uncertainty about) increasing expenditure
Ethical and social impacts	Equity ("dispossess subgroups of patients"), patient involvement and education ("informed consent")	Equity ("ignorance seriousness rare diseases"), and expectations ("hope")
	Genetics-specific: confidentiality, "genetic reductionism", "genocide weapons"	-
Utilisation in clinical practice	Importance of medical professionals' awareness ("genomics education")	Importance of medical professionals' awareness
	Experiences and expectations on smaller patient populations ("individualisation", "tailor-made", "customisation")	Experiences and expectations on smaller patient populations ("stratification")
Dissimilarities		
Basic research and clinical trials	"Rescue strategy"	"Lack of mechanistic knowledge about..."
	Insufficient safety	"Clear pharmacological gap"
Post marketing monitoring	Chance and important	Problem, but important
Legal impacts	Legal responsibility	Abuse of regulation ("balkanization", "game the system")
Economic impacts (firms)	Low development costs	High development costs
Role of government	Market chance: no support of research	Market failure: support research with orphan drug regulations ("African-like development")
No clear distinction		
IPR issues		

A difference was also found in observed assumptions and values related to orphan drugs and pharmacogenomics. Table 3 shows different valuing of orphan drugs and pharmacogenomics with metaphors used such as 'African-like developments' for orphan drugs and 'genotypically enriched populations' for pharmacogenomics. Probably these values differ due to the stage of technology development, but also due to the inherent difference in the more general metaphors 'gift' versus 'poison' (or 'chance' versus 'problem')[29].

To compare orphan and pharmacogenomics drugs in order to anticipate the emerging pharmacogenomics future, Table 3 shows a distribution of the similarities and dissimilarities over the domains. Only on certain aspects can orphan drugs be seen as a model for the pharmacogenomics future. These include similarities such as 'first-in-class' and 'salami slicing'. This is in line with what we saw in the metaphors literature: when one type of thing (target) is described in terms of another (source), not all elements of the source need to correspond with those of the target.

Answering the question what we can learn about the pharmacogenomics future, we see that there is a need to emphasise the positive aspects for different actors, e.g. companies can focus on smaller but at the same time monopolistic niche markets, and their registration processes profit from this smaller-scale, more tentative testing. Scientists can position rare idiosyncratic diseases as a model system that might appear beneficial for and spread out to 'neighbouring indications'. Finally, society at large might take advantage and should be preparing for more individualised therapy, considering increased efficacy and lowering adverse drug reactions. Besides these positive outcomes the potential negative impacts should also be acknowledged and prepared for, i.e. equity issues and costs for the health system (society at large), small market revenues (companies), and an educational and knowledge backlog (clinicians).

The methodology used for comparing a current with an emerging technology class might be useful in learning about discourses in drug classes and about how a future emerging technology could be envisaged. Refinements include deepening the metaphor analysis within the discourse of the domains, and differentiating between problems and solutions, and the underlying norms and values. To contextualise the future vision, these norms and values could also be attributed to different kinds of stakeholders. In addition, assessment of the importance of various metaphors extracted from the publications could be enhanced by interviewing actors and also by taking into account differences in actor perspectives when assessing the metaphors used. Furthermore, a drawback of the analysis is that a comparison calls for both classes to state their problems, solutions, etc., on every domain. In this case, for example, IPR issues regarding pharmacogenomics were not articulated at all, and no statements on the ethical and social impacts regarding genetic-specific issues of orphan drugs were found. A subdivision of domains might ameliorate this.

Concerning the choice for orphan drugs as a 'comparing partner' to pharmacogenomics we should add that this has two drawbacks: 1) the premise of this comparison lies heavily on the small patient populations characteristic. The question could be raised whether the focus on small patient groups and the comparison with orphan drugs is the major discourse (as compared to others, such as the convergence of food and health). This discourse choice is based on reviewing the articles and reports, but it has not systematically been tested; 2) although we introduced pharmacogenomics as a technology that will take at least ten

29 Derrida (1981) discusses Plato's use of 'pharmakon' that, interestingly, means both remedy and poison.

years to emerge, its principles can also prove to be crucial in treating and diagnosing rare diseases. In the future the two classes might overlap, making a clear-cut comparison conceptually more difficult.

Exploring emerging technologies using a metaphor assessment gives policymakers, managers and researchers more contextualised prospective images of future pharmacogenomics (and the current orphan drugs) developments. More importantly, we believe that metaphor analysis is a novel way to analyse (other) emerging technologies.

The comparison of pharmacogenomics and orphan drugs shows that these two fields cannot be compared on all domains. In terms of metaphors or analogies we see that these drug classes agree with each other on some – but not all! – aspects. If we regard orphan drugs as a metaphor or analogy of pharmacogenomics, this would only be valid on topics like registration, reimbursement, economic impacts for the health system, ethical and social impacts, and the utilisation of drugs in clinical practice. Other domains, such as basic research, clinical trials, and economic impacts for companies, show a partial, mixed level of agreement. Finally, dissimilarities or no clear distinctions are found on the domains of post-marketing monitoring, the role of the government, and IPR issues (see Table 3).

Although orphan drugs and pharmacogenomics showed a varied degree of comparability, we decided to treat orphan drugs as an analogy-to-some-extent. This analogy-to-some-extent is primarily used while selecting our cases. This means that intermediary user organisations, which are the units of analysis of these case studies, should deal with pharmacogenomics or with those aspects (domains) of orphan drugs that show a large extent of similarity to pharmacogenomics. The next methodology chapter explains this case selection in depth. Furthermore, the last chapter (Chapter 9) discusses the use of this analogy-to-some-extent and the influence it might have on the answers to the research questions.

Chapter 4
Methodology

This chapter outlines the methodology that was used while studying the research questions. The central research question, as was introduced in the first chapter reads: "*how to understand the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies?*" This question is subdivided into different (sub-) questions concerning demand articulation processes inside intermediaries, demand articulation processes in interaction with other stakeholders, and questions about how the answers to the questions can be used by innovation managers and policymakers. These research questions reflect several research types. They include:

- Descriptive questions, e.g. while narrating the demand articulation dynamics.
- Explanatory questions, e.g. while connecting these narratives to the central conceptual framework as presented in Chapter 2.
- Exploratory questions: studying the aforementioned central framework, among other things yielding findings about the order of events in first-order and second-order learning loops. Based on these outcomes different types of demand articulation mechanisms and interface strategies are proposed.

The 'how' questions take a prominent place in the research (sub)questions. They deal with a contemporary situation over which the investigator has little or no control. Moreover, the questions are studied in a holistic manner, with a high sensitivity to the context of the subject. The best way to treat these questions is by using the case study approach (Yin, 2003). The choice for a case study research design is motivated by the fact that it is not the purpose of this research to generalise the outcomes to populations rather than to theoretical propositions. Generalisation to populations would be impossible as the number of cases and respondents within these cases is not so high that it would make them statistically significant. In contrast, the strategy of this research project is to study a few intermediary user organisations in-depth. The case study design best fits this point of departure.

This chapter illustrates how the case selection was done (section 4.1). Hereafter, section 4.2 presents the general methodology based on process theory and methodology, as well as the data collection methods. Finally, section 4.3 goes into the specific analysis methods for every research question.

4.1 Case-study selection

As follows from the introductory and theoretical chapters this thesis focuses on intermediary user organisations. In Chapter 2 these were defined as: stakeholders that facilitate interactions between users and one or more other actors. These intermediaries constitute the units of analysis of this study. *Multiple-case design* was chosen to base the analysis on more than one case study, because 1) intermediary user organisations are a heterogeneous type of actor: they constantly need to position themselves within the

innovation arena and can perform a variety of tasks and functions (see section 2.2.4); 2) the reasons to choose for a single case design did not apply to this study, i.e. there is no critical, extreme/unique, representative/typical, revelatory, longitudinal case to be found among intermediary user organisations that should be selected above others with good reasons.

We defined the following criteria to guide the case selection:

- Following the definition of intermediary user organisations and the discussion in section 2.2.4, we focused on those organisations that are part of the same 'social world' as the users it represents, i.e. the representative and coordinating types.
- These intermediary organisations should be interested in emerging pharmaceutical technologies. Ideally, they are actively occupied with the future of pharmacogenomics or its analogy, orphan drugs. In the previous chapter a metaphor analysis illustrated that orphan drugs can be seen as an analogy-to-some-extent for the pharmacogenomics future. This comparison holds true at least on certain important domains, such as registration, reimbursement, economic impacts for the health system, ethical and social impacts, and the utilisation of drugs in clinical practice. Other domains, such as basic research, clinical trials, and economic impacts for firms showed a partial, mixed level of agreement. When selecting an intermediary that deals mainly with orphan drugs, we should take these reservations into account.
- Time delineation: the previous chapter illustrated that pharmacogenomics is an example of a currently emerging pharmaceutical technology. Therefore, this led to a contemporary focus of our analysis, i.e. the cases should focus at least on the last decade (1997-2007). While the narrative should not exclude older events, they should have direct bearings on more recent events.
- Geographical delineation: the concept of demand articulation in intermediary organisations sketched in this thesis presupposes a democratic, deliberative politico-economic tradition and governance culture that is supportive to discourse-based decision-making procedures, both in the public and the private sector, like in the Netherlands. Intermediary user organisations in other countries operate in distinct political and policy realities. For example, personal communication[30] with social scientists in the UK and US showed that in these countries patient representation is less consensus-oriented but more direct and activist (Oudshoorn and Pinch, 2003; Rabeharisoa, 2003). Personal communication with Chinese and African scholars suggested that health intermediaries and NGOs scarcely exist in China because they do not have government support, whereas in African countries, NGOs are important but are mostly oriented to HIV/AIDS and access problems. Therefore, questions can be asked about the usefulness of this approach in different political cultures. It is assumed that in advanced technological areas, characterised by complexity and unexplored potential and risk, concerning diverse groups of stakeholders, discourse-based deliberation as described in this thesis is a necessary precondition for successful and competitive innovation trajectories. In this respect the approach explored in this thesis might bear relevance beyond the Netherlands. For the benefit of comparability we chose to concentrate on Dutch intermediaries.

The issue of generalisability was mentioned in the introduction of this chapter. Yin (2003) states that case studies strive after analytical instead of statistical generalisation, i.e.

30 By the author of this thesis.

results cannot be generalised to all cases (the total population) but to the theory, just as in experiments. Following this analogy, Yin encourages case study researchers to follow the 'replication logic' as opposed to logic based on sampling: "each case must be carefully selected so that it either (a) predicts similar results (a literal replication) or (b) predicts contrasting results but for predictable reasons (a theoretical replication)" (Yin, 2003). We did not seek literal replication over the three cases because other measures were taken to boost the reliability of the research, e.g. by triangulation of methods (see below). On the other hand, we were interested in theoretical replication because this might illustrate the external validity of the conceptual framework presented in Chapter 2. Therefore, cases were selected that varied regarding: 1) the stage of the drug R&D innovation process in which the intermediary user organisation most prominently tried to engage itself in pursuit of its own objectives; 2) the type of intermediary user organisation as proposed in Chapter 2 (representative and coordinating). These variations are anchored in theory and it is assumed that these differences result in distinct demand articulation processes. Nevertheless, they do not take on the role of hypotheses here but are needed to produce necessary contrasts between the cases.

Table 4 illustrates the three cases and the differences on the two varieties presented above. Ultimately, the three cases were searched using the aforementioned criteria and varieties, making use of suggestions made in the series of explorative interviews with 24 people working for actors in the Dutch health care sector (see Chapter 2).

Intermediary user organisations are involved in a large range of activities related to different tasks and functions. This variability elicits a need for selecting events while collecting and analysing data. Studying the accumulation of demands in articulation processes involves looking at demands that are thematically coherent, revolve around one topic, and span a substantial period of time. We call the sequence of events on one topic *event themes*. One intermediary user organisations can be engaged in several event themes related to emerging technologies. We selected the most prominent ones, based on the alignment of the subject matter with the organisation's objectives, and importance the individuals inside and outside the organisation assign to these activities. These event themes are thus cases-within-cases, or what Yin calls 'embedded cases'. For example, the study of the Dutch Neuromuscular Disease Association (VSN) involves six embedded cases – and thus six event themes, namely gene therapy, stem cell therapy, exon-skipping, enzyme replacement therapy for Pompe disease, and clinical trials for idebenone and TCH346.

The last point we want to make is that the period after market introduction, the post-marketing stage of the R&D pipeline (involving reimbursement, etc.), is seen as an integral part of the innovation process, as was introduced in section 2.2.1 and 2.2.2. This focus on the later stage of the innovation process still agrees with the concepts of emerging

Table 4 - demarcating cases based on two selection criteria.

Cases on intermediary user organisations[a]	Stage of innovation process	Type of intermediary
Neuromuscular Diseases Association (VSN)	Mostly R&D	Representative
Steering Committee on Orphan drugs (WGM)	R&D and market stage	Coordinating
Breast Cancer Association (BVN)	Mostly market stage	Representative

a This table presents the cases in the order in which they appear in this study. This order is not theoretically-driven.

technologies and demand articulation because we envisage that these later-stage issues cast a shadow over decisions made in the emergent phase. In line with this, the previous chapter showed that pharmacogenomics was envisaged to have impacts on all stages of the innovation process and that Herceptin and orphan drugs can be regarded as predecessors and/or analogies of the pharmacogenomics future. Having selected the (embedded) cases, the next sections focus on how the data was collected and which analyses were applied.

4.2 Process approach, methodology and data collection

There are several ways to look at processes from a conceptual or methodological point of view (Poole et al., 2000). In variance theory, independent variables (inputs) influence dependent variables (outcomes) in a causal relationship. In some variance studies this relationship or the variables themselves refer to processes, e.g. workflows and communication activities, as compared to more structure-based variables. The variance approach concerns finding statistically relevant explanations between a fixed array of independent and dependent variables, which holds true for different contexts without taking into account time-ordering between the independent variables. In contrast to the variance model, the *process approach* focuses on the time-ordering of variables. Factors that influence the outcomes of a process may change over time ("different factors come into play at different stages of the development or change process"), which leaves more room for serendipity and chance (Van de Ven and Engleman, 2004). Processes are regarded as a sequence of events that together forms a narrative that describes how things change over time (Mohr, 1982).

An analysis of demand articulation processes in intermediary organisations imposes the importance of time-ordering and changing entities that are studied over time. In the process approach a unit of analysis is called a *central subject*. This is the "individual entit[y] [...] around which the narrative is woven" (Van de Ven and Engleman, 2004). In this thesis intermediary user organisations are regarded as the central subjects, or units of analysis.

Within these intermediary user organisations, the units of measurement that carry these processes are formed by so-called *events*, which "are what central subjects do or what happens to them" (Poole et al., 2000). Abbott (1990) claimed that these events should be used instead of attempting to regard a process as an interaction between (in)dependent variables because this would make analysis and conceptualisation of processes too complex. Moreover, events should be categorised into typologies in order to describe processes on a higher level of abstraction, which makes it possible to compare different units of analysis (cases) and narratives with each other. This higher level of abstraction should be balanced with the accuracy of interpretation of the typology, measured by construct and face validity.

In studying demand articulation processes we used the so-called *event history analysis* based on Van de Ven and colleagues (1990; 1999; 2000) by following these steps:

1. *Selection of intermediaries*: as we described in the previous section we selected intermediary user organisations that would be interesting to study following the selection criteria mentioned in Table 4. We then contacted representatives of these organisations and discussed the possibilities of carrying out research including archival investigations and conducting interviews. The discussions included issues such as privacy, confidentiality, access to archives, and data transferability. The latter varied from case to case, depending on whether or not archives were digitally stored.

When material was only available on paper, it was transformed into digital documents using a scanner.

2. *Quick scan for event theme topics*: using introductory interviews with the intermediary's representatives, as well as reading (annual) reports of the organisation led to discerning interesting topics or event themes that could be studied. This selection was guided by the degree of relevance concerning emerging technologies and user involvement.
3. *Collecting raw data inside intermediaries*: the intermediary organisations were studied using the event theme topics as a guide. Moreover, concerning the underlying assumptions, i.e. the organisation's objectives, and preferences, we also took a more general search focus. Data were obtained from the intermediary archives, including minutes of (board and committee) meetings, letters, reports, and evaluations. The searches were not fully structured in order to stay close to the data. The data referred not only to the fact *that* something has happened. In the context of demand articulation processes, studying the related dynamics of the *content* of demand (statements) and observations on events and demand contents (how they were evaluated) are relevant as well. Other information sources include more open-access data, such as the organisation's public website. In addition, we conducted interviews with several representatives of these organisations ranging from chairmen and managing directors to researchers and secretaries. These interviews were primarily meant to clarify archival information, provide the easiest inroads to the data, and uncover the underlying assumptions behind the demands that were found (asking 'why-questions'). Furthermore, for some cases observation methods were also applied because it was possible to be present during (invitational) conferences and meetings organised by the intermediaries.
4. *Collecting raw data from the 'interacting partners'*: this collection mainly involved using open-access material, such as reports and minutes from parliament, reports available through websites, and annual reports. Moreover, interviews were conducted, especially to clarify underlying assumptions. To minimise problems that respondents might have with stating their underlying assumptions connected to past events[31], we used an event time line as a mnemonic device. The interacting partners were selected based on the frequency with which the intermediary mentioned them in archival material, etc. This approach was substantiated by asking interview respondents who they thought were the most important actors in the event theme.
5. *Enter raw data into a database in the form of incidents*. These are strings of words that concern a discrete incidence, occurrence, statement or observation on a discrete moment in time (Poole et al., 2000). A methodological issue concerned the cutting of these occurrences into discrete database entries, and omitting irrelevant fragments. Incidents were only included that concerned the event theme topic and the actor's underlying assumptions. These entries featured 'incident date', the incident itself, the primary actor (who initiated the incident), the secondary actors (who also feature in the incident), source type, and source date. As was mentioned in the previous steps, we used several data sources and kinds of data material, which is an important feature of case study research (Eisenhardt, 1989). In this way, data and methodological triangulation was ensured and the advantages of methods might

31 Such as problems with remembering precise details, and providing non-nuanced views on past issues using the benefits of present insights.

Table 5 - statistics about time-span, incidents and sources of the three case studies.

Intermediary	Time (time-span covered)[a]	Total # incidents	# Incidents with intermediary as primary actor[b]	# Incidents with interacting partner as primary actor	Total # of sources	Sources of evidence	Number of interview respondents
VSN	1-1-1968 to 11-10-2007	2087	708	1382	229	Archive material, interviews	7
WGM	28-4-1997 to 19-10-2006	1022	617	423	131	Archive material, interviews, observations	13
BVN	1-10-1985 to 31-5-2007	3780	905	2958	578	Archive material, interviews, observations	8

a The cases do not end at the same time because we performed them in sequential order.
b Some incidents have both the intermediary and an interacting partner as the primary actor.

cancel out disadvantages of others (Verschuren and Doorewaard, 1999; Baarda and de Goede, 2001; Yin, 2003). For example, archival research is associated with broad coverage and possibilities of unobtrusive and repeated access, although there are biases in storing and selecting records. Interviews also have upsides, such as gaining a quick insight into a topic, its background, the respondents' emotions; and downsides such as problems with recall, giving socially desirable answers, and (non-)response bias. Additionally, we also included articles taken from Dutch newspapers[32] and international scientific literature concerning the event themes. Table 5 lists statistics about the raw data of the three case studies.

6. *Identifying events from incidents*: Abbott (1984) saw events as constructs "just as 'concepts' are constructs in the usual approach". Here, incidents were translated into events through coding. During this coding exercise a coding scheme was developed and optimised, taking into account research reliability and validity.
7. *Analysis*: the database consisting of the coded events structured the data on an event theme and by this eased the building of a narrative. This was complemented with qualitative and quantitative representations of the demand articulation processes, such as learning loops, how these loops interconnect, demand articulation mechanisms, and interface strategies. In this way, the research (sub-)questions could be treated step-by-step (see next section).
8. *Triangulation of results*: the narrative, the analyses, and conclusions were presented to representatives of the intermediary, their interacting partners and more independent experts in order to obtain verification of the results found. In the case of the WGM

32 The Lexus Nexus database was used, which contains all articles of major broadsheet and regional newspapers in the Netherlands. This database was searched using keywords that at least included (all variations of) the name of the intermediary user organisation.

and the BVN the results were presented and discussed during a regular meeting of the intermediary, whereas in the VSN case a meeting was held with the managers.

9. *Conclusions are drawn concerning the research questions.* Some of them are based on a tentative comparison of the different intermediary user organisations studied.

The next section elaborates on steps 6 and 7, which explain the methodology used for each part of the research question.

4.3 Data analysis (per research question)

Previous sections laid the groundwork for this section in which we deal with the methodology used for the specific research (sub-)questions. These questions are each dealt with in turn below.

The ***first research question*** concerns *how to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?*

In order to follow the dynamics of the two learning loops of the central conceptual model (see Chapters 1 and 2), the incidents contained in the database needed to be translated or coded into qualitative event categories encompassing the different stages of these loops. These stages include: agenda-setting – demand synthesis – expression – evaluation, and self-positioning – and other-positioning respectively. Substance was added to these categories by defining several dimensions of these variables. Subsequently, these dimensions were operationalised into measurable characteristics that represent the theoretical concepts. Table 6 summarises this train of operationalisation. It explicates that the type of coding was based on classifying incidents into event categories by either counting them in ('1') or out ('0') in a non-mutually exclusive way, i.e. incidents can belong to more than one event category.

During this coding activity attention was devoted to the consistency of classification (reliability) and accuracy of interpretation (validity) (Poole et al., 2000; Yin, 2003; Baarda et al., 2005). Reliability concerns whether the results were obtained independent of chance and would yield the same findings when the case was replicated, e.g. by other researchers (level of intersubjectivity). Although an exact replication is sometimes difficult in qualitative research because observations and interviews are time-dependent, exactly documenting the procedures enhances reliability, and by this makes the investigation verifiable and insightful.

The validity of the research is about the correctness of the findings: do you measure what you intend to measure? There are several components to this validity concept, such as construct validity (do the variables and their operationalisation properly represent the concepts under study?), internal validity (are the causal relationships found influenced by other, spurious variables?), and external validity (are the results generalisable to other case studies?). Internal and external validity do not entirely apply because this study is not about causal relationships, and external generalisability is restricted in case studies to replicating the results in support of theory, as was explained above in the context of case study selection.

Table 6 - operationalisation of event categories (see sections 2.3 and 2.4 for theoretical background).

Event categories	Dimensions	Presence of statements	Content of statements
Agenda-setting	• Decisions on agenda entrance of problems, ideas, solutions, needs, etc.	1/0	Accept/reject
	• Weighing of entries		Important/unimportant
	• Selecting (prioritising) them		Pursue/not pursue
Demand synthesis	• Information gathering about problems, ideas, solutions, needs, etc.	1/0	Statements about information needed and plans to obtain it
	• Discussing and the forming of problems, ideas, solutions, needs, etc.		Statements about the pros and cons of demands, argumentations, timing of issuing, etc.
Demand expression	Expression of:	1/0	
	• Science fictions, visions, 'Leitbilder'/'guiding visions', expectations, promises		Statements on the future ("we expect...", "we anticipate...", etc.)
	• Problems, obstacles		Current situation is problematic
	• Ideas, solutions, applications		The actor acknowledges a problem, knows a direction for solutions, and has some concrete ideas about how this end state should be reached
	• Needs		The actor wants something
	• Ethical, legal and social implications		Statements on ethical, legal or social impacts
Evaluation	• Discussing validity of expression	1/0	Statements on whether expressions still hold or should be amended
	• Discussing whether other actors (re)acted on expressed demands		Statements on whether demands were heard by others and acted upon (and whether action by the intermediary is needed again)
Self-position	• Ex-ante position by intermediary	1/0	Reasoning behind operations, strategy, demands, problem-solving ('how to get from the current to the perfect end situation') stated before or after the event
	• Ex-post position by intermediary		
	• Ultimate preferences		Desired identity or attitude, desired social order or desired position in the field, major goals of the organisation ('perfect end situation')
Other-position	Other actor's opinion about an organisation's position and ultimate preferences	1/0	Objectives and ultimate goal attributed to intermediary by others

Solutions to deal with the reliability and validity questions were to document the research set-up carefully, to be aware of possible biases, to apply different kinds of research methods and data sources (triangulation), and to use intrarater and interrater tests in various stages of the research (especially during step 6 in the previous section). Intrarater tests mean that

the principal investigator rechecked the coding work for inconsistencies and instabilities. Interrater tests refer to coding performed independently by other researchers (peers) that was subsequently compared to the principal investigator's coding. This comparison led to discussions about differences and difficulties, and eventually to adjustments made to either the codes in the database or the coding scheme (Table 6). This automatically entailed an iterative approach to coding, which is not all that uncommon in event history analysis (Poole et al., 2000) and qualitative methods in general (Yin, 2003).

The resulting database containing the coded event categories was used to answer the research questions. How this was done is discussed below. Before answering these sub-questions a narrative of the event theme was provided, based on events that were identified in the database. Experts in the field and representatives of the intermediary user organisation proofread the story, and by doing so checked its validity.

1a. Does first-order learning take place inside intermediary user organisations?

First-order learning concerns explicating, concretising and narrowing-down the contents and directions of demand statements (see Table 6). While studying the event themes, we focused on:

- Whether the statements related to this event theme increased in number. Diagrams presented the cumulative growth of statements over time. These diagrams were also used to identify 'leaps' in demand statements, i.e. sudden increases in the number of statements. These leaps contributed to discerning thematically-coherent periods in the narratives. This was either because a leap signalled a certain 'break away' from then-current practice, and thus the beginning or ending of a period; or the leap was the main topic of the period itself. The subdivision in periods was subsequently substantiated by crosschecking this with the logic of the narrative and with the persons involved (through proofreading the narrative).
- Whether these statements were converging or diverging in relation to their content. We measured this by taking the sequence of demand statements concerning an event theme over time, and coded whether a statement on a certain point in time was more ('+1') or less concrete ('-1') as compared to previous statements. We aggregated these scores for each period and concluded per period whether or not demands converged or diverged in comparison with the previous period(s). Special attention was given to the question whether the convergence and divergence of demands made sense in relation to their content because otherwise these changes cannot be regarded as learning.
- Whether the direction of the demands (in favour or against an issue) was changing. We coded this in the same way as the convergence and divergence of the content of the demands: whether there was a change ('1') or no change ('0'). This was again done on the level of periods.

1b. Does second-order learning take place inside intermediary user organisations and how is this connected with first-order learning?

In Chapter 2 it was hypothesised that learning concerning demand articulation takes place in two interconnected processes: the first-order and second-order learning loops. Whether first-order learning occurred was investigated in the previous research sub-question (1a). Second-order learning was measured in the same vein, i.e. looking at the number of statements about underlying assumptions, and whether its content and direction was converging or diverging.

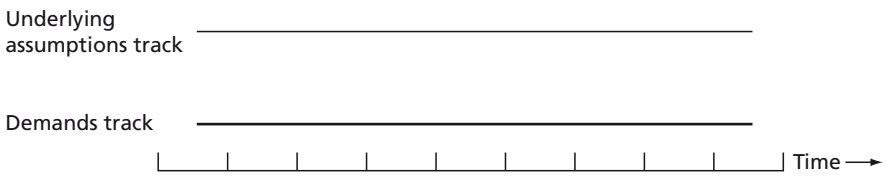

Figure 22 - following demands and underlying assumptions over time.

The second element of this research sub-question is whether these two learning loops are interconnected. To analyse this, we mapped the demand statements (first-order) and the underlying assumption statements (second-order) on two tracks followed over time (Figure 22). Focusing in particular on the periods in the event theme, we delved into the content of the statements on the two tracks and looked into whether they referred to each other or co-occurred. For example, were demand statements in a report substantiated with the objectives and ultimate preferences of the intermediary? Because we obtained a good overview of the organisation's underlying assumptions it was also possible to uncover more implicit references to second-order positionings.

1c. What 'demand articulation mechanisms' can be discerned from studying these learning processes?

Process models not only give a description of a process but by studying a particular course of a process it explains why in that instance its outcomes were more or less effective (Baarda et al., 2005). Poole and colleagues (2000) discerned four different 'archetypical' forms of processes, which they call 'motors'. They include: life cycle theory (progress through necessary pre-programmed stages), teleological theory (process with a certain end goal), dialectical theory (process based on conflict and confrontation) and evolutionary theory (variation-selection-retention). These ideal type motors, or a combination of these types, can be used to describe processes. They describe so-called cumulative causation, i.e. changes that do not result in equilibrium but support other changes (Skott, 1994). This circular process might lead to accumulation and acceleration. It should be noted that this causation could have both an unfavourable (vicious cycles) and a favourable direction (virtuous cycles).

These motors or cycles can also be discerned on a less abstract level. Both Negro (2007) and Suurs and Hekkert (in review) used Van de Ven's event history analysis to identify cumulative causation in technological innovation systems around biomass and biofuels. Here, as was described in Chapter 2, we want to find similar motors: the so-called demand articulation mechanisms.

As was hypothesised in Chapter 2 and operationalised above, the first-order learning loop consists of the following stages: agenda-setting – demand synthesis – expression – evaluation. We mapped these event categories over time and investigated whether they showed up in the order that was hypothesised in the central conceptual model. Moreover, by delving into the content of these categories and their sequence, we investigated whether the order of event categories was the result of chance, or that the event categories influenced each other in a hypothesised and meaningful way. The discerned loops were then scrutinised and characterised in an explorative way. Different circumstances or types of demand might result in a distinct filling-out of the first-order learning loops, i.e. different types of demand articulation mechanisms.

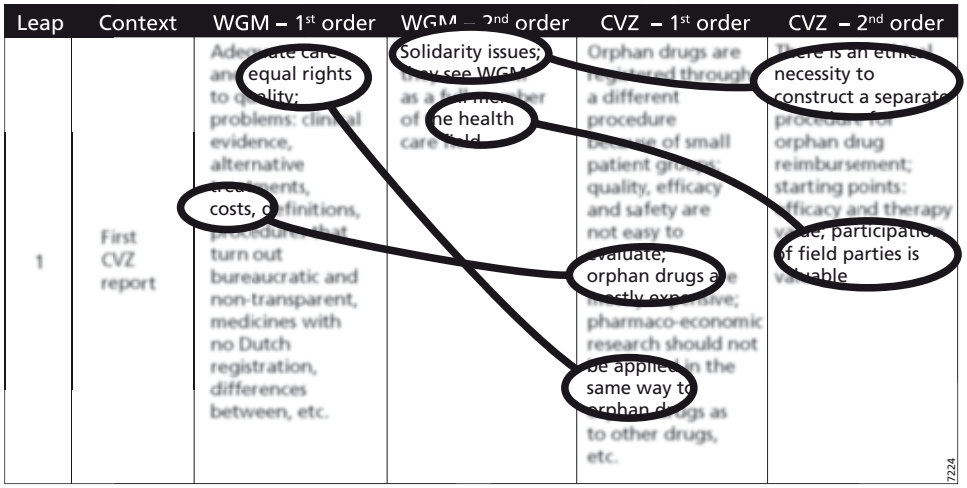

Figure 23 - indication of how first-order and second-order statements of the intermediary and its interacting partner was compared.

The ***second research question*** is about *how to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies?*

2a. Does demand articulation take place in a multi-actor innovation arena involving interactions between an intermediary user organisation and its representing actors (As) and other relevant actors (Bs)?

To answer this research sub-question, we followed first-order and second-order learning for the intermediary and their interacting partners on one event theme per case[33]. For the intermediary this had already been done in the context of research sub-questions 1a and 1b. To uncover the changes in first-order and second-order statements of the interacting partners who did play a role in the event theme, interviews were conducted with representatives of these partners and open-access material was studied, just as we discussed in section 4.2. We then examined whether the first-order and second-order statements of all actors (intermediary and interacting partners A and B) were in agreement or disagreement. That is, we compared demand statements and underlying assumptions of the intermediary (e.g. WGM in Figure 23) with those of actor B (e.g. CVZ in Figure 23) at a particular point of time on the event time line, and analysed whether or not they corresponded to each other.

33 We chose to analyse research question 2 for only one event theme because of the elaborateness of data collection, analysis and presentation. For the VSN and WGM cases this meant that a choice needed to be made about which event theme to select. We chose the event theme that the representatives of the intermediary, and the actors interacting with them, regarded as the most important topic it had been engaged in. These actors were (surprisingly) unanimous about this decision. This led to selecting the enzyme replacement therapy development for Pompe disease (VSN), the orphan drug reimbursement (WGM), and Herceptin case (BVN).

Table 7 - typology concerning the organisation of interfaces.

Types of interface	Indicators
Consultation: relevant information is generated and clarified	One-way communication (to intermediary) aimed at obtaining relevant information on certain subjects through, e.g. questionnaires and interviews
Education: understanding is raised and knowledge is shared	One-way communication (from intermediary) aimed at informing and teaching others.
Presenting, advocating: points of view are brought forward	One-way communication (from intermediary) aimed at presenting results or points of view, e.g. by publications, mission statements, press announcements, etc.
Mediation: conflicting ideas are aligned (also: negotiating)	Other parties have conflicting interests and these are managed by the intermediary through, e.g. alignment meetings, discussions, a series of one-to-one conferences.
Coordination: different interests and opinions are tuned	Alignment of current and future activities without there necessarily being conflicting interests. Examples: distribution of resources, distribution of media attention, presenting the spectrum of possible interests and opinions.
Deliberation: same as coordination but without having a predefined topic from the start	Meeting with no preconceived agenda.
Anticipation: different future options are explored and assessed (if it is about current options, it can be called prioritisation)	Distant futures are explored by deploying strategic intelligence instruments. Results include technology assessments, foresight studies, scenarios, etc. Differences in interests and opinions are summed up as well as weighed and compared.
Co-production: activities or projects are taken up in association with other actors	Organising things together, such as workshops, conferences, publishing of reports, etc.

This gave us hints about the joint construction state in which these actors could be placed. Because we determined this state per period of the event theme we could also show whether moves between the four construction states occurred over time (see Figure 14). These changes indicated the joint construction of demands on a particular issue.

2b. What strategies do intermediary user organisations deploy in the different interfaces with representing actors and other relevant actors?
Communication between the intermediary and these actors goes through so-called 'interfaces'. The *organisation* of these interfaces was characterised in section 2.5 and follow a typology. The events in the database were coded for these types making use of the indicators in Table 7.

The *interface strategies* revolve around access strategies to involve all relevant actors; empowerment strategies to supply them with sufficient (knowledge) resources to make contributions to the debate; and impact strategies to make sure that statements are taken seriously and are even appropriated. We scanned the strategies pursued by the intermediaries in interaction with other actors, mostly communicated through the interfaces. This scanning was done in an exploratory way, first classifying the strategies found under the three hypothesised strategies (access, empowerment, impact), and

second, making an attempt to deepen this classification. A difference was made between communication with actors A (represented actors) and with actors B (other relevant actors).

2c. To what extent can the joint construction of demands by the intermediary user organisation and their interacting partners (following shifts over time in Figure 14) be attributed to the interface strategies used? And how effective were those interface strategies?
The shifts in Figure 14 for the intermediary organisation and their interacting partners under study were recorded in research sub-question 2a. In this part of the research sub-question we examined the extent to which the interface strategies identified in research sub-question 2b had an influence on these shifts. Therefore, when in the event sequence a shift occurred from one state to another, we identified the strategies that were employed at the time of (or just before) the shift, and had an effect on these shifts. The extent of these effects was characterised as negative, neutral or positive.

Finally, the ***third research question*** mainly concerns the repercussions of our findings for technology development, intermediary user organisations, governments, the pharmaceutical industry, and other stakeholders, as well as recommendations based on these findings. More explicitly, the analyses of the learning processes, demand articulation mechanisms, and interface strategies obtained a clearer picture of how to organise the demand articulation. The final chapter features the conclusions and discussion after answering the three research questions for each case. This ultimately leads to answering the central research question: *how to understand the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies?* The next chapters present the findings of our study of the three intermediary user organisations.

Chapter 5

Case study Dutch Neuromuscular Diseases Association

5.1 Introduction to the Dutch Neuromuscular Diseases Association

The Dutch Neuromuscular Diseases Association (*Vereniging Spierziekten Nederland*, VSN) is a patient organisation founded in 1967 by a group of parents with children who suffered from a neuromuscular disease. At first, objectives included taking care of the welfare of and communication to patients and parents, and stimulating research into neuromuscular diseases. Quickly the patient organisation established contact with several medical professionals, scientists, and the neuromuscular charity fund 'Prinses Beatrix Fonds'. The VSN also promoted the organisation of documentation centres, and multidisciplinary teams in hospitals. The information provision and mutual help functions of the patient organisation became organised through regional working groups, and working groups that were centred on different types of neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS) and Friedreich's ataxia.

Research that would improve the diagnosis of neuromuscular diseases was first put on the agenda, as well as the importance of cooperation between scientists. The latter led to the founding of the European Alliance of Neuromuscular Disorders Associations (EAMDA) in cooperation with other patient groups in 1971. The objectives of this alliance included improving the lives of patients, coordinating and stimulating international research, and setting up comparative quantitative data inventories on therapy, diagnostics, research, prevalence, and information provision on neuromuscular diseases. Genetics and physiotherapy were the initial focal points of the EAMDA.

The research working group of the VSN occupied itself with genetics and neuromuscular diseases, and also financially supported some Dutch academic physiotherapy and epidemiological research groups. It also maintained frequent contact with medical professionals and scientists through meetings and asking advice. Meanwhile, the EAMDA, used its international character to set up research into genetics, registration of patients, and newborn screening because for these projects large numbers of patients were needed. In 1984 the VSN and the EAMDA organised an international scientific conference on Duchenne muscular dystrophy (DMD), resulting in a coordinated research effort that led to finding the gene responsible for the disease. This also marked the start of the VSN's interest into translating this genetic information into diagnostics and therapy.

In 1985 the VSN founded the Dutch Foundation for Neuromuscular Research (SONMZ) together with doctors and researchers. Its objectives included the stimulation and exchange of research into neuromuscular diseases. One year later, the EAMDA changed its objectives to put more emphasis on searching for the causes, care and cure of neuromuscular diseases, and communicating these research results. In 1988 the European Neuromuscular Centre (ENMC) was founded with the VSN as one of its initiators, together with other patient organisations such as the Association Française contre les Myopathies (AFM). The ENMC stimulated international researchers, notably through the organisation of scientific

workshops, an information gateway, and a clinical trial network. Up to mid-2007, 150 workshops have so far been held. Issues that were discussed during these workshops included diagnostics criteria, standardising clinical trials, and gene location.

In the 1990s, research stimulation on patient registration, respiration support for patients, and technical devices remained one of the key goals of the VSN, which also corresponded well with the wishes of their members.

In 1993, the research stimulation department of the VSN was expanded. The VSN channelled this by making an analysis of the organisation's 'blind spots'. In the autumn of that same year the Dutch Neuromuscular Research Support Centre (ISNO) was established, which accommodates both the SONMZ office and a network of Dutch neuromuscular researchers. It also organised courses on neuromuscular diseases. Later, in 1998, the VSN reflected once again on its research steering and stimulating role, and also widened its attention to include cooperation with pharmaceutical companies, since therapies were increasingly moving to the market. One of the diseases for which this was topical at the time was Pompe disease. Once again the VSN thought that this could best be done on the international level and co-founded the International Pompe Association.

In this context the VSN reiterated its own objectives and mission as well. Their strategic principles remained the same as before: "identify opportunities and threats on patients behalf; be constructive and cooperative; work towards upscaling (number of patients, multidisciplinary, link technological innovation to neuromuscular disease research, expert centres for diagnosis and care, stimulate European cooperation)". The organisation also increasingly used the concept of rare diseases and orphan drugs in its rhetorics coming from documents and interviews. Patient organisations should take the lead in these disease areas because other players would be less willing to do so. Patients were regarded as the most important stakeholders. "And even on this difficult domain, such as scientific research, patient organisations can achieve important results with good policy, strategic action, and purposeful cooperation." The patient organisations can serve as "lubricating oil in the difficult relationship between industry and science". Moreover, patients themselves are highly knowledgeable about their disease, and that knowledge could be used by companies and scientists. In 2006 the EAMDA increasingly started to focus on pharmaceutical research as well. The international level was appropriate to discuss drug innovations because major players like companies and regulatory agencies had an international focus. The VSN also focused their efforts more strongly on advocacy, emphasising awareness of other actors in the medical, health care and scientific sector; empowering patients; and finally attracting the attention of policymakers and the media. Besides recruiting patients for scientific projects and communicating scientific results, the VSN also tried to build networks with pharmaceutical companies, e.g. for propagating the registration of existing medicines for neuromuscular disease indications. The VSN is aware of the fact that patient recruitment does not only improve clinical trial design but for pharmaceutical companies also means market formation.

Lastly, from 2007 onwards the ENMC and VSN participated in the EU programme TREAT-NMD, together with other medical professionals, scientists and patient groups. This is a network of excellence "aiming at improving treatment and finding cures for patients with neuromuscular disorders." By taking on board patient representatives, and designing work packages related to patient needs, this initiative learns from the International Pompe Association and takes the patient perspective into account.

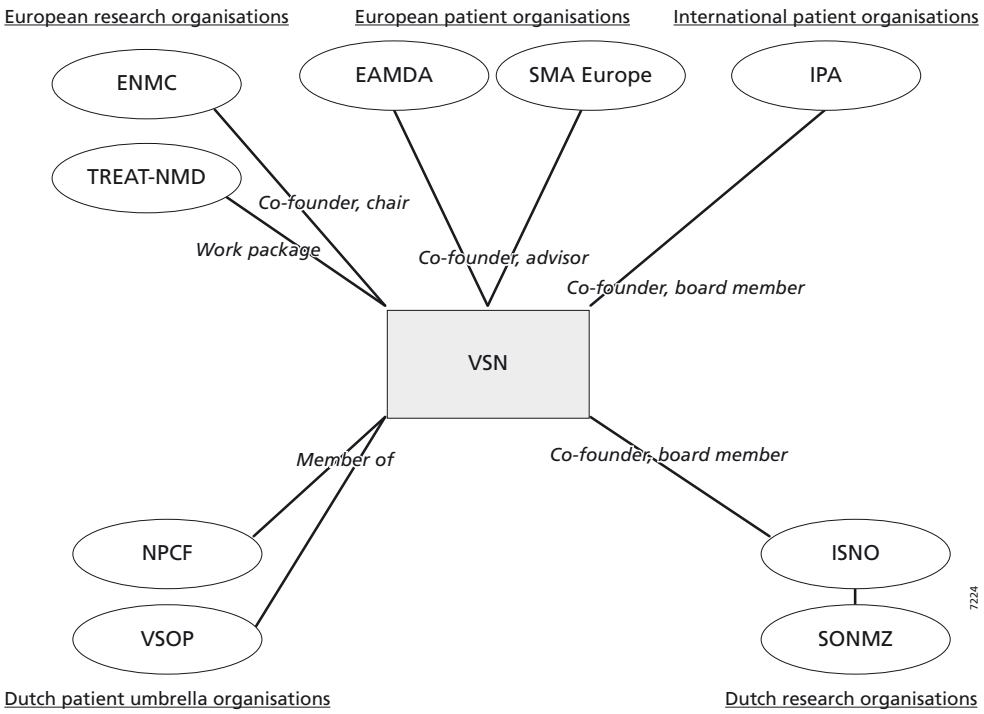

Figure 24 - network of national and international partners in which the VSN operates.

All in all, the VSN can be characterised as a representative user organisation and one of the few Dutch patient organisations that is engaged in research on diseases related diagnostics and therapies in early stages of development. It regards research as something that requires long-term planning and policy. It finds it important to be involved in vision creation and steering the direction of science and technology, and does not want to leave these matters to scientists and technology developers alone. Genetics was one of the major scientific areas for which the VSN created a vision; a vision which it propagated and committed resources to. The VSN closely monitored scientific achievements, assessed their impact, and communicated them to patients. Moreover, it recruited patients for scientific projects, but only if the projects complied with conditions on information provision, informed consent, etc.

The VSN cooperates with many organisations, some of which it co-founded and/or is a member of the board. Figure 24 illustrates this.

In this case study six different event themes are discussed, which take on the form of what Yin (2003) calls 'embedded cases'. Figure 25 shows the themes, all of which focus on therapies, in some cases for a particular disease. Some of the embedded cases concern more established therapies, including clinical trials for a drug called idebenone (Friedreich's ataxia), whereas others are more concerned with emerging technologies, such as gene therapy (e.g. Duchenne and Pompe disease) and stem cell therapy (e.g. ALS).

Most event themes deal with rare (muscular) diseases and orphan drugs, whereas others are about emerging technologies, such as gene and stem cell therapy. Both rare

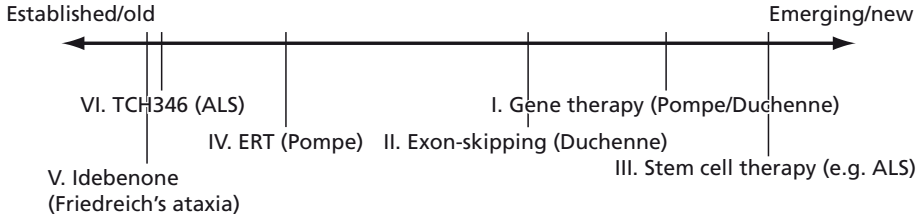

Figure 25 - overview of event themes (I-VI) ranging from emerging/new to established/older technologies (ERT means enzyme replacement therapy).

diseases (see Chapter 3) and emerging technologies bare resemblances with the emergent pharmacogenomics future.

The criteria for selecting the embedded cases were discussed in the previous chapter. Nevertheless, it should be emphasised that we focused on those drug-related cases that were prominently visible in the studied archival material and which the VSN's representatives underlined during conversations. One event theme, about the development of a drug for Pompe disease, is described more in-depth than the other themes because the VSN itself regards this as one of the most prominent cases in which it has been engaged. The embedded Pompe case is also used to answer research question 2 for this case study (section 5.3).

For the six event themes we first answer research question 1, which concerns the demand articulation processes inside the VSN: *how to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?*

5.2 Demand articulation processes inside the VSN (research question 1)

The sub-questions treated here are answered by studying six event themes (see Figure 25). The stories of these event themes are narrated as part of research sub-question 1a.

1a. Does first-order learning take place inside the VSN?

Event theme I: Gene therapy
If a patient has a defective allele, a viable and structural solution would be to replace or insert such an allele. This has been publicised as gene therapy. The main problem for this kind of therapy is how these functional alleles are placed in the target cells. So-called vectors are used to deliver these genes to the cells. Several vectors have been tested over the years, most of them viruses. Table 8 shows a brief history of gene therapy developments.

The first gene therapy applications were not expected in the field of muscular diseases. However, with the discovery of a gene related to Duchenne muscular dystrophy (DMD) this disease became a possible target for gene therapy. The gene was discovered as a result of an increase in cooperation and coordination in hereditary muscular disease research, following an international workshop about research on causes and treatment of muscular dystrophy organised by the VSN in 1984. The gene is responsible for creating dystrophin, which is a protein that takes care of muscle cell wall elasticity and strength: it binds the muscle protein

actin to the plasma membrane. A mutation in this gene causes a deficiency in dystrophin production. Patients with this disease have progressively weaker muscles. The mutation can be present on the X chromosome and is recessively inherited.

Given that hope was often spuriously and falsely created, in 1984 the VSN also founded an internal committee that would advise on policy and publications concerning new treatments. It proved to be useful in reflecting on advances in gene therapy.

For over a decade only a few research results on gene therapy and muscular diseases had been reported, and the VSN consequentially did not engage in work in this field to a large extent. In 1990 Wolff and colleagues made a "major breakthrough" (McC. Howell, 1999) by proving that gene therapy for inherited muscular disease was theoretically possible. This was quickly followed by tests in mouse and dog models for DMD. The American Muscular Dystrophy Association subsequently started a clinical trial in 1998. The increase in publications and clinical trials, as illustrated in Figure 26, suggested that gene therapy might not only be applicable for cancer, the then most often researched indication for gene therapy, but that it also opened possibilities for muscular diseases.

Table 8 - general events around gene therapy[a].

Year	Event
1968	First proposal for gene therapy: Stanfield Rogers proposed to build modified viruses into plant cells to transport information.
1970	Unsuccessful tests with papillomavirus for two girls suffering from hereditary arginase deficiency.
1980	Martin Cline (University of California) experimented with two patients with the genetic disease beta thalassaemia. These tests were done outside the US, in Italy and Israel. Critics claimed that he did this to avoid strict regulatory oversight. Although the scientific results were insignificant, it led to a heavy ethical debate, known as 'the Cline affair'.
1980s	Increase in expectations about gene therapy.
1989	Anderson, Blaese and Rosenberg performed favourable first human safety tests for gene therapy.
1990	Anderson and colleagues followed this with the first clinical trial with a four-year old patient suffering from severe combined immune-deficiency (SCID; ADA variant). Retrovirus treatment was efficacious but only temporal.
1990s	Increased knowledge about the chances and potential dangers of gene therapy. Possible candidate diseases, such as AIDS and cancer, caused patient advocacy groups to push for gene therapy R&D.
1999	Jesse Gelsinger died as participant of a clinical trial for gene therapy to cure ornithine transcarbamylase deficiency after an immune response on an injected adenovirus. Later it appeared that the clinicians had failed to comply with several rules of conduct.
2000	Alain Fischer performed a clinical trial on children with X-linked SCID in Paris and achieved durable results. Nevertheless, two of the ten participating children died because they developed leukaemia.
2000s	As a result, the clinical trials were stopped, but they resumed after regulatory review of the trial protocol. After the technological setbacks and fatal adverse reactions, the 'revolutionary' therapy had been re-conceptualised as a 'tool' by scientists, and expectations had been heavily toned down. Expectations became more realistic and there was a drop in enthusiasm and the number of clinical trials that were approved. Despite this, gene therapy again started to gain momentum from 2003 onwards.

a Based on Rosenberg et al. (1990), Cavvazano-Calvo et al. (2000), Thompson (2000), Hoeben (2001), Smith and Byers (2002), Young (2002), Brown and Webster (2004), Selkirk (2004), Schuttelaar (2007).

In the 1998 VSN annual report, just before the gene therapy hype in general had reached its peak, questions were raised about whether gene therapy would be the best direction to take for solutions because other treatment options could provide shorter-term answers. Both the Rathenau Institute for Technology Assessment and the Advisory Council on Health Research (RGO) recognised that despite the high expectations of gene therapy, the absence of results might lead to pessimism about this technology direction. Developments took longer than patients expected and too much pressure from them could work counterproductively.

By 1999 researchers were also spreading the opportunities of gene therapy to other muscular diseases such as Pompe disease. Dr. Andrea Amalfitano of Duke University presented work on a modified adenovirus that carries corrective genes to intended sites without triggering the immune system and with some level of persistence. The International Pompe Association acknowledged his work but also warned against too high expectations in the short term: "Although short term effects of gene therapy are unlikely, it has great potential for an effective treatment in the future". Genzyme, a company also working on Pompe treatments, was less enthusiastic about gene therapy. They emphasised that scientific problems, such as maintaining gene expression, would have to be solved before clinical trials could commence.

In 1999 and 2000 gene therapy was confronted with two major drawbacks resulting from clinical trials with lethal consequences (see Table 8). This meant that scientists

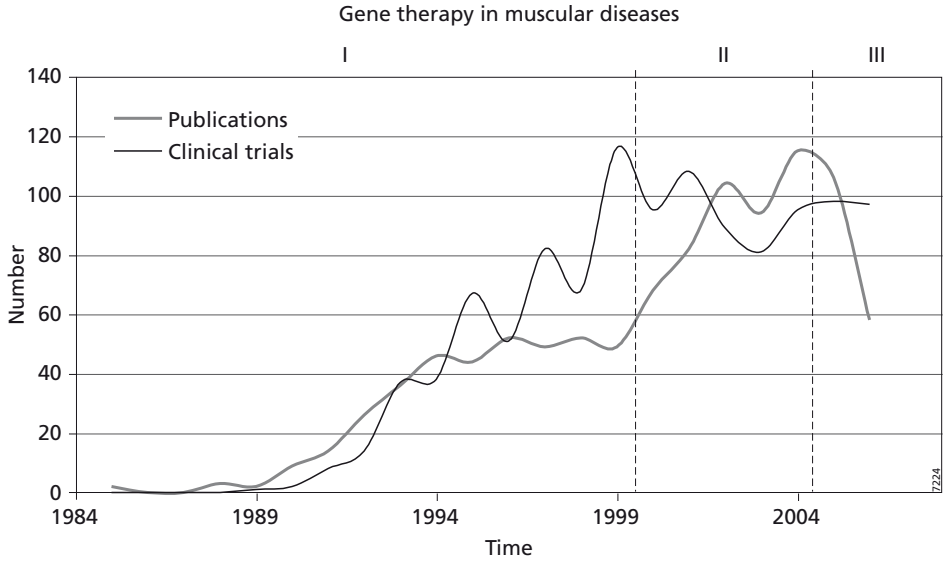

Figure 26 - number of muscular disease gene therapy publications and clinical trials over time[a]. The three periods are in line with the periods identified in this event theme in Figure 27. The significance of including these periods here becomes clear when answering sub-question 1b for the gene therapy theme.

a Publications: searched in scopus.com for ("muscular" OR "duchenne") AND ("gene therapy" OR "gene transfer"); clinical trials: http://www.wiley.co.uk/genmed/clinical/

encountered more resistance if they wanted to pursue the gene therapy route, or they simply decided to abandon this alternative. Others proceeded with their research using arguments that clinical trial protocols were not followed correctly (in the Gelsinger case) or that the patients would have died anyway (in the Paris case). Also some patient alliances on genetic diseases advocated these views, stating that the balance between positive and negative news was more geared towards the latter. For example, the emphasis was more on the patients who died in the Paris clinical trial than on those that survived.

At the end of November 2001 the European neuromuscular Centre (ENMC) organised a special workshop on Duchenne dystrophy, discussing the advent of gene therapy. Research was being conducted in animal models, although preliminary safety studies were undertaken as well. Around that same period, scientists from Leiden University Medical Centre presented results from their experiments on exon-skipping for DMD (see event theme II).

Meanwhile, the VSN started to assume the role of assessor of scientific findings aimed at providing sufficient and balanced information to their members with regard to gene therapy and later also for other technologies. Patients constantly scan the Internet for information that is not necessarily to be trusted. Therefore, the VSN started an overview of scientific research in which also a short explanation and significance were stated.

In 2004 scientists successfully treated mice and isolated human muscle cells with DMD with gene therapy methods but these methods would still have to be proven in humans. Dr. Amalfitano also presented animal model results for Pompe disease and emphasised the upcoming difficulty in translating these results into clinical settings.

In this context Genzyme put gene therapy firmly on the agenda as the next step in their Pompe disease programme alongside second-generation enzyme replacement therapy. Nevertheless, Genzyme remained cautious when a representative was asked about promising technologies: "Looking ahead twenty years, there are two that I'm very excited about. One of them is gene therapy [...] This is a huge subject of debate, which gives people the impression that one day it will solve all the world's problems. People underestimate how long that will take. That's how it always goes in biotechnology. We make a new discovery, and then we forget that it takes ten to twenty years before we can use it to treat patients."

The VSN commented on gene therapy in its 2005 annual report on a rather positive note: "Of course we spoke about gene therapy ten, fifteen years ago [...] but in general these dreams did not root in reality [...] In recent years increasingly hopeful messages surfaced. Bit by bit puzzles are solved and compounds are discovered that might be efficacious for certain muscular diseases. Trials are taking place, not only in animals, but also in humans. These are exciting times." In the annual report of 2006 this was repeated and the emphasis was put on the number of scientific achievements over the last decade. The VSN found it important to be involved in clinical trials, e.g. by producing patient information, in order to manage the expectations patients have about potential therapies.

In the gene therapy event theme the VSN was mainly occupied with articulating expectations, promises and visions as is illustrated in Figure 27. Later, in answering research sub-question 1c we return to what we call this 'management of expectations'. Other demand types, such as problems and ideas, were not present. This is mainly because the developments are still in their early stages, and thinking about concrete needs and ideas is more problematic. Neither did the VSN provide many ethical viewpoints, because its board thought that its members might be divided on this topic as well.

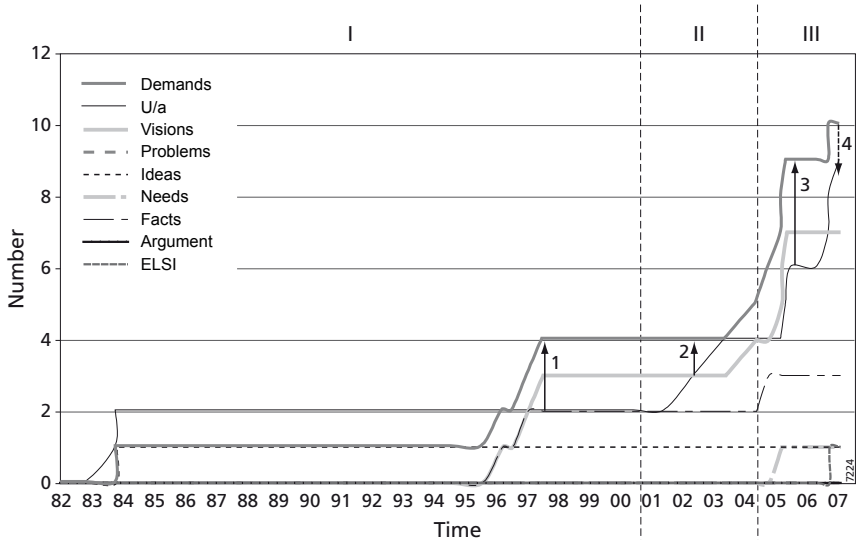

Figure 27 - cumulative number of demand and underlying assumption statements in the VSN event theme on gene therapy. The arrows are explained in answering research sub-question 1b.

Figure 27 discerns three content-coherent periods into which the event theme can be subdivided (I-III). They correspond to three striking leaps in the number of demand statements. The level of abstraction remained the same over all three periods (Table 9) and no changes occurred in the level of concreteness. Concerning the direction of the demands it was noted that from the VSN annual report of 2005 onwards gene therapy was regarded as a development that could become reality in the mid-term as opposed to a long-term time frame. This low degree of increase and changes in concreteness and direction of demand statements, leads to the conclusion that first-order learning is only moderate for this event theme.

Event theme II: Exon-skipping therapy for Duchenne muscular dystrophy

The previous event theme touched upon gene therapy in the context of Duchenne muscular dystrophy (DMD). The VSN had been working on DMD from the early 1980s onwards and particularly supported research projects in the Netherlands. The VSN were the initiators of these projects, assisted in finding the finances and emphasised the needs of patients with a chronically-debilitating and – ultimately – lethal disease (Nelis, 1998). These projects included a project to find genetic markers (or 'DNA probes') for DMD conducted by Prof. Peter Pearson (Leiden University) for the benefit of finding a diagnostic tool, and epistemological research by Dr. Leo ten Kate (Groningen University; both started in 1982). The former project was inspired by recent findings at the time showing that the DMD gene was located on the X chromosome, and by the first genetic mapping of the human genome resulting in localising disease genes of single-gene disorders such as Huntington's disease following genetic markers ('Restriction Fragment Length Polymorphism', RFLP). The VSN regarded these research projects as successful. The VSN's task was to inform the patients participating in the projects, to present the results to the media, and maintain contact with other patient groups abroad.

Table 9 - changes in concreteness and direction of demand statements (gene therapy event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	Scientific advances	Internal advisory committee on new treatments founded for management of expectations.	-	-
		Annual report: Gene therapy best direction of solutions? There are other options that could provide answers in the shorter term.	No change	No
II	Scientific advances	The VSN started to draw up an overview of scientific research that includes annotations (explanations and significance).	No change	No
III	Scientific advances	Annual report: Positive about gene therapy developments.	More	Yes
		Annual report: Positive about gene therapy developments.	No change	No

These projects were followed by a workshop organised in 1984 that enhanced coordination and cooperation between the leading institutes that were searching for the gene location of dystrophyn production. A total of 32 leading scientists and representatives of large Duchenne patient groups and charity funds from the US and UK were present. These patient's organisations presented their approach that primarily focused on financing and steering scientific research. DNA research, uniform patient registries, neonatal screening, epidemiology, and potential treatment options were part of the workshop agenda. One major outcome of this workshop was the emphasis on international cooperation between scientists as a prerequisite for success.

The scientists presented the results they had achieved up to then and it appeared that many pieces of the puzzle, i.e. the identification of the DMD gene, were already there. It was agreed that the Pearson-group would coordinate the search by collecting and distributing DNA probes that could be used while carrying out tests on Duchenne patients to find out whether these markers were a valid predictor for the disease.

As was mentioned in the previous section, the VSN regarded this meeting as the starting point of a scientific journey that ultimately ended in identifying the gene in 1986 by Prof. Louis Kunkel and his group at the Children's Hospital in Boston. Later, Kunkel and colleagues identified the mutations that lead to differences in DMD as compared to the related Becker muscular dystrophy (BMD). Most DMD patients do not produce any dystrophin protein because of out-of-frame deletions in the gene, whereas other DMD patients and the BMD patients have point mutations that lead to a reduced production of the protein (Davies, 1997). Moreover, the VSN regarded this collaborative effort as an example for research on other neuromuscular diseases, which resulted in the foundation of the European Neuromuscular Centre (ENMC). One of the main topics on the Centre's agenda was to find a cure for DMD.

A second EAMDA workshop on the epidemiology of DMD soon followed. The participating patient groups were convinced of the importance of a patient registry because this could make the planning for diagnosis, information provision, care facilities, and treatment easier. It was decided to found a European registry centre. In the Netherlands, the VSN positioned itself as having a liaison function in the setting up of the Dutch registry. The third 1984 workshop focused on treatment of DMD. One of the topics was the

wrongful hope that was sometimes raised among patients about new treatments and how this should be dealt with. The research on gene identification and related genetic diagnosis by Pearson also continued. In 1985 the combined international collaboration resulted in a genetic diagnostic tool that became part of clinical application.

The VSN had played a large part in stimulating and initiating research and development by organising international workshops, creating finances for projects, and supporting researchers in their search for research subjects. The position the VSN had taken up, namely that research regarding neuromuscular diseases and their genetic sources was important, was put into practice, as well as acknowledged by other actors, such as scientists and clinicians. The VSN also contributed to the fact that the resultant diagnostic test was effortlessly implemented in clinical practice because it had already created a demand among patients and physicians (Nelis, 1998). After the identification of the DMD gene, scientific efforts were put into different strategies to build further on this discovery and to find treatment options.

At the end of November 2001 a special ENMC centennial workshop was organised about the therapeutic possibilities in Duchenne Muscular Dystrophy. Judith van Deutekom, together with Gert-Jan van Ommen and others from Leiden University Medical Centre (LUMC) had published about a possible therapy just before the workshop (Van Deutekom et al., 2001).

Their proposal was based on the antisense biological mechanism. In standard gene expression DNA sequences in the gene are transcribed into pre-mRNA. This pre-mRNA is then processed to a shorter mRNA product through 'splicing': the coding parts of the gene (exons) are spliced together after the deletion of the intervening sequences (introns). mRNA subsequently instructs the ordering of amino acids that form a protein (translation). The complementary oligonucleotide (strand of nucleic acid) that can block the translation is called an antisense RNA. Antisense therapy is about inactivating the translation process by applying antisense oligonucleotides and by doing so inactivating the gene.

In DMD some exons are not present (deleted) and in this way cause the interruption of the reading of the exon-sequence and ultimately the production of a truncated dystrophin protein. To restore the so-called open reading frame it is necessary to 'skip' the stop-inducing exon. This exon-skipping is done through the binding of antisense oligonucleotides to the pre-mRNA, which blocks the exon. The resultant in-frame transcript is the same as that of patients with the comparatively less severe Becker muscular dystrophy.

Van Deutekom and colleagues tested this hypothesis in vivo in an mdx mouse model, and in vitro in human DMD muscle cells for skipping exon 46, which is the most frequently occurring DMD-causing mutation. The feasibility of exon-skipping was shown in these two tests, but more work needed to be done on targeting other exons, better understanding the biological processes underlying exon-skipping, making a chemically stable drug, and designing a safe and efficient delivery system (Van Deutekom and Van Ommen, 2003).

In October 2004 the ENMC organised an International Workshop on "Antisense Oligonucleotides in Duchenne muscular dystrophy" in Naarden, the Netherlands. Two European research consortia were present, as well as other prominent scientists in this field, the representatives of four companies, and a parent's representative. The objective was to talk about the planned clinical trials by these consortia building on the recent work on exon-skipping and comparing trial protocols. The first consortium (Dutch/Belgian) consisted of scientists from LUMC, Amsterdam Medical Centre, Leuven University, and two companies (Prosensa and Afforce Healthcare) working on the Leiden exon-skipping

concept. The second consortium was mainly composed of scientists from several Newcastle and London universities and hospitals.

During the workshop a representative of the United Parent Project for Muscular Dystrophy (UPPMD) discussed the patients' expectations and confusion about the clinical trials. She claimed that for DMD patients the "concept of being made 'better like a patient with BMD [being a milder version of DMD]' is not very clear" because DMD patients probably had met only patients with severe versions of BMD. She ended by claiming "while this is a very exciting time for the DMD community, it is very important not to get carried away by the enthusiasm and plan carefully each individual step so that any possible side effect or damage to children taking part in these studies is avoided". Moreover, she regarded collaboration between scientists as imperative for rapid advances.

The workshop concluded with the intention to form an international consortium working on antisense oligonucleotides in neuromuscular diseases aimed at cross-validating clinical trial results, working on new mouse models, and disseminating the latest results through a bulletin and websites. The ENMC took up this initiative and made their resources available for these purposes. It saw itself as "an inclusive catalyst for future collaborative research" and also wanted to keep the options open for other research groups to join. It was also proposed to organise another such a workshop to discuss the trial results on local administration and make progress on systemic delivery systems.

Several advances in science and business regarding exon-skipping occurred. It was envisaged that the Dutch/Belgian consortium would start with their small 'first-in-man' trial before the end of the year. Prosensa received the Orphan Drug status of both the FDA (2005) and the EMEA (2006) for their exon-skipping therapy. Moreover, the UK consortium too planned to start their clinical trials at the end of 2005.

At the beginning of 2007 the exon-skipping research results intensified the feeling that treatment was near. The Dutch governmental subsidy provider for medical research (ZonMw) regarded the involvement of the Duchenne Parent Project, a dedicated disease advocacy group associated to the VSN, in the exon-skipping developments as important. In turn, the VSN met up with the Duchenne Parent Project to convey what it had learnt during its advocacy for Pompe disease therapy. Moreover, the EU network of excellence TREAT-NMD was launched on the 1st of January 2007 which included medical professionals, scientists, businesses, and patient organisations such as the VSN. DMD formed one of the focal disease areas of the network, because they first wanted to learn how procedures and mechanisms work in this disease in order to apply them later to other muscular disease types. TREAT-NMD "will provide an infrastructure that will allow the neuromuscular community to address the challenges of developing new therapeutics and diagnostics in a coordinated and integrated fashion".

The ENMC and TREAT-NMD organised a workshop about the planning of phase I/II trials using systematically delivered antisense oligonucleotides in DMD in March 2007. Scientists and companies discussed their findings and plans for clinical trials. This workshop resulted in the planning of a TREAT-NMD workshop about outcome measures of the clinical trials and the set-up of a web forum to further discuss the protocols.

The VSN and its working group DMD was in the meantime engaged in informing their members about the new treatment options. To do this, among other things they invited scientists and other sources of information to answer questions about DMD research and development. Among the questions posed were, for example: what were the chances of

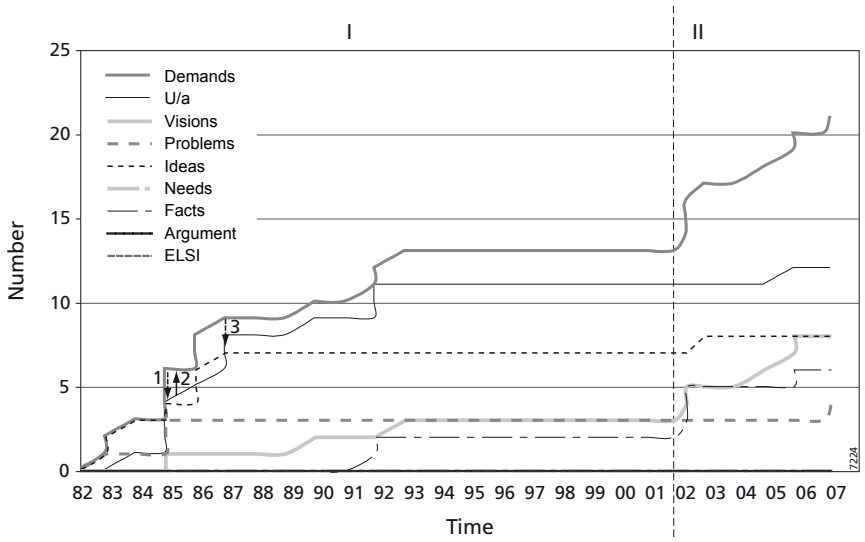

Figure 28 - cumulative number of demand and underlying assumption statements in the event theme on exon-skipping. The arrows are explained in answering research sub-question 1b.

being enrolled for clinical trials, the necessity of clinical trials, and how long will it take for a DMD therapy to enter the market?

In June 2007 the Association Monégasque contre les Myopathies and the Duchenne Parent Project France organised a Round Table meeting. The objectives of the meeting included discussing the progress from phase I trials in DMD to the development of therapies in clinical use. TREAT-NMD, which presented itself during this meeting, hoped to learn from such trials for future developments: they "will begin to collect this kind of information systematically as a resource for the community in collaboration with the teams performing these studies." Moreover, TREAT-NMD envisaged a role for itself as a discussion partner with regulatory authorities and funding actors. In this context it had learnt from how the International Pompe Association (IPA) was engaged in the Myozyme development through IPA and VSN representatives.

What is surprising in this event theme on exon-skipping is that the VSN itself has not been engaged that much, whereas interacting partners such as the ENMC *were* involved. Figure 28 and Table 10 show that the majority of demand statements were made in the early part of the theme, which is all the more striking because the exon-skipping method did not come to the fore until 2001 onwards. In the first part of the theme (I; before 2001) the VSN worked intensely with Dutch scientists and (financially) stimulated investigation of the genetic basis of DMD. Therefore, in this period many ideas were proposed, some of which were becoming increasingly concrete, e.g. to set-up an epistemological project to serve as a registry including all DMD patients. In this period, the VSN was also engaged in founding European platforms to stimulate research into neuromuscular diseases, not in the least coordinating the setting up of a European-wide registry. This would also explain why later on in the event theme (period II), the bulk of demand statements originated from these international organisations. The VSN confined itself to articulating visions, the same as it had done in the previous event theme about gene therapy. Not only the toning down of

Table 10 - changes in concreteness and direction of demand statements (exon-skipping event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	Stimulating scientific advances	VSN initiated two scientific projects.	-	-
		VSN co-organised an EAMDA workshop emphasising and leading to international cooperation between scientists as a prerequisite for successful DMD gene location.	More	No
		Second EAMDA workshop: epidemiology of DMD. VSN took on a liaison function in the setting up of the Dutch registry.	More	No
	Scientific advances	Third EAMDA workshop: one of the topics was the wrongful hopes that were sometimes raised about new treatments and how this should be dealt with.	More	No
		Annual report: great expectations about the human genome project and its potential for unveiling the secrets of diseases like DMD.	More	No
II	Share information	VSN shared with the Duchenne Parent Project what it had learnt during its Pompe disease advocacy efforts.	More	No
		VSN informed its members about the new treatment options.	No change	No

expectations featured in these demand articulations but also the vision that the DMD model could be used for other muscular diseases, while at the same time one could learn from experiences from the event theme (IV) on Pompe disease, e.g. concerning clinical trials and reimbursement. Thus, first-order learning has been moderate in this event theme so far.

Event theme III: Stem cell therapy

Stem cells are cells that have two distinctive characteristics: they can differentiate into various specialised cell types, and they can renew themselves practically limitless (proliferation). After conception, the fertilised egg divides itself into cells that are totipotent: they can take on any identity. A few days later the blastocyst is formed of which the inner cells are pluripotent. These are the so-called embryonic stem cells. The umbilical cord of newborns contains stem cells as well. Adult humans also possess stem cells in almost all organs, the adult stem cells, but these are less easy to isolate and are present in much lower quantities. On the other hand, embryonic stem cells are more controversial because their extraction requires destruction of embryos or therapeutic cloning. Just as with pharmacogenomics, the concept of stem cells had already been attracting attention since the 1960s, and the 1990s and 2000s saw an increase in developments (see Figure 29)[34]. Examples include the production of embryonic stem cell lines for humans in 1998 by Thompson and colleagues, and the alleged creation of embryonic stem cells through cloning in 2004 and 2005 by the Korean scientist Hwang Woo-Suk, which later proved to be a fraudulent claim.

34 Publications were extracted from Scopus searching for (TITLE-ABS-KEY("stem cell")).

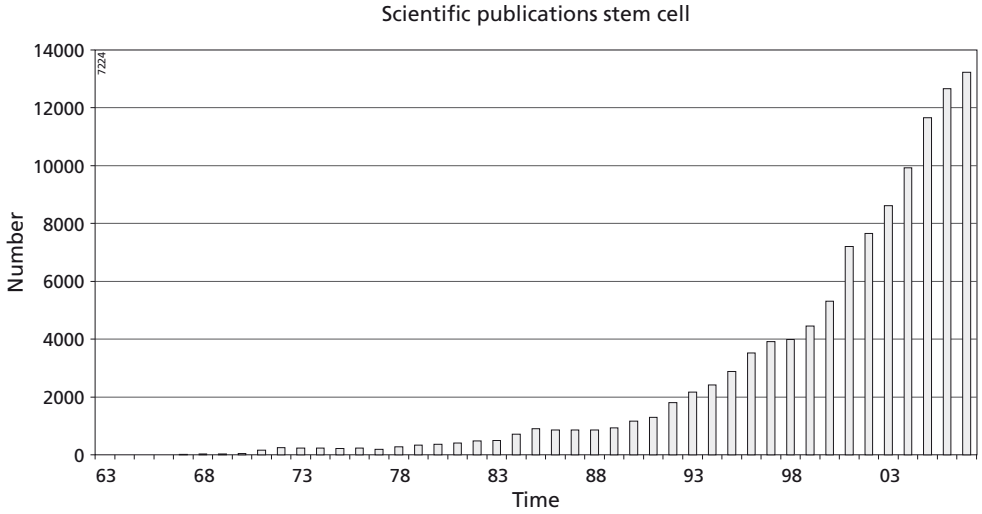

Figure 29 - number of stem cell publications over time.

Stem cells can be used to specialise in any kind of cell and in this way can contribute to repairing damaged tissue. Currently, stem cells from bone marrow or umbilical cord are used to treat patients with cancer by replacing blood cells that have been damaged by chemotherapy. Other potential areas of application include heart damage, Parkinson's and Alzheimer's disease, diabetes, and burns. None of these treatments are available at present, and for most of these applications it will take another decade before full development.

The 13th International Symposium on amyotrophic lateral sclerosis (ALS) and motor neurone disease (MND) in Melbourne in November 2002 presented the results of a pilot study conducted by Italian scientist Mazzini in which a patient's own stem cells were isolated from bone marrow and subsequently injected in her spinal cord. The premise of the project was based on tests performed on mice suffering from ALS, which showed life prolongation but no increase in muscle strength. Critical questions were posed regarding the scientific basis, long-term effects, safety, and delivery of the stem cells. Despite the promising and hopeful approaches, the chairman of the conference concluded that a great deal was still unknown and that a reserved attitude towards application of the technology on humans should be taken. At the next conference in Milan a year later, Mazzani reported on the follow-up. Seven patients took part in the tests and it appeared that none of them suffered from any adverse side effects, but effects were not easy to explicate at such short notice. Some conference participants were quite positive about the project because delivery work of this kind would become topical when the right stem cells become known in the future. Nevertheless, others were quite critical about the "careless" use of patients without preceding these tests with animal experiments and before gaining more knowledge about the side effects.

The VSN drew up a report about the conference for the benefit of its members and stated that stem cell therapy was then unavailable for ALS patients, but that scientists called the results hopeful. The VSN used its website to post these kinds of reports and annotated versions of scientific publications, as was also the case in event theme I on gene therapy, in order to provide its members with balanced information.

Meanwhile, the Dutch government slightly changed its position on stem cell research based on two reports by the Health Council creating more opportunities for stem cell research. In June 2002 the Dutch Embryo Bill came into effect, which stated that it was prohibited to create embryos for scientific research on embryonic stem cell lines, but that it was permitted to do so with existing embryos, e.g. remaining after in vitro fertilisation ('rest embryos'). It was also agreed that this ban would be lifted in the future if stem cell research leads to medicines for serious diseases. In June 2004 this Bill was evaluated and the Ministry of Health saw no reason to amend it. The Ministry regarded stem cell research as highly emergent: while there was a great deal that still went wrong, the expectations were high. The VSN reacted to this by stressing that stimulating a sound national and international research infrastructure should also be taken into account when making these decisions.

The Mazzani research project was quickly followed by news from a Chinese physician, Dr. Huang Hongyun, who offered a new therapy for ALS based on injecting stem cells into the spinal cord. He received much media attention around the world and patients were said to show "subjective" muscle improvements that could not been measured or compared to a placebo treatment. In September 2004 the ALS Centre, in which Dutch scientists are organised and which are in frequent contact with the VSN, reacted on this by stating that Huang's reputation and the side effects were unknown, and the surgical operation was not without risk. They claimed that stem cell therapy should first be well researched and advised patients not to go to China for treatment. A month later the first Dutch patient to visit the Chinese physician recounted his experiences in a newspaper. He did not know at that time whether the therapy would have a long-lasting impact but he was feeling better. He did not want to raise the hopes of other ALS patients but he himself had great faith in Huang's achievements despite the views of the ALS Centre. Through the VSN website the ALS Centre reacted by claiming that they were "reserved" about the Chinese therapy because it had not been subjected to internationally-agreed scientific and ethical criteria. The Centre found it inappropriate to treat patients with a severe disease such as ALS with the Chinese therapy that is extremely expensive and had neither been proven effective nor safe. The scientists could imagine that in spite of these reservations, patients still wanted the treatment. For them, the Centre offered care and monitoring. This offer was also meant to keep track on whether the treatment was really working.

Many other national and international media channels covered the issue in November-December 2004 and the VSN reacted with a statement on its website. They agreed with the Dutch ALS Centre and the Flemish ALS-Liga that it was "immoral" to treat patients for a great deal of money (30,000 Euro) without published scientific evidence proving efficacy or safety. However, the VSN understood the difficult situation that faced ALS patients, and still thought that the decision to undergo treatment would remain a private one. The VSN referred their members to a questionnaire that would provide insight into whether or not a patient should decide to pursue a therapy. Moreover, the organisation made a request to Huang for more information.

The VSN reported on several scientific publications and conferences, such as the annual ALS conference in Philadelphia. The Huang therapy was fiercely debated and it was disappointing that Dr. Huang was not present himself, although the conference organisation had explicitly invited him. A Dutch representative stated that it was Huang's moral obligation to present his results – the content of the findings and the related promises – and in this way stimulate further scientific research on ALS.

The ALS Centre tried to react once more on the expectations that had been raised by the Italian and Chinese developments by providing a statement containing scientific arguments. Problematic hurdles that would still have to be overcome were raised, such as the subsistence of stem cells, the formation of connections between neurons and muscle fibres, etc. It once again questioned the ethical aspects around existing stem cell therapies, as well as more specific issues regarding the Chinese therapy, such as the unproven effectiveness, the physical and emotional side effects, the fact that the positive impacts were experienced almost immediately after surgery combined with the inability to stop further progression of the disease.

In April 2005 the Belgian ALS-Liga celebrated its tenth anniversary by organising a conference. The organisers presented a scoop: they had invited Dr. Huang to speak about his therapy. His presentation was not very clear and the scientific argumentation remained somewhat vague. He retorted to allegations of his resistance to organise a placebo-controlled trial by claiming that Chinese legislation would not allow prescribing patients with placebo treatments. He also answered questions about his custom to inject anabolic steroids in patients, something a Dutch nurse had observed. While some delegates claimed that Dr. Huang was a fraud, others still believed in him and his therapy.

In the meantime, the VSN continued to inform its members and other patients about stem cell science and technology. The organisation stated that although this kind of therapy is highly promising, it remained emergent. Mouse experiments were undertaken, for example to investigate the prolongation of stem cells. Two applications were envisaged for ALS: first the replacement of motor neurons, and second the slowing down of neuron cell death. Progress on the latter was illustrated but clinical use was still not expected in the near future.

Special attention was paid to a Dutch company called Cells4Health, which in the autumn of 2005 appeared on the radar of both the VSN and the ALS Centre and its medical specialists. This company was offering stem cell treatment and had already treated some ALS patients. With the help of an associated medical professional the VSN took a stance on Cells4Health. This company had responded to questions about their therapy. For example, they had explained how their therapy worked: blood was removed from the patient's bone marrow, and after a week of isolating and growing stem cells it was injected again into the blood. Scientists reacted to this by saying that this treatment could never work because the nervous system was protected from the blood by the blood-brain barrier. In a meeting between the medical specialists and the VSN the therapy was said to be ethically inappropriate, worthless and potentially unsafe. One medical specialist also sent a letter to the Inspection for Health Care to urge them to take action. The Inspection acknowledged the problems but said that they only could react if things went wrong.

At the end of 2005 MP Arib asked questions in parliament about stem cell therapy offered by Cells4Health, following a newspaper article and pressure from medical specialists. The questions were about the licenses of this company, the assumption that it provided "misleading" information, and that there was no scientific evidence to support the therapy. Moreover, she asked for an in-depth investigation by the Inspection for Health Care and measures that would offer better protection for patients. The Ministry of Health answered that the actual storage and treatment of the stem cells took place abroad, which meant that it fell outside their jurisdiction. Nevertheless, the Ministry of Health pointed out the fact that the Inspection was at that time investigating Cells4Health. The Inspection was to examine whether the information provided was correct, prompted by company

statements underlining that the treatment could help to revolutionise stem cell therapy. Furthermore, the Inspection investigated whether the company complied with legislation pertaining to experimental research, i.e. obtaining informed consent, and obtaining approval from a medical ethics committee.

In January 2006 two English websites mentioned the visit of an English Friedreich's ataxia patient to a private clinic for preventive therapy (Preventief Medisch Centrum) in Rotterdam. She paid 17,000 Euro for a treatment that consisted of injections of stem cells cultivated from blood from the umbilical cords of healthy babies in a Swiss laboratory. The clinic stated on its website that "the regenerative effects [of stem cells] and the clinical results are often spectacular". The VSN asked the opinion of their associated medical specialists who were either surprised or negative. A patient of one of these doctors had already used the therapy. The VSN regretted the claims made by the clinic and found them misleading. The organisation also bemoaned the fact that the clinic would not take part in follow-up monitoring done by medical specialists. The VSN sent a letter to the clinic asking them for more information about licenses, treatment protocols, and scientific evidence about the effectiveness of the treatment.

At the end of April 2006 a large newspaper article drew attention to the problems of the two stem cell therapy companies once again. A Cells4Health executive explained that the drug R&D pipeline was dry and if companies had to wait for facts or confirmation through clinical trials, it means that patients must wait "unethically" long. Moreover, he claimed that he did not promise anything, but just wanted to improve the quality of a patient's life. Medical specialists explicated their main reasons for being against this type of therapy. The costs for the therapy were high, and the treatment was not proven to be effective or safe. Some phrases and metaphors were used as rhetorical devices to underline their argument: "charlatans", "stem cell cowboys", "stem cell piracy", "stem cell hype", and "unauthorised greed". Also the positions of the Inspection and the Ministry of Health were explicated. The Inspection could only act after unlawful or dangerous events, while the Ministry at that time took a liberal view on society and did not prioritise restricting the patient's freedom of choice.

Despite these viewpoints the Inspection for Health Care reacted a month later on pressure coming from the medical profession, patient groups and the media about the treatments that were offered in the two Dutch companies, Cells4Health and 'Preventief Medisch Centrum'. The Inspection stressed the high costs, the risks involved and the unknown consequences, and hoped that patients maintained a cautious and reserved approach to these therapies.

The VSN appreciated this statement but wanted the Inspection to be more rigorous. The availability of these therapies in the Netherlands could give patients the illusion of reliability and false hope. The VSN wanted the Ministry of Health to react to this "quackery". Only in October 2006 did the Inspection order the 'Preventief Medisch Centrum' to stop treating patients with their stem cell therapy because they could not sufficiently underpin its safety. Also the Ministry of Health issued a new rule that banned the clinical application of stem cells because of the emergent phase of this technology. At the same time, the minister acknowledged the promises, the potential safety and efficacy issues: only academic medical centres were allowed to use stem cells in an experimental research setting.

The VSN became engaged in the stem cell therapy debate from 2001 onwards; just at the time that stem cell literature experienced a large boom (Figure 29). The demand

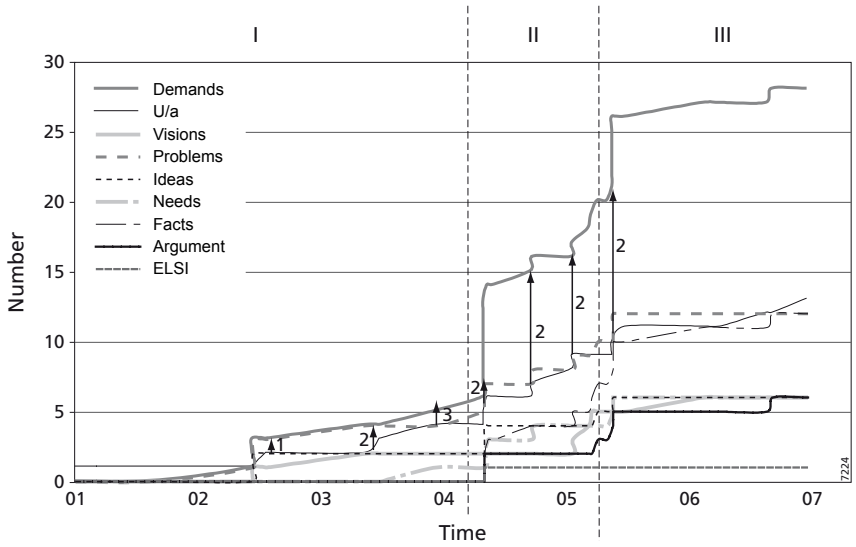

Figure 30 - cumulative number of demand and underlying assumption statements in the event theme on stem cell therapy. The arrows are explained in answering research sub-question 1b.

statements made were largely problem-driven as is illustrated in Figure 30. Numerous scientists jumped on the 'stem cell bandwagon' but some of them actually tried to sprint ahead it. This caused uneasiness among their peers because scientific norms were sometimes violated, e.g. by skipping animal or placebo-controlled testing (period I). This had repercussions on the commercial level as well: some scientists made the move to the clinic with their therapies that were neither proven to be effective or safe. The VSN first had to deal with a physician in China (period II) and later with two private medical centres in the Netherlands (period III).

Table 11 shows the changes in concreteness and direction over the different periods of the stem cell therapy event theme. It can be concluded that both the number and level of concreteness of the demand statements increased over time. Therefore, first-order learning occurred in this embedded case in a more advanced way.

Event theme IV: Enzyme replacement therapy (ERT) for Pompe disease

Pompe disease (glycogen storage disease, acid maltase deficiency) is a genetic, metabolic disorder causing progressive skeletal muscle weakness. The low prevalence, estimated at 1 in 40,000 births (Martiniuk et al., 1998), makes it a rare disease. Glucose is converted into glycogen in the cell's cytoplasm in order to store energy. Through a process called autophagy some of this glycogen is wrapped into a membrane, and transported to lysosomes. A lysosome is an organelle which contains enzymes that digest proteins, lipids, etc. The captured glycogen and the lysosome merge, and one of the digestive enzymes, acid alpha-glucosidase (GAA), degrades the glycogen to glucose (Figure 31).

Pompe patients have an inherited deficiency in the production of acid alpha-glucosidase, which causes glycogen to accumulate inside lysosomes. Pompe disease was one of the first identified, so-called storage diseases (Fabry and Gaucher disease would follow later). The precise route from glucogen abundance in lysosomes to skeletal muscle weakness is as yet

Table 11 - changes in concreteness and direction of demand statements (stem cell therapy event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	Annotations to research	Stem cell therapy could be beneficial but was then unavailable.	-	-
		Reaction on new stem cell bill: should also take the position of research infrastructure into account.	More	No
II	Chinese ALS therapy	Chinese scientist's reputation and side effects unknown; operation risky. Stem cell therapy investigated first. Advice to patients to refrain from going to China.	N/A	N/A
		Therapy did not apply to international scientific and ethical criteria, and it was wrong to treat patients with it. ALS Centre offered monitoring for those who still wanted to go.	More	No
		It was "immoral" to treat patients for a large sum of money without scientific evidence of safety and efficacy. However, the patient's decision remained a private matter. The monitoring was underlined.	More	No
		Request to Huang for more information.	More	No
		Report on annual ALS conference where Huang therapy was fiercely debated. It was Huang's moral obligation to share his results.	No change	No
III	Two Dutch stem cell companies	Stem cell therapy was still very promising, but remained emergent. The VSN asked questions about a stem cell treatment offered by Cells4Health.	More	No
		After consulting scientists the therapy was billed as ethically inappropriate, worthless and potentially unsafe.	More	No
		The claims of the company were misleading. It was bemoaned that it would not take part in follow-up monitoring.	More	No
		Letter to the company asking for more information about licenses, treatment protocols, and scientific evidence.	More	No
		Requesting the Inspection for Health Care to be stricter. Availability of these therapies could underline the illusion of reliability and false hope. The ministry should react to this "quackery".	More	No

poorly understood, but although this process occurs in every cell, it is the greatest nuisance to muscle cells. The clinical features of the disease are heterogeneous, mostly subdivided into three classes following the disease's onset: classic, early-onset or infantile; juvenile; and non-classic, late-onset Pompe disease. Diagnosis takes place via measuring acid alpha-glucosidase deficiency activity or gene mutation analysis. The latter is also available for prenatal diagnosis and newborn screening.

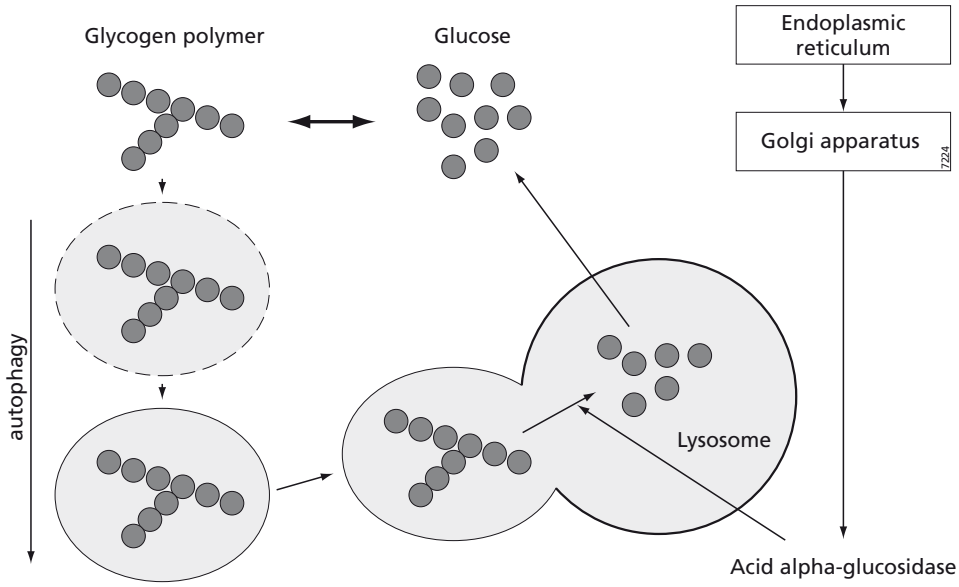

Figure 31 - lysosomal metabolism of glycogen by acid alpha-glucosidase based on Hagemans (2006).

Until recently there were no treatment options available for Pompe disease. Two routes[35] to treatment were gradually hypothesised, following developments in genetics: 1) to correct the gene abnormality by using gene therapy; 2) to mitigate the quantitative and qualitative number of lacking proteins by enzyme replacement therapy. Gene therapy came to the fore in event theme I. We focus on enzyme replacement therapy (ERT) in this theme. Table 12 summarises the main scientific achievements in this field.

Table 12 illustrates that scientific work on Pompe disease has been going on for more than 70 years. Clinical trials on ERT were for the first time organised in the 1960s but only proved to be successful 30 years later. Figure 32 shows the number of scientific publications on Pompe disease[36].

Pompe is sometimes called the 'Dutch disease' because of the discovery of the disease by a Dutch physician, J.C. Pompe, and the prominent role being played by Dutch biotechnology company Pharming (formerly known as Gene Pharming Europe). Moreover, researchers from Erasmus Medical Centre (Arnold Reuser, Ans van der Ploeg and colleagues) discovered and cloned the gene responsible for Pompe disease in 1990. Consequently, this research group looked for possibilities to upscale the production of enzymes using this genetic knowledge. Several paths could be ventured on. For example, inserting human

35 The third, recent development includes pharmacological chaperoning, which will not be dealt with here.

36 Publications were extracted from Scopus searching for (TITLE-ABS-KEY ("pompe disease" OR "glycogen storage disease" OR "acid maltase deficiency") AND TITLE-ABS-KEY ("enzyme therapy" OR "enzyme replacement" OR "alpha-glucosidase" OR "α-glucosidase")).

Table 12 - scientific research events leading to enzyme replacement therapy for Pompe disease; based on Hagemans (2006) and personal communication.

Year	Event
1932	Dutch pathologist J.C. Pompe first described the infantile form of Pompe: glycogen accumulated in many tissues.
1955	G.T. Cori described Pompe disease as a glycogen storage disease (GSD-II).
1960s	Late-onset Pompe was reported.
1963	H.G. Hers found that Pompe was caused by a deficiency of a certain enzyme in lysosomes. This enzyme was identified as acid alpha-glucosidase.
1964	First attempt at enzyme replacement therapy: purification, and uptake in all cells proved to be difficult.
1968	First attempt at prenatal diagnosis of Pompe disease.
1973	ERT with placental GAA.
1979	GAA gene traced to chromosome 17.
1980s	Erasmus MC (A.T. van der Ploeg): biosynthesis and structure of GAA, in vitro studies on feasibility ERT.
1990	Erasmus MC (L. Hoefsloot): cloning, characterisation of human GAA gene.
1991	Erasmus MC: mouse study with GAA injections and uptake in muscles.
1993/1994	ERT for Gaucher disease (another lysosomal storage disease).
1995	Duke University (Y.T. Chen): production of GAA in Chinese hamster ovary (CHO) cells.
1996	Erasmus MC: production of GAA in transgenic mice.
1998	Duke University: preclinical tests with CHO-produced GAA. Erasmus MC: preclinical tests: GAA produced in transgenic rabbits works well in mouse models. Start of phase I clinical trials by Synpac and Pharming.
1999	Phase I clinical trials completed by Pharming.
2000	Erasmus MC (Van den Hout): first evaluation of GAA treatment in patients (phase II results, published in The Lancet).
2001	Duke University (A. Amalfitano): first evaluation of ERT with CHO-produced GAA; Novazyme presents mouse model results of new phosphorylation technology.
2002	Genzyme tests four different Pompe compounds and selects own CHO-derived product.
2003	Start phase III clinical trial by Genzyme under name of Myozyme.
2006	EMEA (29 March) and FDA (28 April) approve Myozyme.

genes in animal DNA resulting into transgenic animals that are induced to produce certain enzymes in the mother's milk. This enzyme could then be purified and used as a drug. The scientists at Erasmus MC chose CHO cells as their platform and tried to make several businesses enthusiastic. Nevertheless, there were no companies willing to invest in the production of enzymes by Chinese hamster ovary (CHO) cells because of inefficient production, a shortage of fermentation reactor producers, and high production costs (Pollock et al., 1999). At that time, Pharming was engaged in work on transgenic animals. They had become known because of the creation of the transgenic bull 'Herman' in 1989. This animal was genetically modified in such a way that his female offspring would produce the human protein lactoferrin for the benefit of baby milk.

Pharming became interested in expanding their portfolio with other transgenic produced products. Erasmus MC and Pharming decided to work together on this project in 1993 and set up preclinical trials. One of the main objectives was to decide which animal should be used for genetic modification. They selected rabbits as opposed to cows (other animals, like

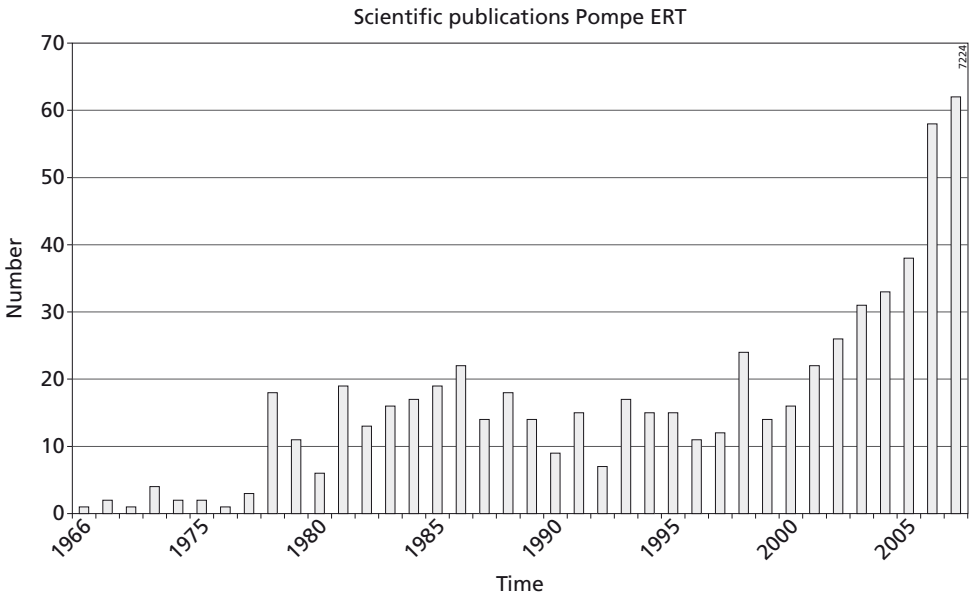

Figure 32 - number of publications about ERT for Pompe disease over time.

sheep and goats, were already patented by other firms) because of the long period before transgenic cows could produce milk containing the enzymes.

The table above also shows that a great deal of research effort has been put in at Duke University, USA. They focused on the production of acid alpha-glucosidase using Chinese hamster ovary cell lines and linked up with the UK company Synpac Inc. in 1993. Later, in 1996, a North Carolina subsidiary was formed and manufacturing of the enzyme was started for clinical trials.

The transgenic animal Herman not only propagated offspring but also generated a large amount of media attention and ethical and political debates in the Netherlands (Theune, 2001): it became a media icon. Principal actors in these debates were Members of Parliament and several interested political parties, the Ministry of Agriculture, and several societal groups like the Dutch Society for the protection of animals (*Dierenbescherming*). They had differing opinions regarding the level of autonomy of animals and the accompanied consequences for the transgenesis of animals. Animal rights groups were totally against animal biotechnology. Pharming, patient advocacy groups, and biomedical scientists took the view that if the cost-benefit ratio was positive and certain ethical conditions were met, it should be possible to conduct biotechnology on animals. A representative of a Dutch patients' alliance for genetic disorders emphasised the interests of patients in biotechnology. He claimed that animal rights and environmental groups too easily dominated the debate because they were more able to anticipate new biotechnology developments. Members of Parliament put several questions to the Ministries of Economic affairs, Agriculture and Health. The Herman case ran in parallel with the discussion on new legislation on animal biotechnology. During these discussions, the Ministry of Agriculture and ethicists favoured a so-called 'no, unless certain conditions are met' stance.

In the meantime, Pharming and the Erasmus MC collaborated on moving rhGAA (recombinant human acid alpha-glucosidase) under the name of 'Pompase' to the clinic.

In vitro studies had been successfully concluded, followed by in vivo tests in mice and later in rabbits. Moreover, a mouse model with glucosidase deficiency was created. In order to produce the GAA through transgenic rabbits Pharming moved its main production facilities to Geel, Belgium in 1996. According to the company they did this because of the substantial financial support they obtained from the Belgian government and contradicted claims that it tried to avoid strict Dutch legislation. Later, a Pharming representative claimed that Belgian experience with breeding rabbits was another reason. Questions were asked in parliament about the need for homogeneous legislation in all EU countries, and about whether there were no alternatives for the use of transgenic animals. Pharming and scientists at Erasmus MC underlined once again that CHO-derived enzyme production was too expensive and not efficient. The GAA produced by these rabbits was first used in the mouse models and showed effectiveness.

In 1996 and early 1997 the animal biotechnology and 'Herman' debate ended as a result of three developments: 1) scientists had investigated whether the offspring of Herman were healthy and did not differ in any way from other cows, and concluded that neither was the case; 2) the Herman experiment was concluded with the sterilisation and handing over of the bull to a natural science museum; 3) on April 1997 the new animal biotechnology legislation came into effect underlining the 'no, unless' policy that the Ministry of Agriculture had favoured during the debate. Experiments were only given a permit if no alternatives were possible, animals were not harmed, there was a substantial societal interest, and an ethics committee (Commissie Biotechnologie bij Dieren) approved them. This committee held public hearings during which all stakeholders learnt to develop their arguments and formulations. Later on, the arguments remained more or less the same and several parties regarded transgenic animal tests as not being significantly different from other animal tests.

Erasmus MC and Pharming started with phase I clinical trials in 1998. As a result of preclinical tests, it soon became apparent that the number of enzymes needed for the successful treatment of Pompe disease (20-40 mg/kg body weight for every 1-2 weeks) was far more than for Gaucher's and Fabry's diseases, which were developed in 1993/1994 by US biotechnology company Genzyme. The resulting scepticism sufficiently delayed development of the product. Nevertheless, the tests showed safety and called for a continuation of working with transgenic animal to produce these increased amounts.

The Herman debate had its repercussions on the scope for manoeuvre of Pharming and the Erasmus team. In 1998 the Ministry of Agriculture granted new permits to Pharming for transgenic animal experiments, amongst others for producing rhGAA with transgenic animals, which led to new upheaval in parliament. Questions were asked about ethical acceptability, and permit-granting procedures. Moreover, parliament decided to totally ban cloning in April 1998 until the Rathenau Institute had obtained more information about the opinions of the general public. Once again, Pharming decided to 'redistribute' their activities to their branches in Belgium and Finland, which led to parliamentary questions about the uniformity of EU rules. Pharming was not content with the position of the Dutch government but their headquarters remained in the Netherlands because of the good opportunities for financing and scientific research.

In the meantime, it seemed that the ethics committee and the Ministry of Agriculture that needed to decide about permits gave Pharming the benefit of the doubt. There were several reasons for this. First, Pharming was regarded as a crown jewel of Dutch biotechnology, primarily by the Ministry of Economic affairs. Second, the drugs that Pharming developed

were intended for rare and serious diseases. Because of lacking economic incentives not many companies were interested in investing in such drugs.

Already in the second half of the 1980s a group of patients within the VSN became interested in the state of the art of Pompe disease research and organised a meeting with scientists. This was the beginning of the collaboration between them and the VSN. The VSN expected a great deal from the relevance of genetics research for neuromuscular diseases and had already in the 1980s remarked that the first results could be anticipated in Pompe disease. It could serve as a model for other diseases because it followed the pattern of gene location, gene identification, gene product identification, and productive enzyme therapy.

The VSN now decided to express their views on the shrinking freedom of movement for biomedical research on transgenic animals, which is imperative for the development of a Pompe drug. They sent a letter to the Ministry of Agriculture, which was also mentioned at the start of the introductory chapter, underlining the importance of this research for patients with a lethal disease and the need for progress. Moreover, the VSN also claimed it was important that the developments remained in the Netherlands because Dutch patients would then have quick access to new medicines. In March 1998 the VSN working group working on Pompe disease met with other foreign patient groups such as the US Acid Maltase Deficiency Association (AMDA). This led to plans for an international Pompe patient group and a conference to be held in 1999. The VSN also maintained a "natural alliance" (interview result) with Pharming: they informed each other on a regular basis, and the patient group even owned a few shares in the company. In turn, Pharming tried to keep a low profile because the company did not want to raise expectations too high. In the meantime, Pharming announced that it had attracted substantial venture capital for their development work on several drugs.

In June 1998 Pharming announced that they successfully completed the phase I clinical trials and planned to start a combined phase II/III trial after the summer. The company expected to start marketing the Pompe product in 2000. At the same time, Erasmus MC scientists were also enthusiastic but tried to tone down potential euphoria. In the autumn of 1998 it appeared that the phase II and III trials needed to be split and that the former would commence in early 1999. The Erasmus MC team gained permission from the hospital's medical ethics committee to conduct trials on four early-onset and three juvenile Pompe patients. In the meantime another company, Synpac Inc. was also working hard on Pompe disease ERT. This company applied for an Investigational New Drug with the FDA (April 1999), followed by phase II clinical trials in three Pompe babies (June 1999). During this period Pharming became listed on the stock exchange and announced that the phase II trials were going exceptionally well.

In October 1998 Pharming and Genzyme formed a joint venture to develop ERT-based Pompe medicines of which both companies owned half. Genzyme had successfully developed an ERT for another lysosomal storage disease, Gaucher, and had a sufficient sales and marketing apparatus in place. In November 1998, the Dutch Ministry of Agriculture and parliament discussed the import of genetically-modified animals. Before that, no permit had been required for the import of such animals, in contrast to the production of these animals. A moral dilemma appeared on the agenda: were Dutch patients allowed to use medicines produced abroad; medicines that had been developed using technologies that were banned in the Netherlands?

The VSN reacted on this by sending a letter to the Ministry of Agriculture expressing their anxiety about putting serious obstacles in the path of genetic modification that

benefits biomedical research. Genetics research had shown major promises for treatment and diagnosis but its potential could not be fulfilled when the governments throw up legal hurdles. The VSN did not denounce the discussions on biotechnology and hoped for an open debate in which several parties, such as politicians, did not automatically side with those articulating the excesses of these new technologies. More in particular, the VSN asked the ministry not to thwart the clinical trials with Pompe patients that were to start soon. They asked for abolition of the ban on production of genetically-modified animals. Moreover, the VSN prepared for a new role when treatments for a neuromuscular disease came onto the market, such as guiding patients in their drug use.

On 2 July 1999 representatives of a large number of international patient groups met in Naarden (the Netherlands) for the first meeting of the International Pompe Association (IPA). Several stakeholders from industry, science, physicians, and patient groups presented their work on Pompe disease. Treatment options like ERT and gene therapy were discussed as also was the need for early diagnosis. Attention was devoted to the progress of bringing ERT to the market, e.g. issues around enzyme production and market approval. Patients were in an uncertain position, ranging from hope to unanswered questions. Patient representatives emphasised the importance of "information, support and ethical debate". Several viewpoints and messages that came to the fore during this meeting were:

- Erasmus MC: reported that their trial was "underway to meet its objectives".
- Pharming and Genzyme: Genzyme referred to its experience with the development and market introduction of drugs for other lysosomal storage diseases, and stressed that awareness should be raised in the medical community about these diseases and organising patient access.
- Duke University: reported on gene therapy work on Pompe disease.
- Synpac Inc.: put to the fore their "aggressive timeline" of introducing their Pompe medicines on the market.
- A patient: claimed that patient groups should anticipate on future developments by informing patients and the general public, and organise market access. Empowerment of patients was needed.
- Association for Glycogen Storage Disease (UK): empowering patients needs to be accompanied with proper provision of information.
- Acid Maltase Deficiency Association (US): presented its objectives, which included ensuring access, supporting patient groups in low-income countries, supporting R&D, and setting up a patient registry.
- VSN: sketched the opportunities for the IPA and the objectives that the IPA should strive after: "social support, advocacy, information provision, networking, stimulation and facilitation of research".

At the end of the meeting the mission statement and objectives of the IPA were decided upon (Figure 33). This served as input for the IPA policy document that was published a month later. The mission statement read as follows: "Assure that there is early diagnosis and effective, affordable and safe treatment and therapy, reliable information and support to all patients and their families and other involved parties with Pompe disease". Several points were raised, such as potential problems with expensive drugs, speed of market introduction, underdiagnosis of Pompe disease, and long-term effects of the treatment. The document was positive about the position that patient advocacy groups like the IPA could take and proclaimed the importance of maintaining contacts with a diverse range of partners, like industries, and the medical community.

"I. Assure that there is early diagnosis and effective, affordable and safe treatment and therapy for all patients and their families and other involved parties with Pompe disease.
a. Stimulate research into the causes, treatment and prevention of Pompe disease
b. Stimulate the rapid application of research into the causes, treatment and prevention of Pompe disease [e.g. by recruiting patients for clinical trials using the Internet]
c. Promote early and accurate diagnosis of Pompe disease
d. Support national organisations obtaining Government Health Approval
e. Use the best efforts concerning availability and affordability of medicine and treatments
f. Encourage other organisations or individuals to establish a mechanism for the more indigent patient to apply for or to have access to treatment or therapy
g. Engage in revenue generation and/or fundraising activities to support and defray organisations and operational needs of the organisation and the support of projects and programmes that are to the best interest of the patients, families and the organisation
h. Encourage the establishment of national Pompe-organisations
II. Assure that there is reliable information and support to all patients and their families and other involved parties with Pompe disease.
a. Organise an annual international meeting
b. Provide 'on-line' information by Internet and other sources
c. Collect information on respiratory support and other aids
d. Co-ordinate and support the activities and formation of national groups."

Figure 33 - objectives of the International Pompe Association

In 2000 health minister Els Borst admitted during a speech that the banning of Pharming activities in the Netherlands, and subsequently allowing imports and use is not a "logical sequence of events" and the Ministry needed to clarify its position. This was not the first example of ambiguity: while the Ministry of Economic affairs granted research money to Pharming, the Ministry of Agriculture was banning its activities. These tensions came to the fore again when discussing a new programme aimed at stimulating new dedicated life sciences firms ('Biopartner programme'). The ministers now wanted to raise the ban on medical biotechnology research but parliament was still not enthusiastic about it.

In March 2000 Pharming and Genzyme presented the results of the phase II trials that "exceeded [...] expectations". Filing was expected in 2001 and phase II/III trials had just started in Essen, Germany. Scientists at Erasmus MC reacted angrily in the media that their peers had not verified the phase II-trial results made by Pharming, and scientific publication was required first before patients and their families raised too much hope and high expectations. Pharming defended themselves by claiming that they needed to release the results because their company was listed on the stock exchange.

The Dutch Association against animal testing (*Proefdiervrij*) organised demonstrations against Pharming in Leiden and Geel in April 2000. The association protested against the use of rabbits for the production of rhGAA. Pharming reacted to the accusations by stating that the rabbits were treated well and that genetic modification had not resulted in

different animals. Moreover, they declared that alternatives, like using cell cultures, were not real options because they did not yield the same quality of enzymes. Radio commercials and newspaper advertisements announcing these demonstrations showed a five-year-old child who suffered from the "creepy" Pompe disease. While he liked rabbits, he was being treated with enzymes produced by rabbits in an animal-unfriendly way, while there was an alternative available that did not rely on the use of animals. The VSN received many reactions to this advertisement and promptly sent letters to the Dutch Association against animal testing, the editors-in-chief of the newspapers and the Advertising Code Committee. They protested against the use of the word "creepy", and said that the claim about the investigation of an alternative way of producing a Pompe drug was deceiving, especially for patients who lived in the hope of a new therapy. Later, the Advertising Code Committee agreed with the VSN, and many newspapers reported the rift between the VSN and opponents of animal testing.

A few days later Genzyme announced the signing of a deal with Synpac to take over its competitive Pompe R&D that was based on CHO-cell lines. Genzyme would continue the developments and commercialisation together with their partner Pharming. Pharming would abandon their own rabbit-based rhGAA production because of strategic reasons. Both products were in the same phase of development and also on the brink of filing for Orphan drug status. But the first company that requested and obtained this status would make the efforts of the other one obsolete because it would obtain seven years of market exclusivity. Although Pharming were convinced of the quality of their compound, they feared that their novel transgenic animal-based technology would make the approval procedure with the FDA and EMEA even longer. The technology that used CHO-cell lines had already been known to the regulatory authorities and thus would probably cause fewer problems. Moreover, it appeared that larger quantities of the compound were needed than had been expected, for which too many rabbits were required (estimates varied from 4,500 to 70,000 a year). These new developments caused Pharming to suffer some major blows. First, the management needed to reverse the statement made only a few days earlier about the fact that there was no real alternative for rabbit-produced rhGAA (although the Synpac option differed from the one suggested in the *Proefdiervrij* commercials). A Member of Parliament also questioned this in the light of the procedures around animal biotechnology, and called for the withdrawal of the company's permits (the Ministry did so later that year). Second, Pharming employees, the IPA, Erasmus scientists, and investment consultants alike did not appreciate the developments. The IPA disliked the increase in uncertainty and the decrease in competitiveness. Third, it became apparent that the balance of power in the joint venture between Pharming and Genzyme was starting to shift to the latter. One of the reasons being that Pharming could not finance their part of the acquisition price of Synpac.

Two months later another company, Novazyme Pharmaceuticals, which had been founded by John F. Crowley[37], the father of two children with Pompe disease, announced that they had developed phosphorylation technologies that could be used as a treatment for lysosomal storage diseases like Pompe. The basis of this technology had not been widely published in scientific journals though, and their claim that Pharming's product was not good enough was unsubstantiated.

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37 His quest for a Pompe drug is described in Greta Anand's 'The cure'. He is currently working on chaperone technologies through a company called Amicus.

The VSN in the meantime evaluated the then-current situation in the light of the results of the phase II-trial that was published in The Lancet. The organisation agreed that there was good hope of a therapy, but maintained that the road to market introduction was still long and expectations should be brought into proportion. In August 2000 Pharming conclusively announced that they would stop following rabbit-produced rhGAA in favour of the Synpac method. Some Members of Parliament abused this strategically-driven decision by stressing the importance of animal welfare. Moreover, a few months later the Minister of Economic affairs claimed that until clinical trials had finished it would be impossible for the government to know which alternative was better.

Pharming and Genzyme proclaimed that besides the Erasmus trials also the trials conducted at Duke University had been concluded successfully during the American Society of Human Genetics conference in October 2000. This paved the way for larger-scale phase III trials, and a 2002 market introduction. They also claimed that they had problems in maintaining sufficient production levels. One day later Novazyme announced that their technology had been granted Orphan drug status by the FDA based on preclinical evidence.

At the end of March 2001 the IPA published an interview with Genzyme in which the patient representatives had been given the opportunity to ask questions about issues around Pompe drug R&D that bothered them. These issues included: the necessity of lengthy phase III trials, the priority for testing the drugs in juvenile and adult patients, the need for a placebo control group, production processes, timescale of registration, the continuation of rabbit enzyme production for the benefit of patients enrolled in the Erasmus and Essen trials, and the planned transition of these patients to the CHO-derived product. The role of Novazyme was discussed. Genzyme saw them as "a challenge, not a threat" and the competition would result in an increased effort to be the first with the best product. The compassionate use of the drug was an important issue because the IPA saw a role for itself here. Genzyme was not fond of this concept because it had no wish to annoy the regulatory authorities, and because the production capacity was lacking at that time. Also the role of patient groups was discussed. Genzyme saw the greatest impact of these organisations in putting pressure on regulatory authorities with their patient testimonies, by urging for quick access, and by assisting with the setting up of a patient registry by creating awareness with patients and physicians. The registry would follow the example of those set up for Gaucher and Fabry disease. It was meant as an open resource for physicians, in which the variability, progression, and natural history of Pompe disease was monitored over time using several parameters. Other objectives included optimising patient care, and characterisation of the Pompe population. Communication of the latest news to the patients was also important for Genzyme. Finally, it was debated why the development process took longer than expected. This was partially because of problems encountered in upscaling the enzyme production, and partially because unrealistic expectations were voiced by all parties (including Genzyme). One day later Pharming and Genzyme announced the start of phase II/III trials.

In April 2001 researchers from Novazyme and the University of Florida presented the results of successful in vivo tests in mouse models. Later, the IPA had an interview with the company asking them about their biggest problems, challenges and plans. They wanted to proceed with phase I/II trials and in parallel prepare phase III trials. In this way, the plans were both ambitious and fast-tracked. Its position towards patient groups was characterised as aiming to build a partnership. Finally, questions were asked whether Novazyme would "do a Synpac", but it answered that at the moment "the best way is to be independent".

This moment did not last long though, because two months later Genzyme announced the acquisition of Novazyme, whose "technologies could potentially lead to improved, second-generation versions of its marketed products and optimal first-generation products for the treatment of various lysosomal storage disorders." The Novazyme Pompe compound NZ-1001 had not been tested in patients but promised lower dosages, which would be economically interesting.

This came at a time when Pharming accompanied their half-yearly results with the notion that it needed a loan quickly or would otherwise be unable to continue independently. The Novazyme takeover meant that Genzyme shifted their allegiances away from Pharming. Within a week the stock market price of Pharming slumped and the company faced bankruptcy. Erasmus MC and the VSN immediately expressed their concern in the press about the four Pompe patients whose treatment was in danger. Pharming and Genzyme quickly reacted that they would reserve funds to continue production. They also held firm talks about the future of their collaboration that included the joint Pompe project. Pharming did not want to simply hand over the project to Genzyme, while the latter expressed that in the interests of the project the company was willing to take over "full responsibility". Some of these discussions ended up in newspapers, in which both parties shielded with the welfare of the Pompe patients as argumentation for their own interests. At one stage of the discussions Pharming even suggested that Erasmus MC could eventually support the company financially, which was "absolutely impossible" according to a spokesperson of the hospital. Genzyme also made bold statements to the effect that the Erasmus MC trial results could be based on chance. The Acid Maltase Deficiency Association protested against this, referring to the 2000 Lancet publication. Negotiations continued up to the end of 2001. Genzyme was willing to take over the Geel factory in Belgium but Pharming declined this offer because it had received a better one. Later, a Flemish commercial court forced Pharming to sell the factory to Genzyme. Dutch Parliament briefly discussed the possibility of helping Pharming out. It also discussed the role of the government in the case of abandoned clinical trials, and the university-biotechnology industry relationships. Only in December 2001 did the two companies agree on the takeover of not only the factory, but also the intellectual property rights (Pharming held two patents) and data of the Pompe project. In this way the joint venture project was ended and Pharming was able to make a new start, becoming a technology platform once again and focusing on medicines for hereditary angioedema.

In the middle of this uproar the VSN tried to put the aspect of compassionate use on the agenda, following successful attempts at doing so by the AIDS patient groups in the US. The VSN used this example after a deliberative search for precedents. Scientists understood this need but demanded more clinical research, whereas governmental bodies stalled these developments waiting for more clinical trial results as well. The VSN also sent a letter to the health minister to meet on short notice to discuss whether it would be possible to arrange compassionate use for Pompe therapy. Only the law and practical objections forestalled the use of the new treatment. This might lead to "a horror scenario". The VSN understood the legal and practical problems but decided it had no choice but to speak up for patients who otherwise may invalidate or die in the short term. This letter was accompanied with an interview on the front page of a national newspaper with a Pompe patient who played a prominent role in the VSN and IPA, Maryze Schoneveld van der Linde. She illustrated that it was difficult to digest that an efficacious drug (albeit not proven in phase III-trials) was not available to her and her fellow patients.

The IPA board visited the Genzyme headquarters in April 2002 to discuss the progress of Pompe R&D. The IPA was satisfied with the way Genzyme was striving for the quickest way to market introduction, and acknowledged the importance of meticulous clinical trials in order to make the registration and reimbursement of Pompe ERT easier. Genzyme also presented results of studies they had performed in-house with external investigators with four enzymes: 1) the rabbit-based rhGAA produced with Pharming; 2) the Novazyme enzyme; 3) the Synpac (CHO-derived) enzyme; and 4) a recently internally-developed CHO-derived enzyme by Genzyme. The latter proved to be the most efficacious (later they would talk about a "similarly robust response"). These tests formed the basis for Genzyme's decision to proceed with this compound.

In 2002 the Erasmus MC group started with a PhD project, performed by Marloes Hagemans, to investigate the natural course of Pompe disease for late-onset patients by means of a questionnaire and a registry. Another objective was the construction of measurement scales. After the introduction of ERT this registry would still be important because in this way the efficacy of the therapy – and of the complete treatment – could be measured. The data, partly owned by the IPA, could also feature in the dossier needed for the registration procedures. Erasmus MC also went to court to fight the handing over of a Pompe patent to Genzyme by Pharming. The university hospital was one of the co-owners and wanted to stipulate a license fee. Later, in July 2002 the tension between Erasmus MC and Genzyme grew even more because the company only sent one batch of CHO-derived Pompe drugs to the hospital, despite promises to treat the five patients that originally participated in the clinical trial with rabbit-based rhGAA, and the fact that the CHO-derived product had not shown efficacy. The patients' parents, the VSN and the medical specialists at Erasmus MC invited Genzyme to a crash meeting. Genzyme did not show up but later sent a fax stating that the company would ensure rabbit-derived rhGAA up to 2003. Patients and physicians alike did not have sufficient faith in the CHO-derived compound. In September 2002 Erasmus and the VSN, together with the parents, organised a repeat meeting. This time, Genzyme did attend and produced satisfactory information and promises.

A few days later Genzyme and the IPA held a teleconference along the same lines of the talks they had had in April 2002. Genzyme explained that they were on the brink of discussing phase III trials with the FDA, and the IPA emphasised that the new developments were accompanied with uncertainty and could not be accelerated. Later, in December 2002, another conference revealed that Genzyme had filed an investigational new drug application in November and that enrolment of phase trial III participants would begin that month. The IPA also demanded additional information on compassionate use, but Genzyme revealed that production limitations had prompted the regulatory authorities to focus the company on patients currently on therapy. In February 2003 another teleconference was held. This time Genzyme presented two concrete large-scale clinical trials (1602 and 1702) on early-onset Pompe patients that would start in the spring. Compassionate use and trials for late-onset patients would only then be considered when sufficient rhGAA could be manufactured. Production of the enzyme was a major bottleneck at the time. The two clinical trials would be accompanied with two small compassionate use (expended access) programmes, one for older children with early-onset Pompe disease who did not qualify for the 1602/1702 trials, and one for late-onset patients who would not qualify for inclusion in the late-onset clinical trial that would start in 2004. The latter special access programme could only start as soon as enzyme production was sufficient.

In October 2003 the IPA organised its second International Pompe Conference in Heidelberg where patients, physicians, scientists and the industry met. Some of them also presented their work, such as Erasmus MC scientists about their ongoing research on the patient registration project and rabbit-based rhGAA, Genzyme about its drug development, Duke University about ERT and gene therapy work, and the Adelaide Women's and Children's Hospital about the need for early diagnosis of Pompe and their work on heel prick tests. It also became clear that some time was still needed before market registration, and one of the major problems was establishing the right doses. This, together with the uncertain total number of Pompe patients, made it difficult for Genzyme to plan its production facilities. The Genzyme-sponsored Pompe disease registry, which was complementary to the one developed by Erasmus MC, could assist with these predictions. Genzyme also explained their expanded access programme, the related need for careful enrolment, and the question of reimbursement. Genzyme discussed why prices would be high, and also planned assistance programmes for patients who had problems with payments. The IPA also evaluated their achievements, among other things in becoming a recognised source of information, a global voice, owner of data about the natural course of disease, and the creator of a Pompe community.

Later, more information about the late-onset clinical trial was presented, which led the VSN to interview Genzyme representatives. An observational trial, in which the course of the disease was studied, would precede these clinical trials. Participation in the latter required taking part in the observational study. In August 2004 the late-onset expanded access programme was well underway and revealed high variability between countries and clinical centres on the education of physicians, regulatory requirements, etc. Moreover, it was decided to enrol patients who were not eligible for the programme in a "second round". One reason for this was to increase the statistical power of the study.

In October 2004 the IPA and the UK Association for Glycogen Storage Disease patient group organised an international conference. Genzyme talked about the "good, steady progress" of the clinical trials, and illustrated their plans for the immediate future regarding market introduction, and the more distant future, pledging to invest in "next generation drug therapies, improved diagnostic screening procedures, and health care infrastructure". These results were supported by talks with medical specialists. Also the attention increasingly shifted to eventual reimbursement problems because a patient representative of the MPS Society was invited to talk about their crusade to get MPS I and Fabry drugs financed. Finally, standards for (newborn) diagnosis, follow-up assessment and clinical management were put on the agenda, and an upcoming workshop about these issues was announced, which was organised by the European Neuromuscular Centre (ENMC).

In 2004 the discussions on the reimbursement of orphan drugs in the Netherlands became highly topical. The Steering Committee on Orphan drugs was engaged in attempts to direct the financing of these drugs through a national financing rule instead of via the budgets of academic hospitals (see Chapter 6). These hospitals might refrain from prescribing these medicines because of the extremely high costs involved. The VSN voiced their concerns because of the looming introduction of Genzyme's Pompe drug, Myozyme. The VSN was mainly represented by Johan Bakker, chairman of the VSN Pompe working group, and Maryze Schoneveld van der Linde, who had approached the Health minister directly during the break at the prestigious WHO Priority medicines conference that he organised as part of the Dutch EU presidency in November 2004. Together with the director of the VSN she invited him to visit the VSN bureau in Baarn. He accepted and

went to Baarn a few months later. On his visit he learnt more about rare diseases and the need for proper reimbursement.

In December 2004 Genzyme started the formal procedures for market registration with the EMEA and FDA. Later it also announced that it would replace the rabbits in the Geel factory with cell culture kettles to produce CHO-derived drugs.

In April 2005 the announced ENMC workshop on "Defining the standards of medical management in Pompe disease" was held. The scientists presented work on standards for screening tests, and diagnostic algorithms for the different forms of Pompe. They wanted to apply them in the preparation and monitoring of clinical trials. In the same month Genzyme presented promising interim efficacy data of the enrolled clinical trials. They encountered major safety problems

The next month an IPA conference was organised in Nantes. Erasmus MC presented their IPA/Erasmus MC Patient Survey that "represents a patient-entered, discrete assessment of patient quality of life, fatigue and functional data, which effectively complements the physician-entered, longitudinal collection of clinical data in the [Genzyme] Pompe Registry." Genzyme talked about the clinical trials, the upscaling of the production facilities, the market registration, and laid the focus for the coming period on late-onset population. The company regarded patient organisations like the IPA as important for "building up an infrastructure of expert centres, developing uniform treatment guidelines, disease awareness, the IPA Erasmus survey, early interaction with governments, Pompe disease information, patient stories, and putting newborn screening on the agenda". The IPA underlined this by expressing their need for a hospital Pompe counsellor, the hope for a broad label (not limited to infantile patients), and the importance of registration.

In July 2005 Genzyme announced that they would commence with the enrolment of the clinical trials for late-onset patients (LOTS: late-onset treatment study) as a follow-up to the recently concluded late-onset prospective observational study (LOPOS). It was no longer a requirement to have taken part in the LOPOS in order to participate in the LOTS. Genzyme also filed a biologics license application to the FDA, and in this way was on track for approval in the US and Europe. The FDA granted a "priority review" status to Myozyme. Genzyme once again emphasised their commitment to rare diseases and the willingness to help Pompe patients in low-income countries by setting up special help programmes that would finance treatment. They defended the need to ask high prices by making specific reference to these help programmes and the fact that once they started providing a drug to a patient, it would be ethically wrong to stop treatment.

At the end of the year the VSN once again interfered in the orphan drug reimbursement debate by sending a letter to the Ministry of Health asking for a different solution than having university hospitals pay for these drugs. The VSN claimed that already in the case of Erasmus MC and Pompe disease, the hospital refrained from participating in a clinical trial because it feared heavy future financial burdens. The VSN proposed the solution of allowing the hospitals to receive discounts during the post-marketing phase. After that, the financing of the drug could take place through the normal national reimbursement scheme.

On 26 January 2006 the Committee for Human Medicinal Products (CHMP) of the EMEA adopted a positive attitude towards Myozyme. This was just before the Dutch Pompe patient day which was organised by the VSN. On this occasion the patients could be told the joyful news. Later, on 29 March the EMEA issued the market authorisation for early-onset use of the product, whereas they also asked the company to continue their studies on late-onset use, optimal dosage and timing. Although for the latter application lower

dosages were needed, it was not part of the EMEA and FDA approval. There were not enough data present, and Genzyme had not formally included hypotheses concerning late-onset use at the start of the trials (in clinical trials the only requirement is to prove what is hypothesised). This was also the reason why the most severe cases of Pompe were part of the compassionate use programme. In the wake of this approval the VSN announced that: "For people with Pompe disease, this is a very important moment in history. The approval of this treatment represents great hope and progress for all Pompe patients, which in turn will give them a new perspective on their future".

On 28 April 2006 the FDA followed suit with the US market approval. Now Randall House, chairman of the IPA and president of the AMDA reacted: "The journey from development to approval of a therapy for Pompe disease has been a long and winding road, but we are now at a milestone and are thrilled with the outcome". The FDA also regarded the continuation of the LOTS trial in the post-marketing setting as a necessity. The approval for late-onset patients was provisional and a final decision would be taken after three years. The IPA asked questions about this requirement because they wondered whether keeping up placebo groups was needed. The patient organisations were involved in the regulatory process. The IPA had contributed to obtaining a broad label for Myozyme, including late-onset patients, during patient perspective hearings at the FDA and EMEA ('Official Oral Hearings'). Moreover, the VSN maintained weekly contact with the medical professionals at Erasmus MC to keep up the pace and aim at home treatment.

In June 2006 Marloes Hagemans defended her PhD thesis in which she used a Pompe survey to find more information about the patient's perspective in the assessment of the disease, mapping the health status and natural course of the disease, and to evaluate the self-report measurement scales. The FDA used the results of her thesis for setting up guidance for the treatment of patients. Cooperation between the scientists and the IPA was appreciated by the regulatory agencies, industry and the parties involved.

During the same period, the Council for Public Health and Health Care (RVZ) presented an advisory report in which it discussed the maximum amount of money that should be paid in general for treatment per year. Although the Council excluded expensive drugs for rare disorders it still came as a shock to patients and the VSN condemned the report because it would frighten patients. The VSN made the link with Pompe particularly because a new drug had recently been introduced on the market for this disease and reimbursement decisions were looming. By then, the Ministry of Health had succumbed to pressure from other stakeholders and introduced a special reimbursement rule for expensive orphan drugs on which Myozyme was listed in September 2006.

On 17 November 2006 the AMDA and IPA organised another international Pompe conference during which a diverse range of actors spoke yet again. The conference was mostly about looking back at the "historic event" of the approval and the marketing of Myozyme. Some scientists underlined the unusual order of approval (children before adults), lines for future research (gene therapy, chaperon technology, next generation ERT), and the importance of early treatment. The IPA evaluated its role as instrumental in searching for clinical trial participants, establishing connections between neuromuscular physicians and companies, setting up a Pompe survey, introducing information brochures about Pompe ('Pompe Connections'), engaging in discussions about animal rights, pointing out misleading information (Genzyme promised a therapy for 2000, but it was only marketed in 2006), and the transfer from rabbit-based to CHO-derived drugs. An important future issue would be ensuring sufficient reimbursement for the drug. All

actors present agreed on the significance of collaboration between scientists, medical professionals, companies and patient organisations.

In their annual report the VSN strived for the setting up of feasibility studies for Pompe newborn screening tests. The Dutch Government, supported by several advisory councils, had recently increased the number of diseases tested for in the heel prick, and wished to include new diseases only if sufficient treatment was available. With the advent of Myozyme, Pompe might qualify for this. The VSN, together with scientists, applied for a grant to study the possibilities. What made it ethically more difficult is that during newborn screening, people who would develop late-onset Pompe could probably also be detected, burdening their parents (and themselves) with knowledge they might not want to have.

In 2007 the VSN put the storage of the drug and the continuation of production process on the agenda because Genzyme wanted to introduce a new production method that was not without risk. Moreover, the VSN was involved in problems surrounding the last phases of the Erasmus MC LOTS-study. Moreover, the organisation wanted to convey a positive message about Pompe treatment by sending a letter to the Members of Parliament.

The VSN had always to a large extent been engaged in the Pompe saga because the developments around Pompe disease presented the VSN with one of the first, and therefore hopeful, real cures for a neuromuscular disease. Another reason why the VSN was involved from the start lay in the Dutch focus of the disease. Both the discoverer of the disease (Dr. J.C. Pompe), the first scientists to make a breakthrough based on ERT (the Erasmus MC), and the first company (Pharming) came from the Netherlands. With (and not because of) the entrance of non-Dutch actors the VSN shifted their advocacy activities from the national to the international stage, being one of the founders of the International Pompe Association.

The number of demand statements (Figure 34) increased over time in all five periods, i.e. those on fighting for the transgenic animals for drug R&D (period I and II), involvement in

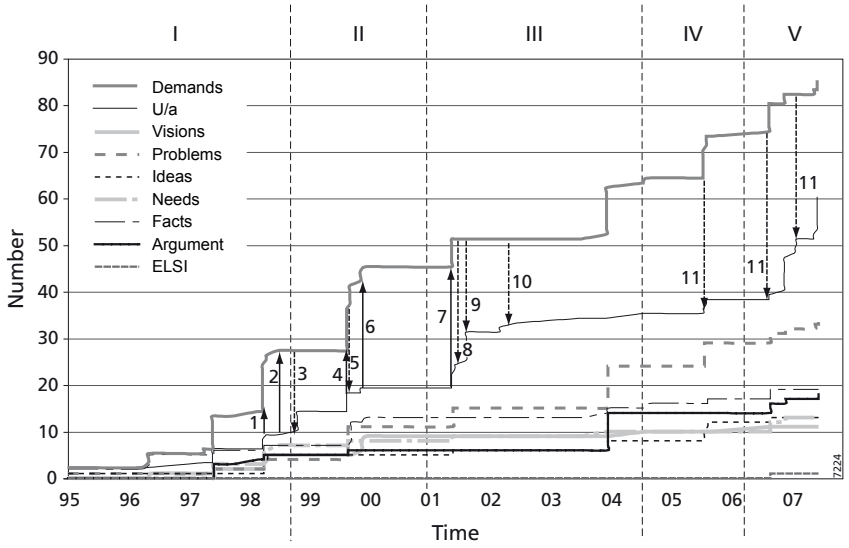

Figure 34 - cumulative number of demand and underlying assumption statements in the event theme on ERT for Pompe disease. The arrows are explained in answering research sub-question 1b.

Table 13 - changes in concreteness and direction of demand statements (Pompe event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	Animals and biotechnology	Expected the first therapies following genetics research in Pompe disease. It could serve as a model	-	-
		Letter to ministry: biomedical research on transgenic animals was important for Pompe patients. Developments should be in the Netherlands: Dutch patients have quick access to new medicines.	More	No
		Plans for international Pompe patient group together with foreign patient groups.	No change	No
		Letter to ministry: no legal hurdles that hinder development of drugs, Pompe clinical trials and transgenic animals for medicines. Hope for an open debate in which parties did not automatically side against biotechnology.	More	No
II	'*Proefdiervrij*' letter, involvement in phase I/II trials	IPA should have as its objectives "social support, advocacy, information provision, networking, stimulation and facilitation of research".	More	No
		Protest against the advertisements of '*Proefdiervrij*' as deceiving.	More	No
		Evaluation of the results of the phase II-trial: good hope for a therapy, but market introduction still far away. Expectations should be brought into proportion.	No change	No
III	Problems with Pharming bankruptcy, compassionate use	Pharming bankruptcy: concern about the four Pompe patients whose treatment was in danger.	More	No
		Advocate compassionate use.	No change	No
		Letter to Ministry of Health: asking for quick access to Pompe medicines through compassionate use because there had not been an alternative available as yet.	More	No
		Data of registry partly owned by the IPA, could be used in registration dossier.	No change	No
		Crash meeting asking for continuation of delivery of rabbit-derived rhGAA up to 2003 by Genzyme.	More	No
		Repeat meeting: again asking for delivery.	No change	No
IV	Reimbursement	Voiced concerns about reimbursement of expensive Pompe drug by contacting health minister directly.	No change	No
		Letter to Ministry of Health: asked for a different solution than having university hospitals pay for these drugs. Some hospitals already refrained from clinical trials because of reimbursement problems. Proposal: allow hospitals to receive discounts and finance drugs through normal national reimbursement scheme.	More	No
		Condemned the report on the maximum amount of reimbursement per treatment because it would frighten patients. Link with Pompe drug was made.	More	No

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
V	Newborn screening	Annual report: applied for a grant to set up feasibility studies for Pompe newborn screening tests. Also taking into account ethical issues.	No change	N/A
		Voice problems with storage of the drug and the continuation of production process. Problems with late-onset clinical study. Convey positive message to parliament about reimbursement	No change	N/A

clinical trials and compassionate use (period II and III), the problems around the Pharming bankruptcy (period III) and reimbursement (period IV), and ideas about newborn screening (period V). Moreover, the level of concreteness (fourth column of Table 13) grew. The high number of 'no changes' in this table does not indicate less development or less sharpening in this case but rather an increase in the number of topics handled. Nevertheless, first-order learning occurred in this event theme to a large degree in terms of increase numbers and concreteness of demand statements.

Event theme V: Idebenone for Friedreich's Ataxia

Friedreich's Ataxia is a rare, genetic and life-shortening disease that was first described by the German physician Nicolaus Friedreich in the 1860s. Ataxia is a group of disorders, of which Friedreich's Ataxia is the most prevalent, which is characterised by uncoordinated muscle movement. Prevalence is 1 in 50,000 in the US but other estimates vary. The first symptoms are mostly observed between the age of 5 and 15. In 1988, Dr. Susan Chamberlain discovered that the gene responsible for Friedreich's Ataxia (FA) was located on chromosome 9. In the subsequent two years linkage studies yielded a more precise location.

The VSN recounted at that time that discovering the so-called "Friedreich gene" would be the start of new research into treatment and most notably diagnosis, including prenatal testing. The VSN wanted to make as many scientists as possible enthusiastic for working on the disease. In January 1991 the patient organisation arranged an information day that featured a small selection of Dutch scientists speaking on several neuromuscular diseases. The main message was that cooperation between scientists was important, even between those working on different types of muscular diseases. The patient organisation Euro-Ataxia organised a conference on European level. Dr. Chamberlain spoke about the hunt for the Friedreich gene and tried to answer the question "why it takes so long". The chairman of Euro-Ataxia emphasised the importance of molecular genetic research: initially it might have been an intellectual exercise but it became increasingly topical. Because of the increasing scale of this kind of research scientists would have to cooperate.

In October 1995 the Dutch committee on Friedreich's Ataxia was responsible for organising the annual meeting of Euro-Ataxia. Speakers included Dr. Chamberlain, and also Ria Broekgaarden of the VSN who stressed the importance of cooperation between scientists. This collaboration seemed to have paid off as in March 1996 Science published the discovery of the Friedreich gene by Massimo Pandolfo (Houston, USA), Michel Koenig (Strasbourg, France) and others. The VSN immediately stressed that this finding should not be overestimated: "In the short term nothing will change for FA patients" in terms

of treatment or cure, although the organisation also underlined that there would be a diagnostic test available immediately.

A mutation causing FA consists of an expanded GAA repeat in the first intron, which results in a faulty transcription of the gene into a protein called frataxin, which is homologous to a yeast protein (YFH1). YFH1 had already been identified in the context of cellular iron metabolism. Analogous to the yeast cell, it is hypothesised that frataxin is responsible for the iron efflux in the human cell's mitochondrion. The results of research into iron deposits in FA patients seemed to confirm this. Excess iron leads to increased levels of produced toxic free radicals, which results in cell damage and death (Delatycki et al., 2000). Communication of these results to patients led scientists to emphasise that although these findings would point to possible therapy options, short-term solutions were not expected. First basic research and clinical trials needed to be done. Moreover, dietary measures, such as toning down iron intake, were discouraged because of uncertain impacts.

Therapy options were focused on next and three main routes were identified: 1) so-called chelators removing excess iron, 2) antioxidant therapy to protect against free radicals, and 3) gene therapy. Two Australian research groups directly responded to the gene discovery by setting up gene therapy research, although they claimed that it would take years before clinical applications were introduced. For the chelator or antioxidant options scientists (Michel Koenig's group) first tried to create a mouse model for FA in order to test their effects. After some unsuccessful attempts they succeeded and produced substantial evidence to support the assumption that an excess of iron and free radicals play a major role in causing FA. The attention given to chelators quickly subsided because the iron levels were high in the mitochondria of some cells but not in most other cells in the blood. One potential free radical scavenger was identified by Rustin (1999).

Already in 1999 French and English trials were held on idebenone, a presumed antioxidant. The scientists involved reported positive results, at least regarding a heart abnormality related to FA, cardiomyopathy, although the trials were not double-blind and controlled by a placebo group.

In 2003 a lot of "well-organised" clinical trials, i.e. trials meeting scientific criteria, were concluded in Germany, Spain, the US and England and nearly all of them failed to find an improvement of the ataxia nor a decrease in heart size, or at least showed identical results. The VSN noted that enthusiastic claims made by the scientists involved were at least premature considering the clinical trial results. During the International Friedreich's Ataxia Research Conference in February 2003 several clinical trials were presented with the same varied and inconclusive results. Also the need for clarifying the precise function of frataxin, the set-up of measurement scales, and the natural history of FA was put on the agenda.

Despite the lack of convincing results the academic hospital in Groningen began with a small-scale clinical trial for children with FA in 2004. The VSN supported this trial by communicating about it, assisting participants with their health insurance claims (because idebenone was not registered for this disorder it would not be reimbursed), and lobbying for a nation-wide clinical trial by assisting patients and their parents in other parts of the country to influence their physician to consider an idebenone trial. Both the VSN and the Groningen medical specialists were cognisant of the lacking efficacy evidence in the context of ataxia but the eventual decrease in heart size still made it worthwhile to support this clinical trial. Once again, the need for monitoring scales was put forward. The Groningen team used cardiac measures, blood levels and video recordings. They produced a strict

test protocol because the health insurance company stipulated that as a requirement for reimbursement.

On 15 May 2005 the VSN was approached by Pierre Vankan, vice-president of the Swiss pharmaceutical company Santhera that focused on neuromuscular diseases. This business wished to set-up clinical trials with the drug idebenone in several European countries and the US. At that point in time it had only been approved in two European countries for Parkinson's disease. The small trials were accepted by the EMEA and FDA. Idebenone also obtained orphan drug status for both FA and Duchenne. Santhera sought assistance in organising the Dutch clinical trial. The VSN immediately recognised the chances for Dutch science and FA patients. Moreover, the drug had already been imported but because of lacking regulatory approval, no reimbursement was possible as yet.

The VSN approached Dr. Ewout Brunt, a medical specialist in Groningen and science advisor to the VSN, who was enthusiastic. The trial protocol was promptly discussed, and it was decided that they would take part. The VSN was very pleased with this movement towards proper FA treatment. The organisation regarded itself not as a research institute but more as a research advocate.

In November another 'investigators meeting' was held between Santhera, a few 'investigator'-scientists and the VSN. The latter played the role of host. The research protocol and additional questions were discussed and solved. For the trial four groups of patients would be formed, amongst which one placebo group. The dosage would be relatively high; this had been tested for safety in trials in the US. The trials were meant for patients with a thickening in their heart muscle. The heart function would be measured with MRI scans, and echoscope, blood, and neurological tests. The VSN was involved in setting up patient information. Among other reasons this was necessary in order to avoid 'tiredness' among patients to participate in trials and questionnaires. The interest and participation of the trial groups in the Groningen hospital had increased over time, and the VSN also observed a high level of dedication in the company.

In the meantime the Groningen group presented their preliminary results of the trial that started in 2004. These outcomes were not very positive, but they did learn about the protocol and process of therapy and monitoring. Nevertheless, they hoped that this would be improved during the Santhera trial in which they would have better tools at their disposal.

The proposed Santhera trial was discussed at the Euro-Ataxia meeting in 2006. Dr. Michel Koenig had tried to set up a trial immediately after his work on the FA mouse models but was unable to bring in the money that was needed. He was enthusiastic about the new initiative. Some participants at the meeting were more sceptical because of the use of a placebo group but overall the new trial was well received given the need to measure the effectiveness of idebenone for FA treatment.

Another VSN project concerning FA was the publication of a brochure on the disease that had been co-produced together with the Dutch College of General Practitioners (NHG). Patients could obtain this publication from the VSN once they were diagnosed and hand it to their general practitioner. In this way the doctor could learn about FA, and it would make future treatment easier.

In March 2007 the medical ethics committee of the Groningen hospital approved the trials, which led the VSN to inform their members about the conditions under which patients could participate. This information included the number of patients needed, the

characteristics of these patients, and the organisation of the participation. Later on the trials started.

The demand articulation process in this event theme can be subdivided into two periods. The first period saw a steady increase of scientific and ultimately also clinical interest in idebenone as a FA drug (Figure 35). During this period the VSN's involvement remained somewhat detached, mostly because the greater part of the developments were taking place abroad. It restricted itself to articulating the expectations and visions (Figure 35 and Table 14), giving its members balanced information about the developments and attempting to enthuse scientists and clinicians to work and cooperate on this drug.

Only after being approached by the Swiss company Santhera in May 2005 did the VSN have the opportunity to become involved (period II; Figure 35 and Table 14). Their input at the meetings and the co-production of the Groningen clinical trial was centred on hosting meetings, bringing major players together, assisting with patient recruitment, and contributing to editing patient information. In this way the organisation made use of its knowledge of previous participation in setting up clinical trials. In some ways it also was engaged in new experiences, though most notably it played host to a pharmaceutical company and scientists, and participated in establishing linkages between these parties.

The demand statements in period I were neither more specific nor did they change direction. The VSN only steered a middle course between hopes and promises, and provided a more toned-down, down-to-earth version of new scientific developments. In the second period (II) the clinical trials came closer to home: first the Groningen academic hospital performed an idebenone trial that was followed by the setting up of the Santhera trial by the same hospital. The VSN's demands became focused on setting up the trial with regard to the interest of the patients themselves. First-order learning occurred to a large extent in the second period of this event theme in terms of increase in numbers and concreteness.

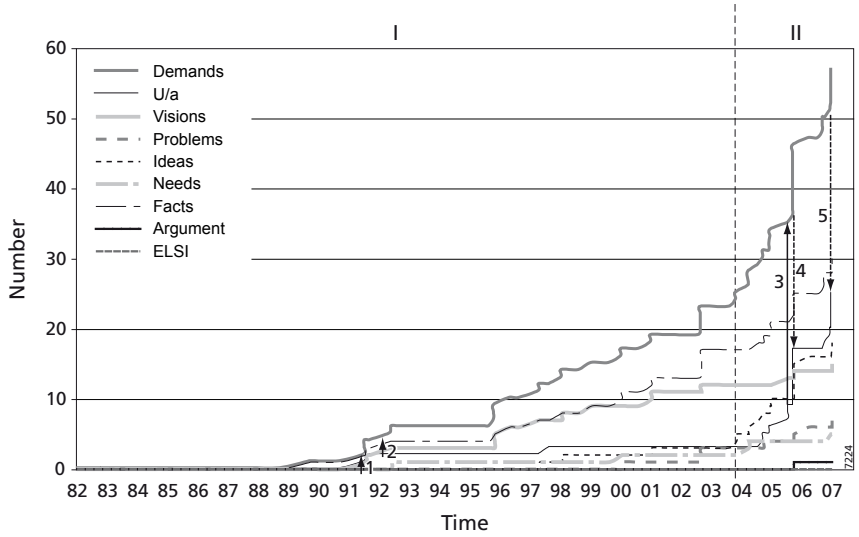

Figure 35 - cumulative number of demand and underlying assumption statements in the event theme on idebenone. The arrows are explained in answering research sub-question 1b.

Table 14 - changes in concreteness and direction of demand statements (idebenone event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	Following and stimulating science	Make as many scientists as possible enthusiastic for working on the disease. Arranged an information day for scientists with main message that cooperation between scientists was important.	-	-
		Ria Broekgaarden of the VSN stressed the importance of cooperation between scientists.	No change	No
		Results of finding FA gene should not be overestimated.	No change	No
		Enthusiastic claims made by scientists involved were at least premature considering the clinical trial results.	More	No
II	Clinical trials	Supported Groningen trial by communicating about it, assisting participants with their health insurance claims, and lobbying for a nationwide clinical trial. Acknowledging lack of efficacy evidence but heart size decrease made it worthwhile. Need for monitoring scales was put forward.	More	No
		Approached by company Santhera to set up idebenone clinical trials. VSN recognised chances for Dutch science and FA patients, and should bring registration and reimbursement closer.	More	No
		Approached medical specialist in Groningen. Trial protocol discussed.	More	No
		'Investigators meeting' held between Santhera, scientists and VSN. Research protocol discussed.	More	No
		Setting up the right patient information.	More	No
		Start with recruiting and informing trial participants.	More	No

Event theme VI: TCH346 in ALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that is also known as the Lou Gehrig's disease in the US, or motor neuron disease. It affects the nerve cells in the brain and spinal cord, the so-called motor neurons, and eventually leads to a situation in which the patient is unable to control muscle movement. Currently there is neither a clear-cut diagnostic test nor cure, although symptoms-relieving and quality of life-improving treatments are available. There is a small portion of patients (5-10%) whose disease has genetic origins, the so-called 'familial ALS' type, whereas the rest is labelled 'sporadic ALS'.

The VSN had been engaged in setting up diagnostic criteria through their dedicated workgroup on ALS and the ENMC international workshops. In November 1991 these criteria were produced and eventually published in an international journal (Jennekens et al., 1991). The intentions for pursuing the criteria were to decrease misdiagnosis and lay a foundation for scientific research. In 1991, the University of Amsterdam, together with the VSN working group on ALS, presented the results of a questionnaire on environmental and lifestyle factors that could explain ALS, but they did not find any useful correlations. During the ENMC workshop one of the major topics also included the search for genetic

factors that influence ALS. Later, in 1993 the VSN also participated with Dutch scientists in founding a biobank that contained (brain) tissue of ALS patients, which is compared to tissue from other kind of patients in order to obtain information on ALS.

Because ALS diagnosis, treatment and pathogenesis is unknown, some scientists, medical professionals and companies tried to set up tests and even clinical trials to validate efficacy and safety for ALS treatments by drugs that had been approved for other indications. These hypotheses were based on the progress in knowledge about ALS, such as mouse models and genetic information. One assumption was that the abnormal metabolism of glutamate, which is the primary excitatory neurotransmitter, results into toxic concentrations. Drugs that modulate this system were put forward as possible treatments. One of these drugs included riluzole (Rilutek) that was found by scientists and the company Rhône-Poulenc SA (now Sanofi-Aventis), organised in the ALS/Riluzole Study Group. These results were published in the New England Journal of Medicine in 1994. The antiglutamate characteristics of the drug had probably been discovered in the company earlier on in the 1980s. Subsequently, this drug was placed at the disposal of medical specialists to test in two large-scale clinical trials, which resulted in the drug receiving approval in June 1996. It was shown that riluzole prolonged life for three months. Many other hypotheses from both scientists and companies followed, most of them unsuccessful.

TCH346 was another compound that was proposed as a potential treatment for ALS. It was originally designed to stop the progression of Parkinson's disease but was hypothesised as also effective in the case of ALS. In March 2000 two scientists from Nijmegen University in the Netherlands claimed that they tested this assumption in ALS mice and could start clinical trials within three months. This news received much media attention because it would be the first real therapy for ALS after riluzole. As a result of this media coverage the VSN received many questions and needed to make a statement about the new developments. It claimed that it was of course good news and it would give ALS patients hope for treatment. Nevertheless, there were some potential pitfalls involved: the translation of the compound's efficacy from Parkinson's to ALS needed testing, the expectations were that ALS progression could only be slowed down or stopped but not cured, and the (long-term) safety issues were unknown. Moreover, clinical application would take a few years, and the results of the two Nijmegen scientists were not peer-reviewed and published.

The VSN moved proactively on these developments by engaging in discussions with the two Nijmegen scientists about how to interpret the results and accelerate ALS research. Scientists from the ALS Centre, including the VSN scientific advisor, participated in these discussions. Also, the VSN approached Novartis, the company that owned the compound, asking whether they would be willing to put the compound at the disposal of scientists to further test its efficacy and safety for ALS treatments. Moreover, the VSN constantly informed its members about the most recent developments.

Later on, the scientists from the Utrecht, Amsterdam and Nijmegen university groups put together a TCH346 research proposal and sent it to the Novartis headquarters. The head of Novartis Netherlands reacted, stating that they were deciding whether the company also wanted to start TCH346 trials for ALS because the compound was originally intended for Parkinson's. The VSN was kept informed by the scientific advisor of Novartis and maintained regular contact with scientists from the three universities in order to learn about the latest developments and to communicate the wishes of the organisation regarding treatment and care for ALS patients.

While the scientists, Novartis and the VSN were discussing the possibilities, an ALS patient went to court in January 2001 to demand access to TCH346 as part of an experimental treatment because he had heard that Novartis did not plan to investigate the drug for ALS indications before 2007. Novartis and the Inspection for Health Care discouraged this claim because they felt it irresponsible to distribute the drug in this experimental phase. The VSN reacted on a dual track: they communicated that they understood the "cry for help" from the patient, but that caution was important in biomedical research, and that scientists should be prudent about the way they presented their findings. In parallel, the VSN urged Novartis, regardless of the court's decision, to put the compound at the disposal of the three university groups for testing. Again, both sides of the story were stressed by the VSN: "it certainly is important to conduct these experiments meticulously. It is impossible to ask these patients to be patient. ALS patients do not have this time."

Later the court ruled that the patient did not have a right to demand this drug. Novartis announced that it was willing to start clinical trials in December 2001, but not in the Netherlands. Phase III trials were expected to be completed in 2003 and market approval in 2006. The VSN kept pushing Novartis for more information to calm the patients' excitement, partly also fed by the inaccurate news that the compound was available for ALS patients in other countries. While the patient appealed against the court decision, the VSN tried to discover through the network of Dutch neuromuscular researchers (ISNO) during meetings with Novartis why it would take so long to start the clinical trials.

In October 2001 a clinical phase IIa trial was completed for Parkinson's disease, which did not reveal principal efficacy improvements. Nevertheless, a second (phase IIb) trial was planned for this disease and in January 2002 also an ALS phase II trial started. It was claimed that by doing this Novartis had caught up on a backlog because a separate phase IIa was unnecessary. This ALS trial, organised in the USA and Canada, was combined with the administration of a biological marker that would provide insight into where in the body the compound could be found. 45 patients were treated with the compound and the trial focused on determining the safe doses. If this trial were to be completed successfully, then phase III trials were planned for 2003.

In anticipation of this, Novartis had already contacted several internationally-renowned US and European scientists, among whom one from Utrecht University, to deliberate about the research set-up. A double-blind, placebo-controlled trial, with a non-blind follow-up was envisaged. It was also expected that Dutch patients could enrol in this study and that registration would take place in 2006. The VSN informed their members about this, saying that they would indicate when patients could apply for trial participation, and warned against too much enthusiasm. From the start of the TCH346 controversy the VSN and its scientific partners held regular meetings (twice or three times a year) with high-level Novartis officers. The first meeting had been mostly about exchanging information and viewpoints, but later meetings focused on ways to accelerate clinical trials for ALS. In 2004 the phase III clinical trial started in Utrecht and other places. The VSN assisted in patient recruitment and information provision. Finally, in 2005 Novartis announced that the clinical trials showed no impact on ALS and Parkinson's disease progression, and therefore decided to discontinue the TCH346 development (Olanow et al., 2006).

The TCH346 theme started with the presentation of scientific results (period I; Figure 36 and Table 15). They were not offered through the regular channels, such as scientific journals or conferences, but through the Dutch media. This required the VSN to react

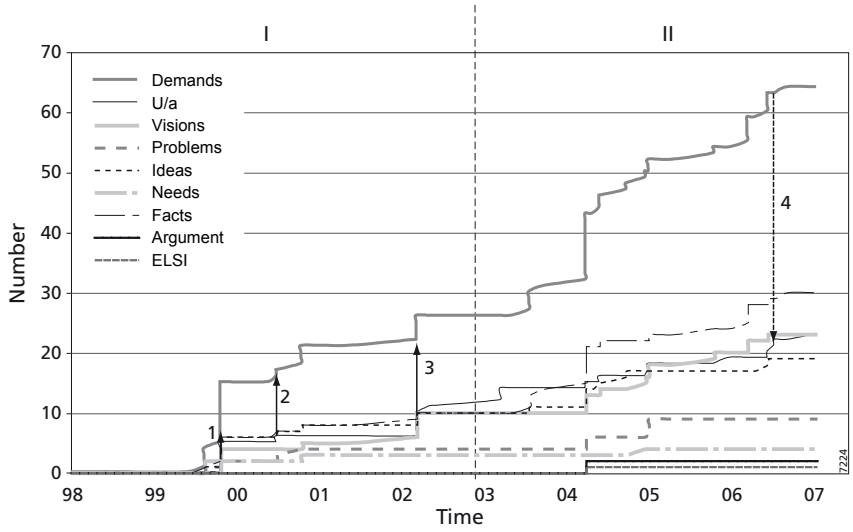

Figure 36 - cumulative number of demand and underlying assumption statements in the event theme on TCH346. The arrows are explained in answering research sub-question 1b.

at short notice, instantly checking the significance of the findings with their scientific partners, and subsequently by presenting balanced information to their members and the general public. The latter was necessary because of the overenthusiastic reactions, most notably by one patient who went to court. On a parallel track it urged Novartis to accelerate ALS clinical trials. This demand became increasingly concrete by asking the company to release the compound to scientists and clinicians to let them do the tests. The demands became less focused again after the start of phase II-clinical trials in North America, but were increasing in concreteness when Novartis started to consider phase III-trials (period II; Figure 36 and Table 15). The VSN had a higher level of involvement in those studies, assisting with informing and recruiting patients. All in all, first-order learning occurred in this event theme to a large degree, as measured by the increase in number and concreteness of demand statements.

When studying first-order learning in the six event themes as part of the first research sub-question we saw moderate (gene therapy and exon-skipping) to more fully-fledged first-order learning (stem cell therapy, Pompe, idebenone, TCH346). The next sub-question deals with second-order learning in the context of the six themes, and the way it relates to first-order learning.

1b. *Does second-order learning take place inside the VSN and how is this connected with first-order learning?*

Event theme I: Gene therapy
The major contribution made by the VSN on this event theme lies in the management of expectations. For example, the VSN constantly tried to downplay the opportunity of short-

Table 15 - changes in concreteness and direction of demand statements (TCH346 event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	Following and stimulating science; promises of new compound	Setting up diagnostic criteria through ENMC workshops.	-	-
		Results of questionnaire on environmental and lifestyle factors that could explain ALS: no useful correlations. Search for genetic factors was important.	No change	No
		Later, co-founding a biobank that comprised of (brain) tissue of ALS patients.	No change	No
		Received many questions after TCH346 claim of two scientists: both good news and need for caution. Potential pitfalls: safety and efficacy testing needed, ALS progression slowed down or cured, clinical application takes years, claim made by scientists was not peer-reviewed.	No change	No
		Proactively engaged in discussions with Nijmegen scientists.	More	No
		Approached Novartis to ask to release compound for testing.	More	No
		Reacted on court claim by patient in two ways: understood patient's "cry for help", but rigorous testing still needed. And renewed request to Novartis to release compound.	More	No
		Calmed patients by correcting inaccurate information and asked Novartis to start with clinical trials.	More	No
II	Phase III clinical trials	Informed members about phase III trials, warned against too much enthusiasm.	No change	No
		Ways to accelerate clinical trials for ALS.	More	No
		Assisted in patient recruitment and information provision for phase III clinical trials.	More	No

term treatment implementation (**1** in Figure 27[38]). Also, the organisation tried to be realistic about the demands made by institutions on the pharmaceutical innovation processes. When asked by patients or scientists about the necessity of clinical trials for gene therapy, probably following the reasoning that more flexible regulations would be appropriate for the severe, life-threatening muscular diseases, the VSN firmly answered that these trials were inevitable. If not properly controlled, these treatments could make the lives of, for example, children worse, and it might turn people against gene therapy research. Hence, risks and forcing should be avoided.

At the same time the VSN, together with other patient groups, found it important not only to downplay the expectations and positive implications of gene therapy, because that

38 The solid arrows indicate the influence second-order underlying assumptions have on first-order demands, whereas the dotted arrows indicate influence in the opposite direction.

could reduce the amount of attention this kind of research generates in terms of policy and finances, and it would only stress the arguments of opposing parties.

What is also striking in terms of the management of expectations is that the development in number of publications and clinical trials (Figure 26), as well as the two distinct periods of VSN's involvement in gene therapy (Figure 27), does show consistency with Gartner consultancy's 'hype cycle' (www.gartner.com). In this cycle the visibility of an emerging technology first dramatically increases to reach a 'peak of inflated expectations' (I). Later, because of the safety issues involved or simply due to a lengthy period with no results, the 'trough of disillusionments' sets in (II) only to make way for an increase in visibility – albeit a slower one than in the first period (III). This cycle is not only applicable to information technology (such as the Internet hype) but probably also on life sciences developments, such as gene therapy.

The VSN's management of expectations includes providing balanced information on current and recent scientific developments, i.e. scanning the scientific fields for new developments and selecting those that are relevant. While articulating their self-positions as part of their underlying assumptions, the importance of this management of expectations is underlined (**3**). The provision of information, especially when in the age of the Internet the threshold to obtain information is lowered, should lead to a well-balanced view on new developments in which both enthusiasm and realism feature (**2**). In other words, patients should of course be well-informed about new technologies, but factual information should also be complemented with caution, realistic expectations, and ideally also teaching patients about how scientific, business and regulatory procedures work in medicine. Realistic visions of the time frames in which gene therapy will be clinically introduced are part of that.

The VSN has three main reasons for the proper management of expectations (**4**): firstly, as described above, overenthusiastic reactions or demands made by patients might trigger risky R&D or being ahead of developments. These patients can be seen as easy targets for opponents of particular technologies. Secondly, in this way patients are educated about the way in which pharmaceutical R&D works. These patients could then be deployed as active 'lay-experts' during the formation of pharmaceutical or basic science policy, advocacy efforts, etc. Lastly, the VSN positions itself as a responsible actor in the field and hopes to be seen as such in order to increase the chances of being involved in management and policy on pharmaceutical and health care innovations.

All in all, the four interactions between demands and underlying assumptions as described above and in Figure 27, indicate that first-order and second-order elements were intertwined. Moreover, second-order learning was prominently present in this event theme, e.g. about how to deal with emerging technologies, how to manage expectations, and why.

Event theme II: Exon-skipping therapy for Duchenne muscular dystrophy

In this event theme stimulating and following science was important. Second-order learning did not occur frequently, i.e. only when evaluating the research steering activities in the 1980s (**1** in Figure 28) and during an EAMDA statute change in 1986 (**3**; more emphasis on research and development). In these instances there were also interactions between first-order and second-order learning. Also, the efforts in the early 1980s (subsidising research projects and organising scientific workshops) were backed (**2**) by what has been VSN's major goal from the time of the organisation's foundation: that neuromuscular disease research is important.

Event theme III: Stem cell therapy

In this event theme the VSN developed their underlying assumptions in different ways. The assumption that research is the most important way to better health care for patients with muscular diseases (**1**) has been present from the VSN's initiation onwards. Therefore, there was no actual second-order learning taking place.

On the other hand, second-order learning did occur because the VSN developed a way to react on the expectations concerning emerging technologies. The organisation increasingly regarded the management of expectations (**2**) as important for patients and science and technology development. For patients there is a balancing act involved between the right to choose the treatment they want versus the education that is needed on the safety and efficacy of therapies and on the way therapeutic R&D is organised. According to a questionnaire, the patient members wanted to be informed by the VSN (**3**). For scientists and technology developers there is another balancing act at stake: prospective images, such as expectations, are used to generate enthusiasm and support for new research. Conversely, there is always the risk to overstate advances which can lead to disappointment or even dangerous situations, which in turn results in a lower level of support.

The VSN envisages that both assumptions call for action by the patient organisation and that it is able to contribute in a singular and significant way. For example, governmental agencies do not see it as their task to inform patients about potentially risky and not scientifically-tested treatments. Also patient perspectives can contribute to R&D into neuromuscular diseases (**1**).

In conclusion, there were interactions between first-order and second-order statements, whereas changes in the underlying assumptions failed to occur very often and thus second-order learning was only modest in the stem cell therapy event theme.

Event theme IV: Enzyme replacement therapy (ERT) for Pompe disease

The positions taken by the VSN in Pompe disease developments largely grew from the general underlying assumptions that the organisation has developed from the 1970s onwards, i.e. the five-part objectives of "social support, advocacy, information provision, networking (gathering patients/families), stimulation and facilitation of research" (**3** in Figure 34). This is in line with the tasks that most patient associations envisage for themselves. The five objectives treated here for this event theme are:

- Social support: the VSN organised this through the Pompe working group.
- Advocacy: the VSN found out that its efforts were becoming effective and that other actors were increasingly recognising the VSN as a partner (**2**). The VSN positioned itself as an organisation that is voicing the interests of its patient members as its most important underlying assumption (**7**).
- Information provision: the VSN saw it as one of the main tasks to keep the Pompe patients well-informed, giving a balanced view of the situation. This was difficult, even for the VSN, because the exciting events sometimes resulted in overenthusiastic rhetorics (again the 'management of expectations'). The expected date for the market introduction of the Pompe medicine was always part of these rhetorics, which over the course of time needed to be adjusted from 2000 to 2006. The VSN also regarded itself as well-informed. The VSN made this self-reflection as part of their argumentation towards *Proefdiervrij* (**4**).
- Networking: because the diseases on which it focuses are themselves rare, and attention for these disorders is therefore not guaranteed, the VSN tries to forge

linkages with a diverse range of actors (8), especially with scientists and medical professionals (from Erasmus MC). The VSN also stimulated cooperation between scientists. The VSN also maintained contact with companies like Pharming and Genzyme, e.g. by assisting them to organise clinical trials and market access (reimbursement issues) (10). It comes as no surprise that the VSN's interests correspond with those of others, because once companies and scientists become engaged in Pompe R&D, they also want a cure as quickly as possible on the market. Nevertheless, in some circumstances the interests of parties can differ. For example, there is a trade-off between statistic significant clinical trial results that the companies strive for, and the patient's organisations that want a broad range of inclusion criteria (compassionate use, no need for placebo-control groups) (7).

- Stimulation and facilitation of research: this is an unusual objective for a patient organisation, but the VSN has always stressed this since its initiation (1). It has recognised that many neuromuscular diseases are genetically determined. This means that in their focus on research the VSN pushed to follow the train of events: gene location – gene identification – diagnostic tool/natural disease course – gene product identification – productive enzyme therapy. In order to control some of these developments the VSN played a part in raising funds, and even setting up their own scientific network. Moreover, the speed of innovation processes was also significant because "time is an important factor in a progressive disease [like Pompe]" (6).

In order to get/keep other actors interested in rare disorders such as Pompe disease, it is important for the VSN to understand not only the scientific side of the story, but also the way pharmaceutical innovation processes are organised. The VSN gradually learns how the drug R&D pipeline works, and eventually begins to master it. The VSN starts to proactively put issues on the agenda that are part of the upcoming steps of the drug R&D pipeline: "we must be prepared for new developments in the future." It also understands that the pipeline itself is not always linear and that it should reckon with feedback and feedforward loops, and eventual failures and delays (11).

Apart from learning about the pharmaceutical innovation process, the VSN also learns about other second-order aspects: it evaluates its role in the event theme as being significant, and tries to regard this role as a model for other neuromuscular disease associations to follow. Moreover, the VSN constantly checks whether it should pursue allocating resources to the advocacy of Pompe. The VSN starts to see itself more as a pioneering than a maintaining organisation. From 2006 onwards a treatment for Pompe had been on the market and major problems were remedied. The VSN should now make a choice whether to pursue their efforts (11).

Other second-order learning aspects concern the timing of actions (11), and the trust the VSN puts in other parties. The latter refers to the fact that they learnt not to trust other parties on face value anymore, but always require some sort of evidence base. For example, on several occasions during the event theme the companies made claims and promises about different technological options that afterwards proved to be non-scientific and misleading. It appeared to be difficult for the VSN to gauge the validity of statements made by companies listed on the stock exchange. A prominent example was the argumentation that Pharming/Genzyme used for taking over Synpac and Novazyme (5). At least in the case of Novazyme there was by no means scientific and commercial proof that its technology would form a serious competitor in the short-term.

All in all, second-order learning took place in this event theme on a large scale, and linkages between the two learning levels were present.

Event theme V: Idebenone for Friedreich's Ataxia

The underlying assumptions played a crucial role in supporting the first-order learning, and second-order learning occurred here as well. In period I (Figure 35) the need for R&D on neuromuscular diseases becomes increasingly important (**1**). Also, the VSN and other (international) patient groups underline the need for collaboration between scientists despite the competitive and secretive nature of the science system (**2**). Their philosophy is that rare disease R&D is so scattered and underfinanced that it will benefit more from combined efforts than from competition. The organisation of the clinical trial in period II (Figure 35) also complies with several underlying assumptions of the VSN. First, the significance of R&D and the related role the VSN sees for itself: not as a research organisation but as an instigator of R&D and coordinator between different types of actors (**3**). The VSN evaluates the involvement of the other actors (Groningen hospital, Santhera) as positive (**4**). Second, the VSN as a representative of Dutch patient-members is emphasised by the fact that the VSN finds it a great advantage to be one of the first contact points for the Swiss company that wants to perform the trials (**5**). In this way, the VSN increases the chances that also a Dutch clinical trial will be organised, and it learns about how to organise such trials (**4**). Third, there is a growing awareness of the VSN that it should not only focus on emerging technologies but also on testing already existing medicines for safety and efficacy in the context of a neuromuscular disease (**5**). This is expressed by its support of the foundation of a public rare disease subsidy programme. The VSN is aware that it is going against the tide, because only a few scientists, physicians and companies will be interested due to the low level of prestige, no possible patenting and small markets.

To conclude, second-order learning did occur and the analysis above shows that first-order and second-order learning interacted in this event theme.

Event theme VI: TCH346 in ALS

The VSN has as one of its most important underlying assumptions the support of neuromuscular disease R&D (1 and 2 in Figure 36). One way of doing this is through collaboration with national (ALS Centre) and international consortia (ENMC), partially set up by the VSN itself. Following other diseases, such as DMD and Pompe, the major route towards a cure is through setting up diagnostic criteria, finding genetic markers, producing diagnostic tools, setting up databases and patients' registries, and delivering information on the natural course of the disease. This should make the search for a treatment and the subsequent preclinical and clinical testing easier. Possibilities regarding clinical testing include trial design, informing and recruiting patients, setting up questionnaires, producing (historical) data on natural disease course, etc.

ALS differs from some other, more successful stories about new therapies in the sense that scientific developments have not produced conclusive treatments as yet. Therefore, therapies merely treat symptoms. Nevertheless, the events and statements on the TCH346 event theme are largely centred on the initiation, set-up and organisation of clinical trials. These trials are the results of 'drug repositioning': TCH346 was developed for another disease and was hypothesised to be effective for ALS.

The VSN learns to take a new position in the TCH346 event theme vis-à-vis roles it has previously played. In the first period the VSN reacts on the scientific breakthrough

by toning down expectations and asking for scientific advice (**1** in Figure 36), but it also asks Novartis to take action because it does not want science to come to a standstill (**2**). In this way it takes a mediating role (**3**). In their deliberations Novartis underlines the equivalence between the company and the VSN. In turn, the VSN values openness as being important because although there are contradictory demands it never becomes a conflict (**3**). The positions and underlying assumptions are clear for all parties. This makes the VSN a full interlocutor (**4**). Gaining insight into one's own viewpoints and those of others is important, as well as following the process of the debate (**4**). From the point of view of the VSN the meetings are directed towards result-based negotiations. It is important for the patient organisation to show its understanding of the innovation process ("it is nonsense to just want a drug without testing") and the advantages that the VSN can bring to the table, namely market access and image building (**4**). The VSN counts the results as substantial: clinical trials (phase II and III) are set up. The VSN is also proud of the speed at which it reacts to the "oversimplified" media attention and commotion of ALS patients (**4**). It can also be flexible and critical: weighing interests of a patient, i.e. the one that went to court, against those of the total group of patients: efficacy and safety should be tested first (**4**).

Again, second-order learning and interactions between first-order and second-order levels were present in this event theme.

1c. What 'demand articulation mechanisms' can be discerned from studying these learning processes?

Answering this research sub-question is an explorative and inductive exercise. The basis of this is the order of event categories encountered in the different periods of the event theme under study. Table 16 to Table 21 show these orders and characteristics for all event themes, which led to tentative ideas about demand articulation mechanisms.

Event theme I: Gene therapy

The first-order learning loops took more or less the same form in all three periods: facts coming from science (either beneficial or detrimental to gene therapy) were put on the VSN's agenda. The VSN scrutinised them, e.g. by discussing their validity and degree of promise. Based on this synthesis, the facts were then recounted and supplemented with disclaimers to put the developments into perspective. At the same time, a second loop was taking a slightly different course: again scientific facts entered the agenda and were validated, but instead of an expression with a warning realistic tone, the VSN was more enthusiastic. Table 16 summarises this.

Table 16 - induced demand articulation mechanisms per period for the VSN gene therapy event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I/II/III	Agenda–synthesis–demand	Reactive	Understanding, validating	Yes, with disclaimers	No	Management of expectations: realism/enthusiasm

Table 17 - induced demand articulation mechanisms per period for the VSN exon-skipping event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda–synthesis–demand–evaluation	Proactive	Preparation and alignment of actors	Ideas for workshops, projects and networks	Yes	Network building
II	Agenda–synthesis–demand	Reactive	Understanding, validating	Yes, with disclaimers	No	Management of expectations: realism/ enthusiasm

This management of expectations loop concerns a balancing exercise between the realistic and enthusiastic framing of new technological developments. Concerning the second-order learning loop an analysis was made as to whether the mutual influencing of self-positioning and other-positioning hypothesised in the conceptual model was present. However, in this event theme other actors did not position the VSN (no other-positioning). So, although second-order learning occurred to a large extent in this event theme, it did not take the form of the hypothesised second-order learning loop.

Event theme II: Exon-skipping therapy for Duchenne muscular dystrophy
As described above, this event theme has two periods with different characteristics. During the first episode the VSN saw stimulating research as one of its main objectives, which was proactively put on the agenda. The VSN dealt with this subject by contacting other actors, primarily scientists, together with whom ideas were developed into research projects and international platforms. The second period resembled the management of expectations loops as seen in the previous event theme on gene therapy, also taking into account both realistic expectations and visions, and enthusiasm. In both periods the hypothesised order of event categories was present (agenda – synthesis – demand) and showed coherence with regard to the content, although the second loop lacked the evaluation part.

Again, there was no second-order learning loop because of lacking other-positioning of the VSN.

Event theme III: Stem cell therapy
The VSN reiterated the promises that stem cell therapy held, and the importance of R&D in neuromuscular diseases. However, the organisation constantly followed the latest scientific and clinical developments critically, after carefully asking advice from medical specialists and scientists, and sometimes even asking the provider of therapies directly for information. This resulted in a balanced picture that was obtained through a demand articulation mechanism that follows this pattern:

- Scanning the scientific and clinical landscape and annotating new developments;
- Obtaining more information about developments through meetings with experts and asking those responsible for the developments themselves;

- Articulating their views about the developments towards their members and requesting action from other stakeholders (policymakers, companies).

This mechanism was repeated at least three times in this event theme: after the presentation of the research results of Mazzini and colleagues (I), during the Dr. Huang saga (II), and during the affairs with 'Preventief Medisch Centrum' and Cells4Health (III). Figure 37 and Table 18 summarise this.

Because other actors did not position the VSN, there was no second-order learning loop present in this event theme.

Event theme IV: Enzyme replacement therapy (ERT) for Pompe disease

Figure 38 illustrates several demand articulation mechanisms, most of which do not match the hypothesised order of event categories. These mechanisms are outlined and identified in Table 19.

Concerning the second-order learning loop we saw a constant mutual influencing of self-positions and other-positions. For example, the VSN found itself increasingly knowledgeable and empowered to be involved in drug R&D. Actors like the scientists at Erasmus MC agreed with this while others, such as the animal rights groups, doubted this positioning. Those who agreed with the VSN's position underlined this by iteratively stating their agreements and translating them into organisational terms by forming alliances and coalitions. On the other hand, the VSN reacted to those actors who rejected the role of the VSN by substantiating its self-positions. In some cases this led other actors to change their opinion about the VSN. In general, stakeholders in this event theme increasingly stated the importance of patient advocacy. All in all, the second-order learning loop was present in this event theme.

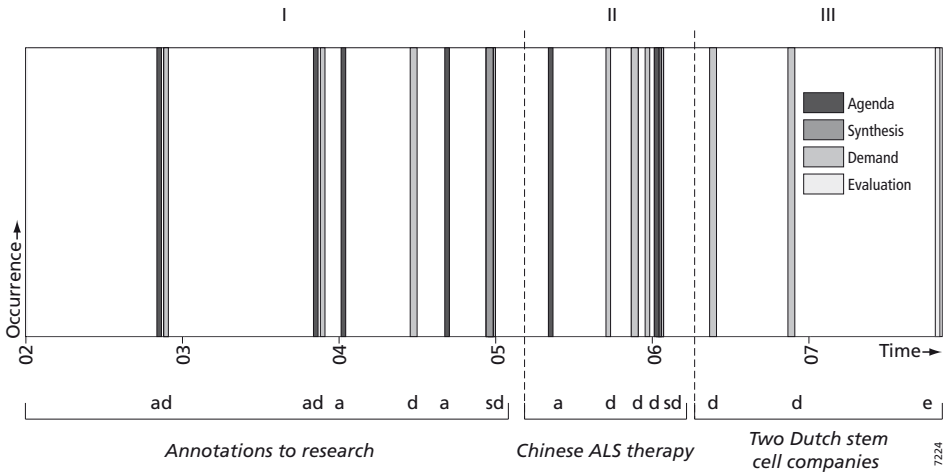

Figure 37 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in the stem cell therapy event theme[a].

a We did not present this kind of figure in the previous two event themes because in these two embedded cases the event categories succeeded fairly quickly. This could not be presented in the form of, for example, Figure 37.

Table 18 - induced demand articulation mechanisms per period for the VSN stem cell event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda/demand–agenda–demand–agenda–synthesis–demand	Proactive scanning of scientific work	Understanding, validating	Yes, with disclaimers	No	Management of expectations: realism/ enthusiasm
II	Agenda–demand–synthesis–demand	Reactive (media reports)	Aligning with scientists	Yes, but balanced	No	Management of expectations: realism
III	Demand–evaluation	No	No	Yes, asking to take action	Yes	Management of expectations: realism Urging for action

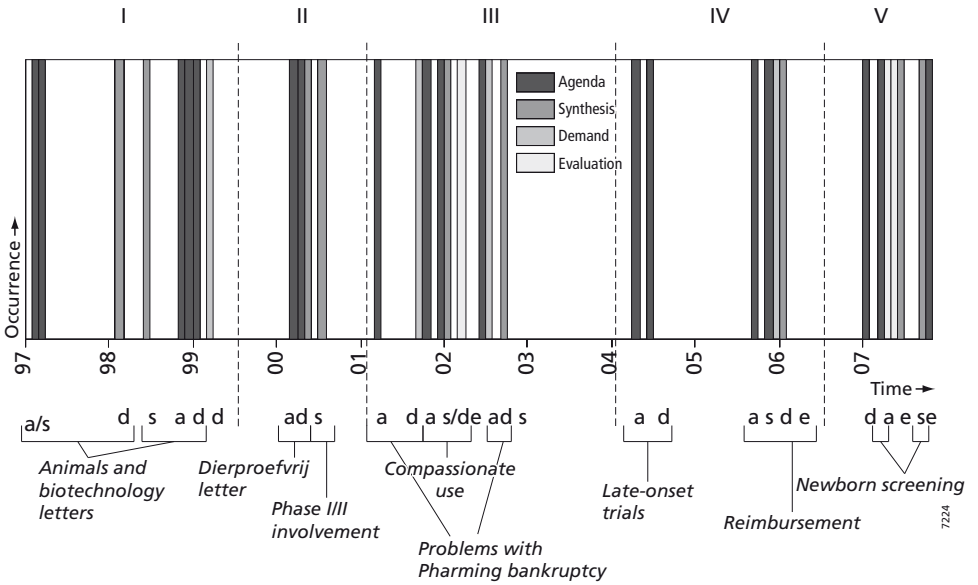

Figure 38 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in the Pompe event theme.

Table 19 - induced demand articulation mechanisms per period for the VSN Pompe event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda/synthesis–demand (2x)	Proactive	Continuous information gathering	Yes	No	Stay on track
II&III	Agenda–demand (*Proefdiervrij* letter and problems about Pharming 2x)	Reactive	No	Yes	No	Knee-jerk reaction
III	Agenda–synthesis/demand–(compassionate use; late-onset trials)	Reactive; done by international patient group (IPA)	Done by IPA	Yes	No	Following others
IV	Agenda–synthesis–demand–evaluation	Proactive	Information gathering	Yes	Yes	Active case building cycle
V	Agenda–synthesis	Proactive	Prepare proposal	Not (yet)	Not (yet)	Unfinished business

Event theme V: Idebenone for Friedreich's Ataxia
Figure 39 shows the ordering of the event categories over time in the two periods. The demand articulation mechanisms are depicted in Table 20. Because of a lack of other-positioning there was no second-order learning loop present in this event theme.

Event theme VI: TCH346 in ALS
The following figure (Figure 40) depicts the ordering of the event categories in this event theme. The identified demand articulation mechanisms are to be found in Table 21.

In the context of the second-order learning loop the VSN positioned itself as having a mediating or interlocutor role, being critical and flexible, quickly anticipating new developments, and representing the interests of 'the' ALS patients. Other actors, such as scientists and clinicians of the ALS Centre and Novartis, endorsed this position by entering into talks with the VSN and taking their views seriously. This reinforced the VSN to continue its advocacy activities. Nevertheless, some actors denounced the position taken by the VSN. The VSN reacted to these views by listening to the actors, seriously weighing and balancing their demands and substantiating the reasons why it did not agree. Thus, second-order learning loops are present.

In answering research sub-question 1c several demand articulation mechanisms were discerned that shed a light on the first-order learning loops as they are run through in this case study. In the conclusions and discussion (Chapter 8) these tentative mechanisms are combined with those found in the other case studies. In this way an overview is produced that shows to what extent comparable mechanisms are found in the different case studies,

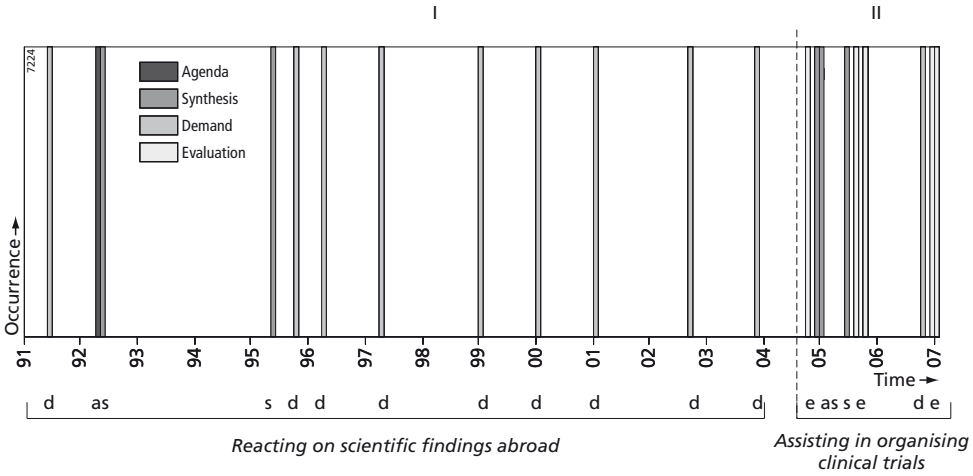

Figure 39 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in the idebenone event theme.

and whether these mechanisms can be summarised in a more abstract, robust list. Moreover, the second-order learning loop was also studied but the interaction between self-positioning and other-positioning was only found in two event themes: the Pompe and the TCH346 cases.

5.3 Demand articulation processes in interaction with others (research question 2)

The VSN is a patient advocacy group that is actively engaged in interacting with a wide range of actors. It maintains contact with its own members (the As in Figure 15), through

Table 20 - induced demand articulation mechanisms per period for the VSN idebenone event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda/synthesis–demand	Reactive on scientific findings abroad	Understanding, validating	Yes, mostly expectations with disclaimers	No	Management of expectations: realism/ enthusiasm
II	Agenda–synthesis–demand–synthesis–evaluation–synthesis–demand–evaluation	Reactive (approached by company)	Validating and aligning with scientists; bridging scientists and company; assist organising trials	Announce trials under conditions	Yes	Following others

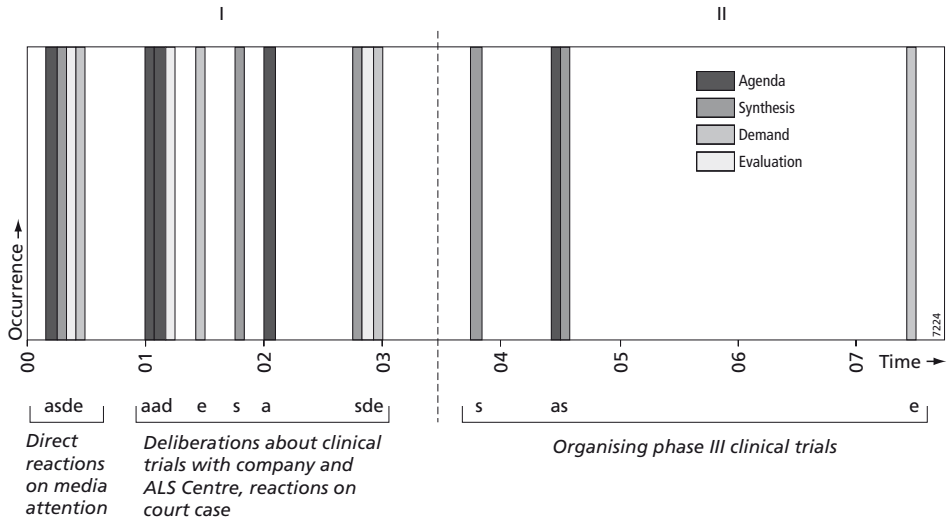

Figure 40 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in the TCH346 event theme.

Table 21 - induced demand articulation mechanisms per period for the VSN TCH346 event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda–synthesis–demand–evaluation	Reactive (instantly, to media outburst)	Understanding, validating, aligning with scientists and company	Yes	Yes, feedforward to next, hence more proactive loop	Quick management of expectations: realism/enthusiasm
I	Agenda–demand–evaluation–synthesis–agenda–synthesis–demand–evaluation	Proactive	Aligning actors	Yes on dual track: management of expectations and pushing for trials	Yes	Management of expectations: realism/enthusiasm and Urging for action and Network building
II	Synthesis–agenda–synthesis–evaluation	Re-/proactive	Bridging scientists and company; assist organising trials	Announce trials under conditions	Yes	Following others

one-way communications, such as newsletters, and two-way communications, such as organising national conferences and setting up disease-related working groups. The VSN also (co-)founded a large group of other organisations, mostly concerning research. Figure 24 provides an overview of these organisations. Lastly, the patient group also actively interacts with other actors in the pharmaceutical and health care innovation arena (the Bs in Figure 15), such as pharmaceutical companies, the government, and the media. This section shows demand articulation processes in the context of one of the event themes introduced in the previous section: the one on enzyme replacement therapy for Pompe disease. This theme is selected because VSN representatives find it the most important topic in which they have been involved within the context of pharmaceutical innovations. This opinion might be biased by the level of success of the patient advocacy and drug R&D itself, which enabled the VSN to participate in all phases of the drug innovation process. The VSN articulated its demands in interaction with both the represented and other actors. How this demand articulation in interaction with others took place is dealt with in the following three research sub-questions.

2a. *Does demand articulation take place in a multi-actor innovation arena involving interactions between the VSN and its representing actors (As) and other relevant actors (Bs)? In other words, to what extent is convergence or joint construction of demands occurring?*

The event theme on Pompe disease consisted of five periods, which are illustrated in Figure 34. We investigated the extent to which several actors agree with the VSN on first-order and second-order level. These actors include government ministries (on health and agriculture), parliament, animal rights groups, scientists at Erasmus MC, and companies like Pharming and Genzyme. These were selected because they featured most prominently in the case study database. Moreover, we took the represented patients and the international leg of Pompe patient representation (IPA) into account. Figure 41 shows the degree of agreement between these actors and the VSN on both first-order and second-order level over the five periods (1-5).

Figure 41 illustrates that some actors, like Erasmus MC, the IPA and the represented patients, agree both on first-order demands and second-order underlying assumptions for all five periods in the Pompe event theme. Therefore, they are in a state of shared demands with the VSN. There has been a strong connection between the scientists at *Erasmus MC,* who started serious attempts at enzyme replacement therapy for Pompe, and the VSN. This could be explained in part by the singularity of having world-leading research on your doorstep with the related enthusiasm and accessibility of the scientists themselves. This might even explain why the VSN sided with Erasmus MC on several occasions, e.g. during the shift from rabbit-based to a CHO-derived enzyme product. Moreover, they cooperated on at least two significant occasions: while setting up a registry of Pompe patients, and during the discussions about the continuation of treatment for the Pompe babies with the rabbit-based product. Furthermore, the VSN evaluated the role of the scientists as influential.

The VSN was the co-founder and a board member of the international branch of Pompe patient advocacy, *IPA*. Therefore, the agreement on second-order elements comes as no surprise, as both parties pursued the same interests and because people at the VSN were, among others things, responsible for drafting IPA's objectives (see Figure 33). During the foundation in 1999 the IPA envisaged that patients were emerging as partners in

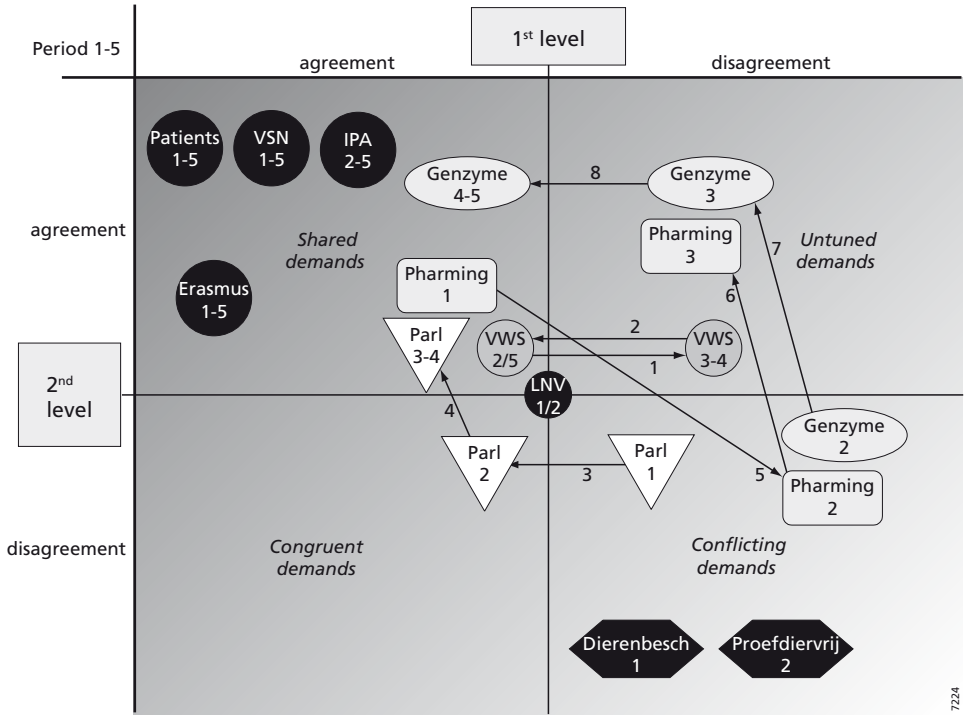

Figure 41 - shifts in the level of joint construction between the VSN and actors A (patients) and actors B (IPA, Erasmus MC, Pharming, Genzyme, parliament, Ministry of Health VWS, Ministry of Agriculture LNV, animal rights groups Dierenbescherming and Proefdiervrij, parliament) for the Pompe event theme. The numbers in the boxes indicate the periods the actors feature in; the arrow numbers are dealt with when answering research sub-question 2c.

the pharmaceutical sector, whereas in 2003 it evaluated its role as a recognised source of information, patient voice, creator of a Pompe community, and owner of scientific data. Furthermore, the international patient advocacy model as initiated by the IPA could serve as an example for other diseases. The same applies with regard to the first-order topics, although some slight differences could be observed. This has to do with the international level on which the IPA inherently acts, e.g. by organising several large international conferences, and meeting with industry representatives, such as Genzyme. It was argued that rare diseases needed this international approach because only then could one obtain some critical mass. Moreover, this sometimes implied that issues were brought earlier to the attention because of comparisons with other disease areas. An example includes the issue of reimbursement.

The VSN gathered the first-order and second-order statements of the *Pompe patients*, which it represented, in two ways: 1) most patients – the 'silent majority' – were reached and drawn into the VSN in differing degrees, e.g. through the annual meeting, newsletters, etc.; and 2) some patients had become more active in the VSN and participated in working groups, activities, communication efforts, and even on the board of the IPA. Notable examples of these 'patient champions' are Maryze Schoneveld van der Linde and Johan Bakker. In some cases, issues were put on VSN's agenda by the first category, the majority

of patients, which was the case during the *Proefdiervrij* saga where the VSN received a large number of complaints. In other instances only a small group of patients tried to influence the agenda, or the active patients received signals through their personal network of patients. This agenda-setting often occurred directly since these active patients mostly were part of or maintained close contact with policy decision-making bodies. In this way the VSN was often well able to sense what patients wanted them to do. In another event theme on TCH346, the VSN and an active patient significantly differed in opinion about how to approach a problem. The patient wanted to enforce drug treatment by going to court. The VSN considered the safety of the patient population as a whole more important and demanded proper clinical trials instead.

Other actors are encountered during one period of this event theme only. Notable examples include the two animal rights groups, the Dutch Society for the Protection of Animals (*Dierenbescherming*) and the Dutch Association Against Animal Testing (*Proefdiervrij*). Both groups differed on both levels with the VSN. Regarding the underlying assumptions the animal rights groups favoured the well-being and self-esteem of animals, thereby denouncing animal testing or using biotechnology on animals. Nevertheless, they would probably make an exception for biotechnology uses for which no alternatives are present and which result in direct significant advances in health care. Health advocacy groups, such as the VSN, had of course fewer qualms about using animals for drug R&D, and they claimed that demanding significant advances was asking too much of biomedical research. Both parties also criticised the way in which discussions were held, stating that the opposition used false or too sentimental arguments, or that they simply failed to grasp the meaning of certain technological developments. The *Dierenbescherming* was engaged in debates on the government regulations on animal biotechnology and there were no direct discussions between the VSN and this animal rights group. This was different in the case of *Proefdiervrij*, in which the VSN sought the confrontation after the publication of unfavourable advertisements.

The Ministry of Agriculture (*LNV*) concentrated on the then-new regulation on animal biotechnology. During the first two periods they were engaged in a delicate balancing act between animal rights groups and biomedical scientists and patients. This discussion was made more complicated because of the transgenic bull 'Herman' that attracted a great deal of media attention and appealed to people's fears on cloning. Nevertheless, permit decisions on this issue, and later on the rabbit-produced rhGAA, were not completely sided against Pharming, the company that owned Herman. This balancing act is illustrated by a central position in Figure 41. Although some actors thought at the time that the Ministry of Agriculture favoured a more strict regulation and were on the same side of the animal rights groups, these groups thought that the Ministry of Agriculture was against them.

The Ministry of Health (*VWS*) made a shift from a state of shared demands to the state in which the VSN and VWS differed on first-order demands (untuned demands), and back again. This shift did not actually occur because of changes within the VSN or VWS about one topic. It was merely because in the third to fifth period a different topic became central in their discussions, namely the reimbursement of orphan drugs instead of regulation on biotechnology. In the second period VWS had little difficulty in choosing sides for the biomedical scientists and companies in the broad debate, although these actors sometimes accused VWS of taking an unclear and inarticulate position in the discussions. This was partially caused by the fact that LNV – and not VWS – was the major 'problem owner' in drafting biotechnology regulations. In discussions on reimbursement, VWS became the

owner of the problem but now it did not agree on the way in which reimbursement should be organised. Later, in the fifth period there was a shift back towards the state of shared demands, because VWS found a solution to the reimbursement problem of orphan drugs that agreed with the one the VSN had in mind.

The Members of *Parliament* were virtually in constant debate with LNV and VWS about the Herman issue, the new regulation on biotechnology, and the Pharming story. The most dominant voices in parliament were in the first period actively trying to confine the room for manoeuvre for biotechnology activity in the Netherlands on grounds that differed significantly from those of the VSN. The VSN even claimed that politicians had a one-sided view of the issue, which was largely influenced by the media. Later the issues moved abroad, first because Pharming shifted some of its operations to other countries, and then because the focal point moved with Genzyme to the US and a less contested technological alternative of CHO-derived rhGAA. This in itself provoked reactions from Members of Parliament because they now wanted to know what the effects would be on biotechnology developments and the economy in the Netherlands. In other words, while they agreed on the need for stronger Dutch biotechnology activity it was on grounds of different underlying reasons (the state of congruent demands). Later, in period three and four, the Members of Parliament began to side with the VSN on another issue: they agreed on both the first-order and second-order level with the VSN on the reimbursement of orphan drugs.

In the first period *Pharming* strongly sided with the scientists from Erasmus MC for practical reasons: they knew a great deal about the disease and had ideas about a therapy. Moreover, they shared the same end goal: bringing Pompe treatment to the clinic. The VSN formed the third element of this triad while Pharming acknowledged the importance of involving patients. The VSN called these interactions part of a "natural alliance", which jointly fought the problems concerning biotechnology regulations. In the second period this hegemony was destroyed because, for Pharming, other underlying assumptions became important and because the VSN sided with Erasmus MC on the rabbit-based product: they thought that switching to a less-proven alternative would delay drug development. Later on, in the third phase, the second-order disagreements were more or less settled because Pharming at least recognised the interests of the patients who participated in the rabbit-based trial. Nevertheless, the company had distinct ideas about how to solve its financial problems and how to proceed with the Pompe drug development.

The other company involved, *Genzyme*, appeared more firmly on the scene from the second period onwards. They followed the same route as Pharming, which makes sense since both are united in a joint venture on Pompe drug R&D. After Pharming had been forced to withdraw from this joint venture, Genzyme headed into a fierce debate with scientists from Erasmus MC and the VSN. This debate concerned the continuation of the rabbit-based drugs production for the four Dutch patients who had participated in earlier trials, as Pharming and later Genzyme had promised. This issue was resolved after constructive talks between Genzyme, Erasmus MC and the VSN. In the fourth and fifth period the VSN and Genzyme moved closer together because the patient organisation was increasingly involved and informed, particularly through the IPA. The patient movement learnt how the drug R&D process was organised and why Genzyme would find it important to engage with patients ("they are not a charity fund, but they can obtain a better picture of and better access to patients"). At the same time, Genzyme also began to learn about the benefits of patient involvement.

To conclude, the VSN remained in a state of shared demands over the various periods with several actors with whom it formed a sort of alliance. Other actors, such as the animal rights groups, were completely at odds with the VSN, although this opposition was only present for some periods. A third group of actors, such as the two biotechnology companies, shifted between the distinct states of joint construction. Demand articulation and convergence is thus occurring but only for several groups of actors who form coalitions. Although a large number of actors end up in a state of shared demands together with the VSN, the road to this state is not a linear one, i.e. sometimes actors shift from a state of shared demands to states of diverging demands and back again.

2b. What strategies does the VSN deploy in the different interfaces with representing actors and other relevant actors?

The first part of this research consists of explicating the organisation of these interface communications. Table 22 summarises the different types of interfaces used, through which the VSN communicated with other interacting partners (actors B), and the methods used in the Pompe event theme. The most prominent interface types appeared to be presentation and deliberation, although other types and methods were applied as well.

It proved difficult to count the number of applied interface methods in the interactions with the represented actors (As), because in some cases the methods used were to a certain extent continuous, such as messages presented through the public website. The prominent interface types include presentation (using newsletters, the Internet, press releases), education (brochures like the 'Pompe Connections'), consultation (requesting data on disease progression for the Pompe registry), and deliberation (annual Pompe patient day, working group meetings in which some 'patient champions' participate).

Apart from the interface methods, Table 23 proposes several interface strategies that were used in interaction with the represented actors (As) and other interacting partners (Bs). These strategies are constructed in a tentative and inductive way using information about interface types (divided in interactions with As and Bs) and access, empowerment and impact characteristics.

The prominent strategies used by the VSN include the representation of others and the meeting sudden anxiety of the represented actors (A), and unasked advocacy and anticipative alignment towards other interacting actors (B). In the concluding chapter

Table 22 - interface types used by the VSN in Pompe event theme and relating methods deployed.

Interface type	Times applied	In Pompe event theme	Methods used (only prominent ones)
Consultation	6	0	-
Education	4	1	Book
Presenting, advocating	31	12	Letters, plans
Mediation	4	0	-
Coordination	28	0	Meetings, workshops
Deliberation	9	2	Meetings, symposium
Anticipation	3	0	-
Co-production	11	0	Founding centre

Table 23 - induced interface strategies per period for the VSN Pompe event theme.

Period	Interface types used	Characteristics	Proposed interface strategy
I			
animals and biotech letters	A: Deliberation (working group)	• Access: N/A • Empowerment: Pompe drug is major news, nothing should hinder its development • Impact: leads to letters	A: agenda-setting
	B: Presenting/ advocating (letters)	• Access: input was not asked • Empowerment: internal knowledge sources • Impact: low; it did not receive any attention in ministry and parliament	B: unasked advocacy
following research	A: Deliberation (working group)	• Access: patients members organised working group and influenced VSN policy • Empowerment: VSN was already geared towards research • Impact: contacts with Erasmus and Pharming	A: agenda-setting
	B: Deliberation (meetings)	• Access: establish contact with other actors • Empowerment: efforts to be better informed • Impact: created mutual understanding	B: anticipative alignment
II			
Proefdiervrij letter	A: Presenting (phone calls)	• Access: existing channels • Empowerment: not important • Impact: full	A: sudden anxiety
	B: Presenting/ advocating (letters)	• Access: low threshold • Empowerment: through contacts with Erasmus MC • Impact: by also sending letters to media and Advertising code committee	B: forceful advocacy
Phase I/II involvement	A: -		A: representation of other's interests
	B: Deliberation (meetings)	• Access: expressing worries in meetings with companies • Empowerment: through contacts with Erasmus MC • Impact: small	B: tentative advocacy
III			
Pharming bankruptcy	A: Presenting (phone calls)	• Access: existing channels • Empowerment: not important • Impact: full	A: sudden anxiety
	B: Presenting/ advocating (press releases), deliberation (meeting)	• Access: making use of existing channels • Empowerment: aligning with others • Impact: first not at all; later bigger through aligning actors	B: alignment of actors

Period	Interface types used	Characteristics	Proposed interface strategy
Compassionate use	A: presenting/ advocating (Internet, phone) B: anticipation, presenting/ advocating (letter)	• Access: existing channels • Empowerment: not important • Impact: full • Access: forced access to Ministry of Health • Empowerment: linking up with international developments • Impact: small (other actors do not agree)	A: advocate personal needs B: unasked advocacy
IV			
Reimbursement	A: Presenting/ advocating (patient champion's actions) B: Presenting/ advocating (letters), deliberation (meeting)	• Access: forced by patient champion • Empowerment: by experiential knowledge • Impact: full • Access: opened up by patient champion • Empowerment: internal knowledge resources • Impact: Ministry of Health listened and it aligned with efforts by others	A: advocate personal needs B: unasked advocacy
V			
Newborn screening	A: - B: Consultation (research)	• Access: forced • Empowerment: through consulting and aligning with others • Impact: none yet	A: representation of other's interests B: anticipative alignment

(Chapter 8) these proposed interface strategies are combined with those found in the other case studies to compile a more robust list of interface strategies.

2c. To what extent can the joint construction of demands by the VSN and their interacting partners be attributed to the interface strategies used? And how effective were those interface strategies?

Figure 41 shows shifts in joint construction states, some of which are the direct result of successful or failing usage of interface strategies by the VSN. The shift of VWS from a state of shared to untuned demand (#1 in Figure 41) stemmed from a change in topic, i.e. from animal biotechnology to reimbursement, and thus was not the result of deliberate VSN strategies. The same applies to shift #4 of parliament. However, it was the VSN that, among others[39], advocated a different solution to the problem. Parliament immediately sided with the VSN; the Ministry of Health only agreed later. Therefore, shift #2 was caused by VSN interface strategies, but once again the advocacy efforts of others should also be taken into account. Shift #3 was caused by external factors, i.e. biotechnology activities moving abroad.

The shifts of Pharming from shared to conflicting (#5), and later untuned demands (#6) were the result of advocacy by the VSN. Frequent deliberations between the VSN and Pharming paid off. The third party on these occasions, Erasmus MC, constantly sided with

39 See the next case study on the Steering Committee on Orphan drugs.

the VSN. Although Erasmus MC was not part of the shifts as illustrated in Figure 41, one might argue that this high degree of shared demands over different periods was the result of effective interface strategies. This also applies with regard to the shifts that Genzyme made (#7 and 8): these arise from effective advocacy by the VSN in cooperation with Erasmus MC.

To sum up, the VSN followed a wide variety of interface strategies and methods. Some of these strategies influence shifts in the joint construction of demands (Figure 41): shifts #2 and 4 in collaboration with others, and shifts #5 to 8 in close cooperation with Erasmus MC. Moreover, communication with actors A can also be described as effective: important issues entered the agenda easily by means of communication channels the VSN had built through patient champions, or by representation of the patients' interests by VSN employees and the Pompe working group. The issues were mostly put on the agenda reactively and with a high sense of urgency. Nevertheless, occasionally, mostly through patient champions or the international branch of Pompe patient representation (IPA), topics were addressed in a more proactive and anticipatory manner. These interface strategies ensured that patients and their representatives (the VSN and IPA) remained in line with each other, i.e. in the same state of shared demands.

Table 24 - summary of major conclusions gathered from several event themes in the VSN case.

Event theme	First-order learning	Demand articulation mechanisms	Second-order learning	Second-order learning loop?	Influencing of first-order and second-order learning
I. gene therapy	Moderate	Management of expectations: realism/enthusiasm	Yes	No	Yes
II. exon-skipping	Moderate	Network building Management of expectations: realism/enthusiasm	Moderate	No	Yes
III. stem cell therapy	Yes	Management of expectations: realism/enthusiasm Urging for action	Moderate	No	Yes
IV. Pompe ERT	Yes	Stay on track Knee-jerk reaction Following others Active case building cycle Unfinished business	Yes	Yes	Yes
V. Idebenone	Yes	Management of expectations: realism/enthusiasm Following others	Yes	No	Yes
VI. TCH346	Yes	Management of expectations: realism/enthusiasm Urging for action Network building Following others	Yes	Yes	Yes

5.4 Preliminary conclusions

The initial impression of the VSN shows that it is a patient organisation that maintains contact with a large variety of actors and that it is able to use these contacts to articulate their demands. The VSN co-founded some of these actors itself, most of which are related to scientific research into neuromuscular diseases. Stimulating scientific research has been one of the most prominent objectives of the VSN since its foundation in the 1960s. This involvement in basic and later clinical drug R&D is quite unique, at least for Dutch patient organisations. Furthermore, it also implies a rare, long-term vision on drug innovation: patience is certainly a virtue here. What is also noticeable is that the organisation strikes a good balance between the representation of patients and maintaining a dignified and semi-impartial stance. It does not pursue 'red herrings' or blind alleys for the sake of the (individual) patients, but is constantly aware of other stakeholders' interests and the pharmaceutical innovation system, which is characterised by strict regulation and extensive procedures, in which drug innovation takes place.

This VSN case was illustrated by observing six different event themes. Table 24 depicts whether first-order and second-order learning occurred in these themes, whether these two types of learning were interconnected, whether second-order learning loops were present, and what kind of demand articulation mechanisms were inductively defined based on the demand articulation processes that were followed.

It can be concluded that first-order and second-order learning occurred quite often in the event themes studied. Moreover, these learning loops are intertwined. A variety of demand articulation mechanisms are characterised, of which the management of expectations is the most frequent. Second-order learning loops were not present in all event themes because of lacking other-positioning. There was only mutual influencing of self-positioning and other-positioning in the event themes on Pompe ERT and TCH346.

With regard to the joint construction of demands, the VSN was at odds with some of the major actors in the Pompe event theme for certain periods of time, as is shown in Figure 41. Some shifts in these demand states were the result of effective interface strategies but some were clearly not (or even led to shift in the opposite, unintended direction). In interaction with the represented actors (A) the VSN used the representation of others' interests and the meeting of sudden anxiety, whereas in interaction with the other actors (B) the VSN applied strategies such as unasked advocacy and anticipative alignment. The most effective interface strategies of the VSN led to maintaining good contact with the patients they represent, its international partner IPA, and the scientists at Erasmus MC who gave them the much-needed empowerment, i.e. knowledge and confidence.

Chapter 6

Case study Steering Committee on Orphan Drugs[40]

6.1 Introduction to the Steering Committee on Orphan Drugs

This case study focuses on the 'Dutch Steering Committee Orphan Drugs' (*Stuurgroep Weesgeneesmiddelen*, hereinafter referred to as WGM). The WGM is an intermediary organisation that aims to stimulate the development of orphan drugs, and improve the cure and care of patients with rare diseases. The Dutch Ministry of Health founded this committee as a policy measure that was in line with European Union regulations aimed at rare diseases. As was defined in Chapter 3, orphan drugs are medicinal products developed for diagnosis, treatment or prevention of rare diseases. Rare diseases are a heterogeneous group of life-threatening or chronically-debilitating conditions, from which no more than 5 out of 10,000 inhabitants of the European Union suffer. Important issues in which the WGM has been engaged over the years were problems concerned with expensive orphan drugs reimbursement, and orphan drug R&D. The first research question, about demand articulation within the WGM, is answered for both these event themes, while the second research question, about demand articulation in interaction with others, is only answered for the reimbursement event theme. This theme was chosen because the WGM representatives felt that this was the most important topic they have been engaged in.

To set the scene, Figure 42 presents a social map around the WGM. Following a typology, presented in Chapter 2, the WGM is an example of a coordinating intermediary user organisation. This means that it interacts with several partners that belong to the same social world of which users are also a part. Therefore, a clear distinction between actors A and B could not be made here. The inner circle in Figure 42 consists of WGM members from different organisations[41] and disciplines. The top boxes are filled out with organisations that often take part in events together with the WGM, or feature in statements made by the WGM. The lower boxes include more indefinite groups of actors that are often cited by the WGM. Also, as an introduction, Figure 43 shows the most prominent events in which the WGM took part or which were important for the WGM, e.g. the invitational conference they organised at the start and the evaluation they went through in 2004.

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40 This chapter is based on Boon et al. (in press).

41 BioFarmind and Nefarma (biotechnology and pharmaceutical company representatives), VSOP and CG-Raad (umbrella organisations of patient groups), CVZ (Dutch Health Care Insurance Board), CBG (Dutch Medicines Evaluation Board), two medical specialists, a pharmacist, a scientist, and a representative of a health care insurance company. VWS (Dutch Ministry of Health) and the Dutch representative in the Committee for Orphan Medicinal Products of the EMEA have an observatory role.

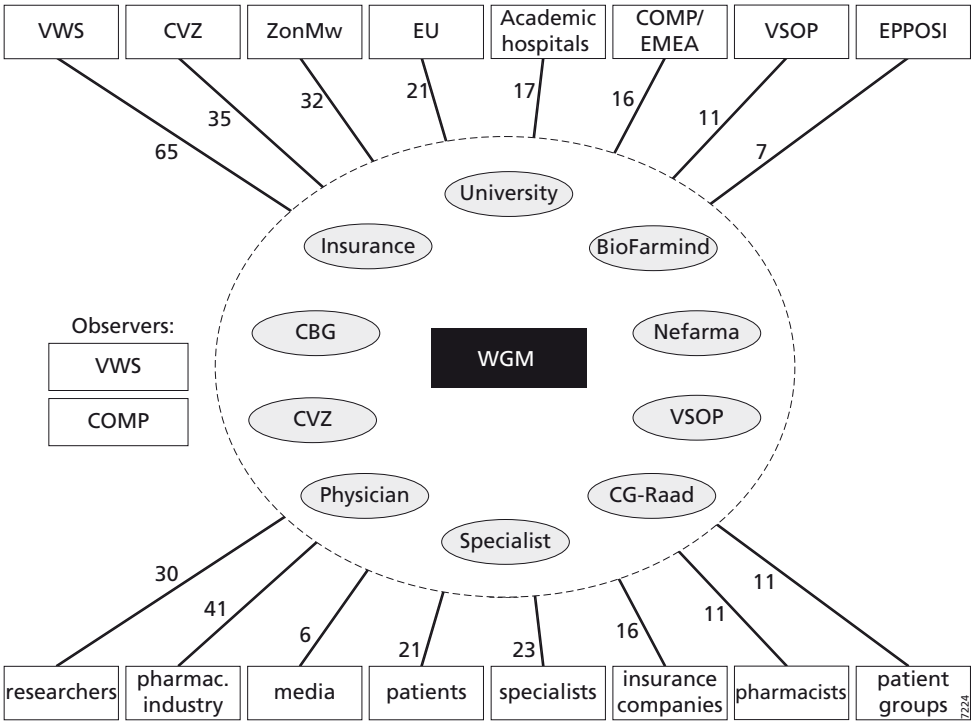

Figure 42 - social map of the Dutch Steering Committee Orphan Drugs and their interacting partners (figures indicate the number of times that they are mentioned in the database).

6.2 Demand articulation processes inside the WGM (research question 1)

The sub-questions treated here are answered by studying two event themes: on orphan drugs reimbursement, and orphan drugs R&D. The narratives of these event themes are presented as part of research sub-question 1a.

1a. Does first-order learning take place inside the WGM?

Event theme I: The reimbursement event theme

The first event theme[42] is about the reimbursement of orphan drugs by public and private health insurance schemes. A few disadvantages are associated with orphan drugs. Most notably, because of the low prevalence of rare diseases some of these drugs are relatively expensive, and there are only a few patients available for clinical trials required for product approval and reimbursement decisions. The Dutch health minister acknowledged these drawbacks and asked the Health Care Insurance Board (CVZ) to investigate possibilities to alleviate them in the late 1990s. At the same time, pressure on the Ministry of Health increased because the European Union requested proper organisation of the reimbursement of orphan drugs, and the first orphan drugs became available on the Dutch market (two medicines for the treatment of Fabry's disease). Over the next two and a half

42 This event theme is presented in full in Appendix C.

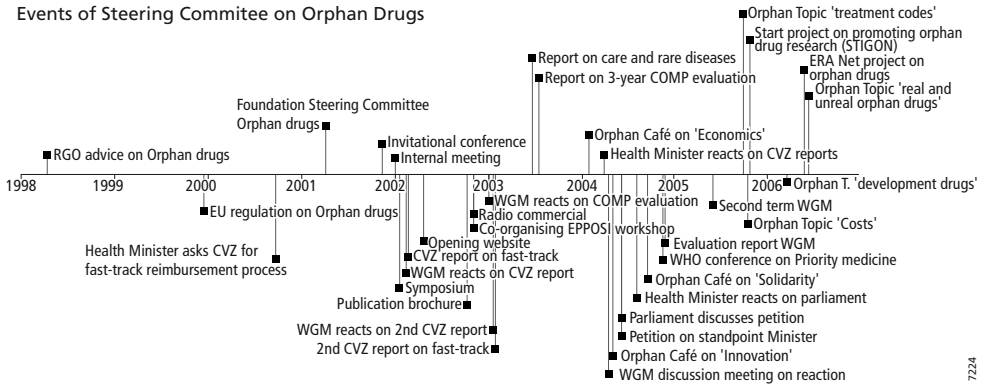

Figure 43 - most prominent WGM events (1998-2006).

years (2000-2003), CVZ produced two reports on this issue. The WGM were given the opportunity to react on these, and in this way influenced the drafts of both CVZ reports. One of the most important recommendations in the reports was to finance these medicinal products through the hospitals' research budgets. However, the WGM, CVZ and Members of Parliament feared a trade-off between economic and medical benefits in hospitals and requested another solution, e.g. financing by way of a *special reimbursement rule* that pays for the drugs straight out of the public or private reimbursement scheme. Despite this resistance, the minister stuck to his opinion of using the hospitals' research budgets. A petition initiated by the WGM, and supported by a large variety of parties, including hospital representatives, was submitted to parliament in June 2004. Parliament discussed the issue with the minister who then commissioned an investigation into the problems expected by the actors in health care. During this investigation he consulted the WGM and other stakeholders. In turn, the WGM, and other parties, started an exploratory study into the ways in which rare diseases were treated and how orphan drugs were administered in academic hospitals. One of the findings was the growing centralisation of rare disease treatment. Several stakeholders, such as the WGM and several patient organisations, underlined that this would be beneficial to the quality of care of rare disease patients, as had been experienced in the context of haemophilia and Gaucher's disease. Hospitals would be less willing to specialise in a few rare diseases with related expensive drugs if they were forced to draw on their research budget to finance them[43]. The minister proved to be amenable to this argument, but for different reasons, including the aspect of economic efficiency. Subsequently, in 2005 he decided in favour of the special reimbursement rule.

Figure 44 shows the occurrences of the demand statements and underlying assumptions over time. Especially the number of demand statements increases steeply. Furthermore, the five dimensions of demand are depicted in Figure 44: expectations, problems, needs, ideas, and ethical, legal and social impacts (ELSI). While the expectations, ELSI impacts, and needs showed moderate growth, the ideas and problems seemed to propel each other as they spiralled into a progressive increase. In the statements this surfaced as the constant and explicit linking of problems with ideas.

43 It should be noted that the WGM and other stakeholders see this centralisation process more as a bottom-up development, rather than something that should be steered.

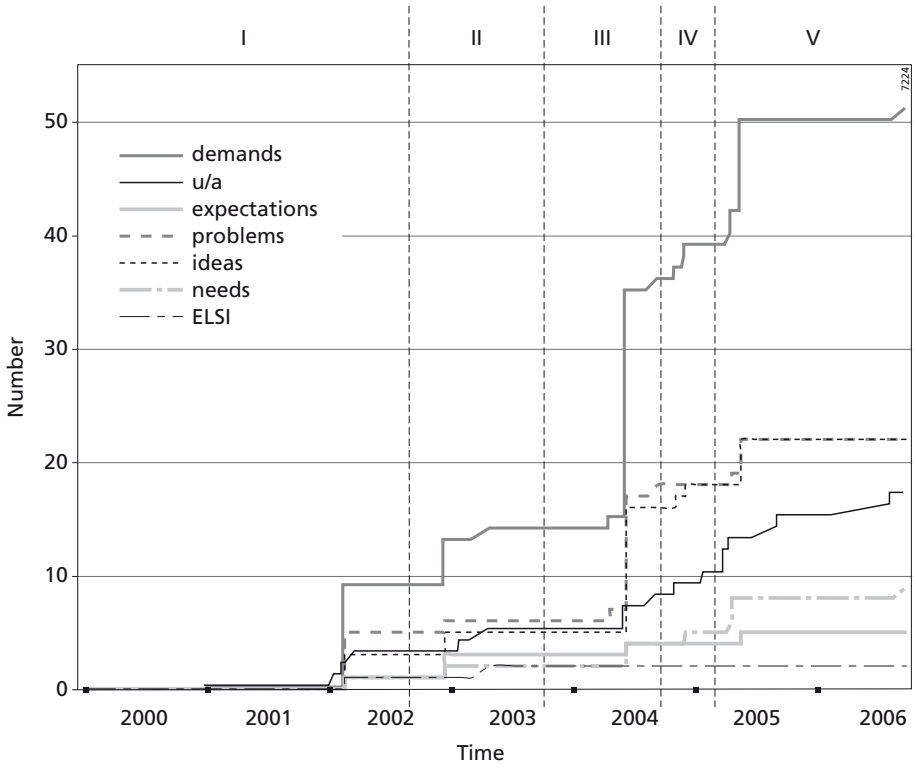

Figure 44 - cumulative number of demand and underlying assumption statements in the reimbursement event theme. Striking demand periods are denoted with numbers I to V.

Furthermore, there are five moments in the event theme when the leaps in demand statements are most striking. They correspond to the periods in which the event theme was subdivided (they are numbered I-V in Figure 44). Table 25 below illustrates the content of the demand statements over these periods. To reflect upon the articulation of demand when following these five periods, the table also illustrates whether demands became more or less concrete, and whether there was a change in orientation towards the topic, e.g. in favour of or against a solution for the reimbursement problems of orphan drugs.

The figure shows that the number of demand statements rose steeply. In addition, the table illustrates that the demand statements became more focused in the sense that only one aspect of the reimbursement problem became central, i.e. financing of orphan drugs used in hospitals (intramural). In a petition dated June 2004 several solutions and ideas were proposed, e.g. concerning the monitoring of rare diseases and setting up a European collaboration. In December 2004 only the special reimbursement rule remained, and the associated argument of expert centres was added. All the other problems and solutions became supportive of this rule. For example, monitoring the benefits of orphan drug treatment legitimises its reimbursement and illuminates the existence of centralised expert centres that could become overburdened with orphan drug costs.

As a result, Table 25 shows that within this topic of intramural reimbursement a narrowing down of ideas initially took place (period I to III: special reimbursement rule).

Table 25 - changes in concreteness and direction of demand statements (reimbursement event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	WGM reaction first CVZ report	Adequate care and equal rights to quality (solidarity).	-	-
		Problems: clinical evidence, alternative treatments, costs, definitions, procedures that turned out bureaucratic and non-transparent, medicines with no Dutch registration, differences between treatment in and outside hospitals.	-	-
		Ideas: stakeholder participation, cooperation with European parties (COMP).	-	-
II	WGM reaction second CVZ report	Reimbursement of intramural medicines through separate reimbursement rule, otherwise: high costs for expert centres.	More	No
		Idea: involve academic hospitals in deliberation.	More	No
		Transparency is important.	Less	No
		Stakeholder participation.	No change	No
III	Petition	Separate reimbursement rule: choice of administering drug should not be a financial one.	More	No
		Slow availability of drugs, amongst others due to lack of transparency.	More	No
		Monitoring benefits of treatment.	New	No
		Early tuning of stakeholders' wishes.	More	No
		Cooperation with European parties, e.g. through Priority Medicine project.	More	No
		Minister wanted every doctor to be able to treat patients with rare diseases. However, treatment was not standardised and knowledge was not well diffused. This called for concentration of treatment.	More	No
IV	Information for debate in parliament	Solutions for reimbursing intramural orphan drugs: adjust current reimbursement rules, introduce new orphan drug reimbursement rule, appoint expert centres that are given special budgets for rare disease treatment, add rare diseases to group of special cases (haemophilia and HIV/AIDS) that have special arrangements.	Less	No
V	WGM answered questions asked by Ministry of Health	Reimbursement through expert centres with special budgets or through special orphan drug reimbursement rule. Adjusting current reimbursement rules or using academic research budgets were not a solution because of steeply rising costs in the future and concentration of treatment.	More	No

Later, under the influence of consultation and deliberation with other parties, the scope of the range of ideas was widened yet again (period IV: e.g. special financing of expert centres). Since the preparation of the petition, the WGM had been more involved with other stakeholders, such as the representative bodies of hospitals and insurance companies, as a "spider in the web" (as one WGM member remarked during a meeting). Finally, a special reimbursement rule was again selected (period V). Also the statements themselves became more concrete: in the first instances "the Steering Committee wants to be involved in the discussion on the reimbursement of orphan drugs", later it was concerned with "the design of a separate reimbursement rule for orphan drugs [as opposed to a more generic one that is valid for all drugs]". Lastly, the orientation of demands showed no changes.

To sum up, the demand statements were increasing in number and showed an increasing sharpening in terms of content. The orientation of demand statements remained the same. Therefore, it can be concluded that in this event theme first-order learning articulation occurred to a large degree.

Event theme II: The R&D event theme

The second event theme focuses on the research and development of orphan drugs[44]. Programming scientific research was an important issue when installing the WGM. The need for coordination, prioritisation and stimulation of research was mentioned in the report drawn up by the Advisory Council on Health Research (RGO), on the basis of which the WGM was instigated. As a legitimisation it was stated that commercial parties would hardly develop orphan drugs because of the small markets involved and the associated commercial unattractiveness. The prioritisation of orphan drug R&D was dropped early on[45] because it would mean that the government could de facto exclude research on certain rare diseases. Meanwhile, other parties continued to stress the importance of coordination and stimulation.

From the start, the WGM decided to first fund its primary tasks, e.g. setting up a communication plan and a database about rare diseases. The remaining funds were used for small projects that either focused on the care of patients with rare diseases or on stimulating research into rare diseases. From 2002 onwards, three external pressures were put on the WGM that steered the direction of this event theme. Firstly, a French and an Italian partner separately approached the WGM to participate in attempts to start a pan-European initiative on rare diseases and orphan drugs. This was inspired by the notion that "orphan drugs could be defined as a volume problem. The solution therefore lies in scaling-up research through European co-operation". These two initiatives in the context of the Sixth EU Framework Programme failed (2002), whereas the ERA-Net Initiative succeeded later on (from 2003 onwards). Secondly, two Dutch public research funding institutes (ZonMw and Top Institute Pharma) stated in 2004 and 2005 that they also wished to allocate part of their research budget to rare diseases. Thirdly, the STIGON programme, which was intended to stimulate the translation of basic research results into the development of innovative therapies, had one part of its funds specifically allotted to rare and chronic diseases (from 2003 onwards). Because of a lack of success of the rare disease-dedicated part of the STIGON programme, the WGM decided to submit two proposals to

44 This event theme is presented in full in Appendix D.

45 Although it kept shimmering in the background: during the evaluation of the WGM some patient groups indicated that they would favour the WGM to prioritise between rare diseases.

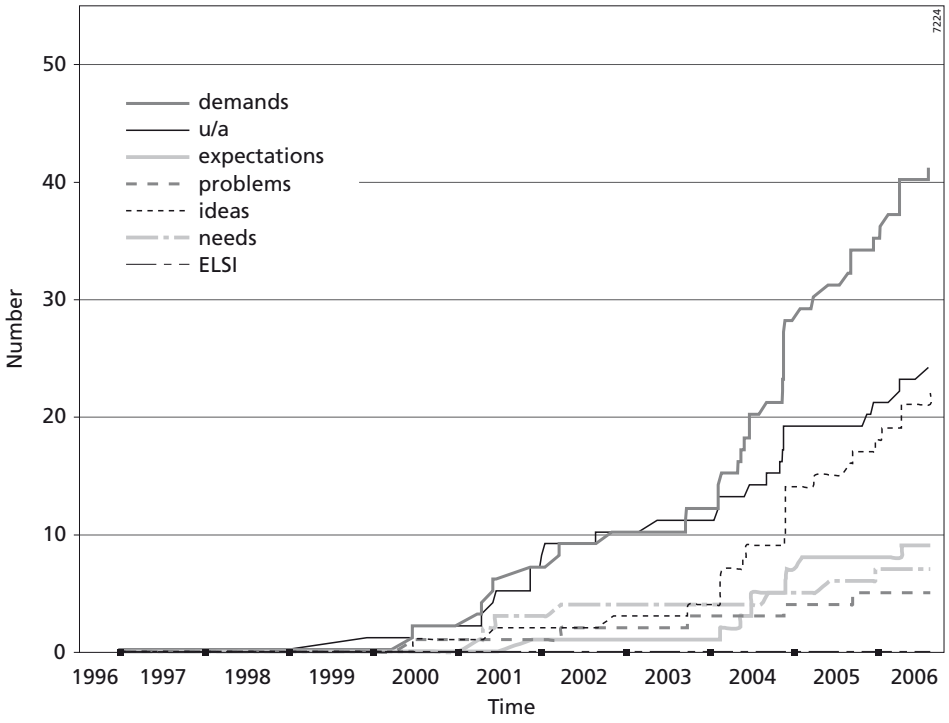

Figure 45 - cumulative number of statements in the event theme on R&D of orphan drugs.

ameliorate this. It consisted of a PhD project on collecting information on orphan drugs and rare disease research in the Netherlands, which could serve as input for setting up a national research subsidy programme. The second proposal concerned an 'orphan drug developer' project that aimed at stimulating companies to work on orphan drugs and rare diseases. The Ministry of Health approved these two projects provided that the development of orphan drugs would benefit directly.

Figure 45 shows the cumulative number of demand statements for the event theme on orphan drugs R&D in total and subdivided into the different dimensions of demand.

Figure 45 shows a sharp increase of demands (mostly ideas). However, unlike the event theme on reimbursement, no clear leaps in statements are visible, with the exception of a leap in ideas around the evaluation of the WGM in 2004. Moreover, the main topics within this event theme are highly dispersed. Therefore, the event theme is not subdivided into different periods. When analysing the statements themselves, it becomes clear that although the number of demand statements obviously grew, the content remained more or less on the same level of concreteness. Table 26 illustrates this. Thus, the prioritisation of orphan drug R&D was discarded at the start and did not enter the discussion again. Financial measures to stimulate orphan drugs R&D were not favoured at the outset as well. Other stimulating options were attempts to set up (European) networks, which at last resulted in cooperation within the context of an ERA-Net project. Furthermore, three times was an inventory made of Dutch orphan drug research: in the context of the RGO advisory report, a European initiative, and the STIGON-project. The last inventory might

be regarded as the starting point of a national research programme for orphan drug R&D. Such a programme has been an objective from the beginning of the WGM as part of the coordination of orphan drug R&D. The programme was often put on the agenda, but has so far not resulted in concrete results.

It can be concluded that although the number of demand statements steadily increased, it failed to lead to a more concrete focus and orientation. In this event theme first-order learning did not occur.

Table 26 - changes in concreteness and direction of demand statements (R&D event theme).

Period	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	RGO reported on orphan drugs R&D, WGM was founded	RGO: coordination, prioritisation, stimulating research.	-	-
		Preparation WGM: coordinate and stimulate (infrastructure for) research, inventory of OD research, point of contact network, inventory is difficult, financial stimulation is necessary. No prioritisation.	More	-
II	WGM explored position by invitational conference and symposium	Invitational conference: focus on orphan drugs R&D was important.	No change	No change
		Symposium: reinforce focus on stimulating orphan drug R&D.	No change	No change
		Projects: stimulate scientific projects on orphan drug and rare disease research.	No change	No change
III	Two EU FP6 initiatives	Network for rare disease research.	No change	No change
		Consultation: database of Dutch rare disease research projects.	No change	No change
IV	STIGON-projects	Programme for stimulation of innovative drug R&D in the Netherlands (STIGON) allocated some funds for stimulating orphan drug R&D. The health research-funding agency ZonMw and the Ministry of Health decided to fund two pilot projects set up by WGM. WGM chose for a project on making an inventory of orphan drug R&D as a starting point of a research subsidy programme, and a project that would stimulate the development of orphan drugs proactively (an 'orphan drug developer'). Focus on development, and research stimulation and monitoring (instead of coordination) was increasing.	More	No change
	ERA-Net	EU Priority medicines conference had drugs for rare diseases as one of its 'priorities'. WGM contributed to the report.	No change	No change
		Project to study the possibility for a Europe-wide rare disease research programme.	No change	No change

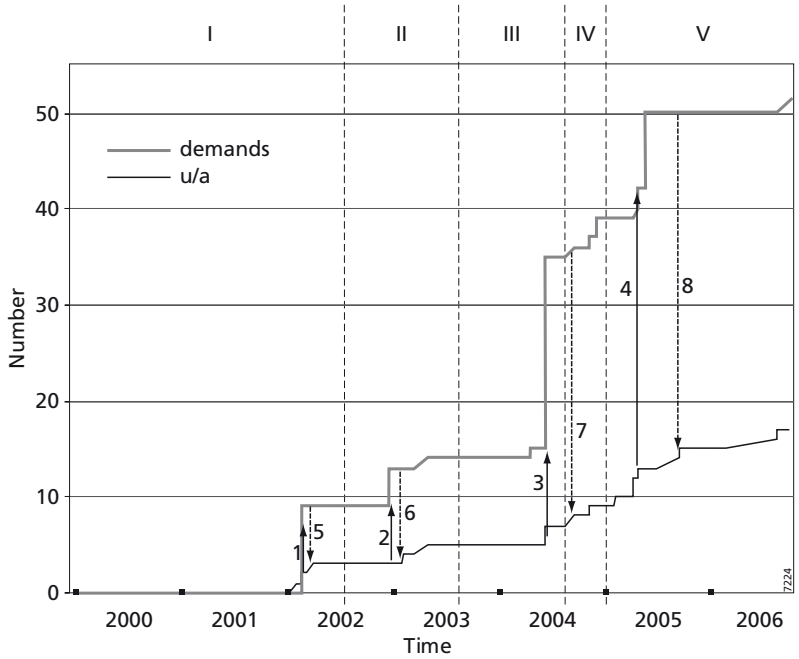

Figure 46 - the influence of demand statements on underlying assumptions (dotted arrows) and vice versa (solid arrows) related to the reimbursement event theme.

1b. Does second-order learning take place inside the WGM and how is this connected with first-order learning?

Event theme I: The reimbursement event theme

The first strand of this sub-question is about whether second-order learning occurred. When focusing on the underlying assumptions, we saw that underlying assumptions were frequently mentioned and even discussed. The ultimate preferences remained relatively stable, whereas the objectives and tasks of the WGM underwent some development. It can be concluded that second-order learning within the WGM occurred to a moderate extent. When discussing the learning loops below, second-order learning is investigated further.

The second strand of this research sub-question is about the level of interconnectedness of the first-order and second-order learning loop. For the reimbursement event theme a new rendering of Figure 44 again shows the five periods and illustrates at these instances the interactions between first-order demand statements and second-order underlying assumptions.

The underlying assumptions supported the demand statements presented above. In this sense, demands were *legitimised* (**1-4**). The demand statements in the petition run closely to the underlying WGM preferences (**3**), namely that patients and improvement of the quality of their life are central, that people with rare diseases have the same right of treatment as people with more prevalent diseases (solidarity principle), and that new treatments should be available to patients as soon as possible. Furthermore, the WGM evaluated and reflected on its contributions and the subsequent impacts. The WGM was satisfied with the way in

which their opinions had been included in the first CVZ report (5), while in the second CVZ report the WGM's input should have been treated more dominantly according to members of the WGM (6). They considered the input into the Ministry of Health's consultation round as "a very important operation that could strengthen the role of the Steering Committee" (7). Moreover, the WGM found the discussions in parliament (8) too focused on financial arguments rather than on patient-centred ones. Members of the WGM also regarded the results of this event theme, of which the special reimbursement rule for orphan drugs is the most notable, as one of its main achievements so far. All in all, the underlying assumptions were highly visible in this event theme but they remained unchanged in terms of concreteness, orientation and content.

In conclusion, the first-order learning influences second-order learning and vice versa. This shaping is legitimised by the relatively stable ultimate preferences, goals, and objectives of organisations[46].

Event theme II: The R&D event theme

Regarding the R&D event theme we have already seen that there was no first-order learning. Moreover, the range of topics that the WGM dealt with was wide. Research sub-question 1c deals with these first-order learning loops in more detail. Learning on the second-order, or on the underlying assumptions, did occur on several occasions:

- The WGM's role concerning R&D was determined when identifying WGM objectives, e.g. also by asking external parties what they considered important during an invitational conference and symposium.
- From granting small projects in the initial years after initiation of the WGM, the WGM learnt how to do this and on what it should focus. Small projects focused either on the care of patients with rare diseases or on stimulating research into rare diseases.
- During the preparation of the evaluation of the WGM and as a result thereof, the WGM and the Ministry of Health put the focus on both the stimulation and monitoring of research and development. In this way, prioritisation and coordination were discarded (once again). This influenced the set-up of the STIGON project.
- Regular evaluation by the WGM of past R&D efforts.

In effect, these topics show that second-order learning influenced the first-order statements. Because there was no profound first-order learning and the first-order topics were dispersed (see Figure 48), the mutual influence of first-order and second-order learning, although present, was not easy to illustrate by means of a figure.

1c. What 'demand articulation mechanisms' can be discerned from studying these learning processes?

Answering this research sub-question is an explorative and inductive exercise. The reason being the order in which the event categories were run through during the different periods of the event themes under study.

Event theme I: The reimbursement event theme

The sub-question deals with mapping the sequence of event categories over time. This sequence is presented in Figure 47 for the reimbursement event theme.

46 Which are closely linked to the reasons for WGM to be established.

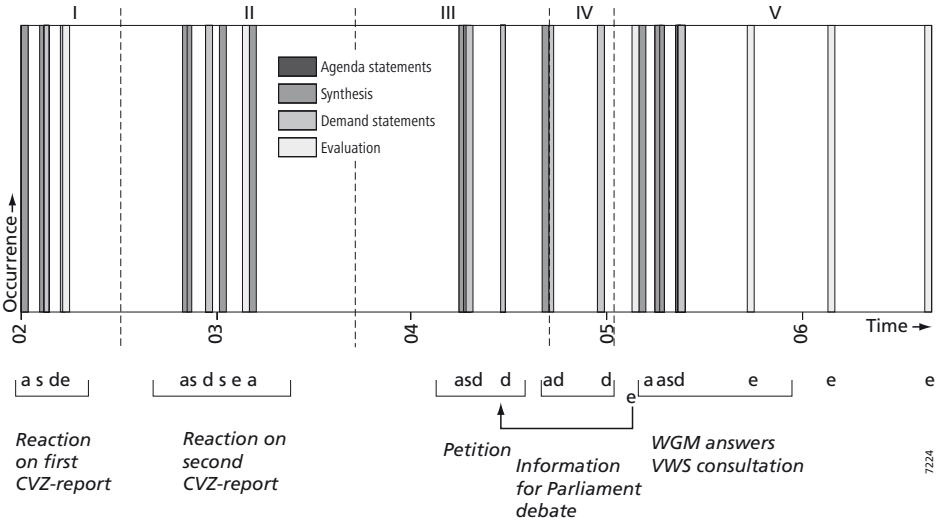

Figure 47 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in the reimbursement event theme.

The order of event categories shown in the figure more or less correspond with the one hypothesised in the central conceptual model (Chapter 2). During the first period this match was even perfect: the draft versions of the CVZ report were put on the agenda and subsequently discussed at a meeting. These views were then parsed a letter, the content and impact of which was internally evaluated later on. The second period actually saw two runs of the first-order demand loop because after the expression of demands the WGM had the chance to react again on a draft version. The third period followed the hypothesised pattern once more. This time the agenda was shaped proactively, by the WGM itself, and not as a reaction to external parties. The elaboration of the loop had also a less formal character. The fourth period consisted of the quick preparation of an input document for discussions in parliament, which resulted in an abridged version of the loop. The last period again showed great similarities with the hypothesised order.

Table 27 shows these orders and characteristics, which led to tentative ideas about demand articulation mechanisms.

Turning again to the second-order learning loop of mutual influencing between self-positions and other-positions as was hypothesised in the conceptual model, the WGM's self-positions show an increasing degree of awareness of their possibilities and responsibilities. During the first two periods, external parties dictated the agenda, whereas later on the WGM began to either set their own agenda or invited others to contribute. Developments were introduced to the daily board of the WGM (chairman and secretary) and they decided to take immediate action (through appointments, letters), put it on the next meeting's agenda, or discard it. Sometimes, discussion at a meeting resulted in agenda items for the next meeting.

The first two periods, in which the WGM took a reactive stance towards the reimbursement problem, were also characterised by the construction of its position by the WGM. The major ultimate preferences, including solidarity ('rare disease patients have the

Table 27 - induced demand articulation mechanisms per period for the WGM reimbursement event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda–synthesis–demand–evaluation	Reactive (part of formal consultation)	Internally-powered	Yes	Yes, but did not lead to new agenda-setting	Administrative consultation
II	Agenda–synthesis–demand–synthesis–evaluation–agenda (two runs)	Reactive (part of formal consultation)	Including 'testing the waters'	Yes	Yes, but did not lead to new agenda-setting	Administrative consultation
III	Agenda–synthesis–demand–evaluation	Proactive	Aligning external actors	Yes	Yes, and led others to ask WGM in period IV	Active case building cycle
IV	Agenda–demand	Reactive	None	Yes	No, but still led others to ask WGM in period V	Administrative consultation
V	Agenda – synthesis–agenda–demand–evaluation	Reactive, emphasis on importance	Proactive character with consultation with many interacting partners	Yes	Yes, and forced changes in priority-setting	Knee-jerk reaction

same right to quality of care'), improvement of the rare disease climate, and the centrality of patient's needs, remained unchanged over time. However, the WGM put efforts into forming its objectives (*self-positioning*, period I-II), e.g. during an invitational conference and a symposium in deliberation with external parties (*other-positioning*, I-II). The participants of these meetings urged the WGM to pursue four objectives: an information window, a catalyst, an architect and a think-tank function. The WGM was advised, especially within the context of the catalyst function, to focus on creating favourable conditions in the final stage of the innovation process, e.g. on reimbursement issues. This was favoured above putting efforts into R&D, prioritisation and drug development. In this case the influence of other-positioning was heavy.

The members of the WGM saw the organisation's independence and objective stance within the health care policy arena as a great asset (*self-positioning*, III-V). This independency was inspired through its public public policy character and also by the fact that its members formed a balanced and multidisciplinary representation of the health care system. It would be difficult for the WGM to form a more activist opinion about a subject because each of their members should agree on it. Nevertheless, the Ministry of Health questioned WGM's independence during the reimbursement event theme because it was contrary to the

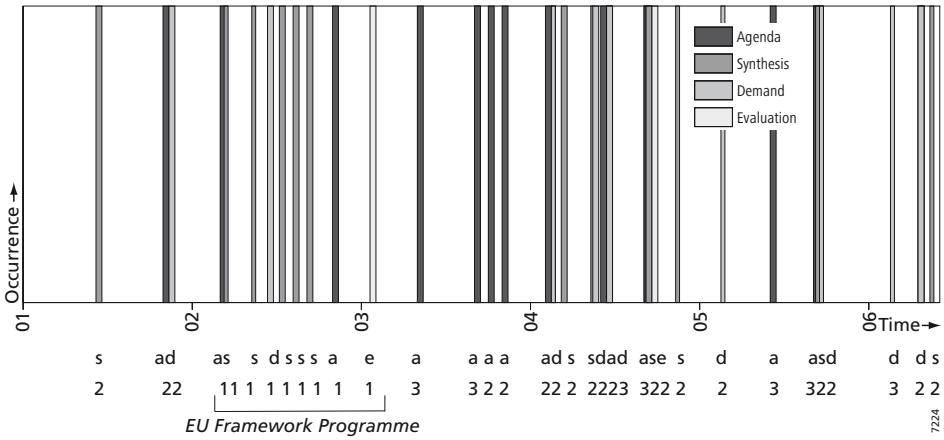

Figure 48 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in R&D event theme (numbers refer to topics).

position the WGM had taken as a critic of government policy. After four years the WGM was evaluated by the Ministry of Health. The WGM was allowed to continue their work but the emphasis was shifted to R&D and communication to specific target groups (*other-positioning*, III-V).

Nevertheless, the events surrounding the reimbursement saga also caused other parties to take the WGM more seriously and view them as an authority on rare disease policy (*other-positioning*, V). This was evinced by the fact that external parties explicitly put forward issues and asked the WGM to take action: "In the beginning the Steering Committee did a lot of sowing and rousing, but now a lot of actors come to us. Expectations also increased" (interview result). This can be seen as a sign of the maturing of the WGM as an intermediary organisation (*self-positioning*, V). All in all, the above shows that the second-order learning loop, consisting of interacting self-positions and other-positions, was in place in this event theme.

Event theme II: The R&D event theme

In the previous two sub-questions we saw that the WGM was engaged in a wide range of activities concerning orphan drug R&D. First-order learning did not occur and these activities were widely dispersed over time. Therefore, the narrative was not subdivided in clear periods (Figure 45). Figure 48 shows the occurrence of different event categories per activity over time. These activities varied from attempts to obtain finances from the EU Framework Programme (1), the STIGON project (2), and the ERA-Net (3). The first set of activities is somewhat centred within a single period, whereas the last two are more spread out over time.

Because of the dispersion of the different topics over time (Figure 48), the loops consisted of events of the same topics and were able to overlap. Therefore, there were no real periods present here. Table 28 illustrates the tentative ideas about demand articulation mechanisms in this event theme.

Table 28 - induced demand articulation mechanisms per period for the WGM R&D event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
1	Agenda/synthesis–synthesis–demand–synthesis–agenda–evaluation	Proactive	Aligning with European partners, collect overview of rare disease research	Yes	Yes, but loop was aborted because of external pressure	Project stimulation
2	Synthesis–agenda/demand–agenda–demand–synthesis–synthesis/demand–agenda–synthesis–evaluation–synthesis–demand–synthesis–demand–demand–synthesis	Reactive/proactive	Including 'testing the waters'	Yes	Yes	Testing the waters (rapid synthesis-demand turnaround)
3	Agenda–demand–agenda–demand	Proactive	Aligning with partners	Yes	No	Network building

The resulting demand articulation mechanisms include network building, i.e. anticipating future issues by actively aligning with other actors, and testing the waters, i.e. developing statements by putting them to the test in rapid succession. In the conclusions and discussion (Chapter 8) we combine these tentative versions of demand articulation mechanisms with those found in the other case studies into a more robust set. Furthermore, it is striking to see that agenda-setting is more prominently present in this event theme. While for a lengthy period of time the WGM had known what to do in terms of research and development, it failed to result in concrete output, e.g. a research programme.

With regard to the second-order learning loop, the self-positions and other-positions had reciprocal influence. From the very beginning the RGO identified objectives for the WGM concerning orphan drug R&D (*other-positioning*), and although the WGM did take them into account (*self-positioning*) the goals were articulated (*other-positioning*) under the pressure of other actors, including the Ministry of Health and the participants of the invitational conference and symposium. Later on, during the granting of small research projects and participation in large research initiatives, the WGM interacted with several parties that imposed their ideas on the WGM (*other-positioning*) and vice versa (*self-positioning*). All in all, the second-order learning loop is present in this event theme.

6.3 Demand articulation processes in interaction with others (research question 2)

This research question deals with the WGM's demand articulation processes in interaction with represented actors (As) and other relevant parties (Bs). Figure 42 shows WGM's interacting partners. It also shows that the WGM is not a representative agent in the same vein as the patient advocacy groups in the other two cases. As was set out in Chapter 2 the WGM is a coordinating intermediary user organisation. The WGM has several members that represent a wide variety of stakeholders in the health care policy arena. However, these members do not formally represent their organisations and only express their own opinions. Moreover, while the Ministry of Health actually founded the WGM, the ministry's interests are not directly represented. All in all, the distinction between actors A and B was not explicit in this case because most actors with whom the WGM interacted, such as the Ministry of Health and CVZ, were also WGM members. The analysis of this research question concentrates on the event theme of the reimbursement of orphan drugs in hospitals as set out at the beginning of this chapter.

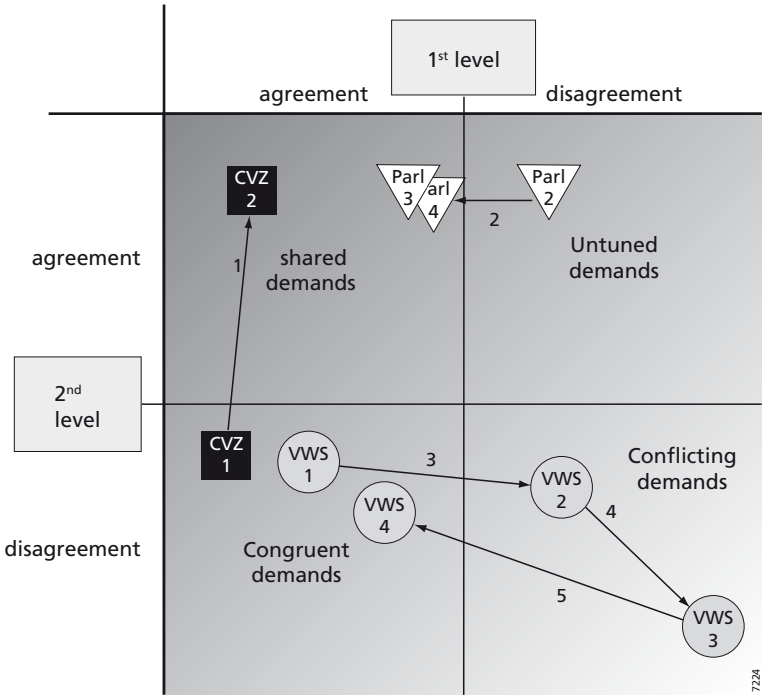

Figure 49 - shifts in the level of joint construction between the WGM and VWS/parliament/ CVZ[1]. Numbers in the boxes indicate the periods the actors feature in; the arrow numbers are dealt with when answering research sub-question 2c.

1 First-order and second-order statements of parliament in stage 1 were not specific for the event theme, while CVZ did not have an explicit opinion in the later two stages of the event theme.

2a. Does demand articulation take place in a multi-actor innovation arena involving interactions between the WGM and other relevant actors? In other words, to what extent is convergence or joint construction of demands occurring?

The demand articulation processes taking place within the WGM (analysed in the previous section) did not occur in isolation. Apart from the first-level and second-level statements that had already come out of the documents studied, we interviewed the representatives of several interacting partners of the WGM and asked them about their demands and underlying assumptions at different stages in the event theme on reimbursement. This led to conclusions on the 'construction states' in which the WGM, together with other interacting partners, were in at a specific point of time (Figure 14).

The event theme on reimbursement consists of five periods (Table 25), four of which are included in the analysis presented in Figure 49[47]. The most prominent interacting partners in this event theme were taken into account and include the Dutch Ministry of Health (VWS), parliament (Parl.), and the Health Care Insurance Board (CVZ). Figure 49 illustrates the states of agreement and disagreement between the first-order and second-order levels of the WGM, and the three interacting partners in four periods of the reimbursement event theme.

Figure 49 illustrates that *CVZ* (shift #1) and the members of *parliament* (#2) move towards a 'construction state' that can be characterised as shared demand. CVZ first disagreed on the assumptions underlying the demand, i.e. preferences based on efficacy, therapeutic value of drugs, and good care for insured persons, whereas later on solidarity became important, just as it was important for the WGM. Parliament differed on first-order demands because initially most MPs did not regard a separate reimbursement rule as feasible. Later, they agreed on both first-order and second-order level with the WGM. The *Ministry of Health (VWS)* moves from a congruent demand state to a conflicting demand state (shift #3 and #4) and back again (#5). For all three interacting partners, just as for the WGM, the demands became more and more articulated over time in the event theme. This might explain the detour of VWS into the conflicting demand state: the first-order and second-order statements were in the first stage not well articulated and therefore not differentiated enough to be conflicting. Later the differentiation and related conflicts on both levels became more visible (following shift #3 and #4): VWS wanted to finance the orphan drugs by using the research-related hospital (academic) budgets and were mainly driven by the need for the effective use of financial resources. The last stage (after shift #5) does not imply another turn in articulation, but a change in orientation on the first-order level: VWS now embraced the idea of a special reimbursement rule for orphan drugs, but used a different legitimisation for this (again the effective use of finances).

Several difficulties in sketching the level of joint construction also became apparent. Firstly, the agreements and disagreements between the WGM and the three interacting partners separately, are well underlined in Figure 49. At the same time no attention is given to the differences and similarities between the three interacting partners. For example, in period 1, CVZ and VWS did have conflicting demand statements (first-order), although

47 We combined periods four and five of Table 25, because they both referred to the consultation that the Ministry of Health initiated on behalf of parliament and to which a contribution was made by the WGM.

they are both in the state of congruent demands. Secondly, the ultimate preferences that are part of the second-order level were assimilated well in the analysis. Several parties mentioned solidarity as an important principle that should be the basis of policy on the reimbursement of orphan drugs. Nevertheless, the evaluative second-order statements turned out to be of less value: they are organisation-specific and, obviously, a comparison on the level of agreement would not yield any interesting results. Thirdly, we did not include 'not articulating articulations'. In other words, when actors did not address an issue, either deliberately or not, and others did, then a comparison on the level of agreement on that issue turned out to be complex. For example, when the Ministry of Health found the principle of 'value for money' important and the WGM did not touch upon this subject because it stressed the significance of 'solidarity', it was an indication that either the WGM did not appreciate the former as VWS did, or that they found it of value but simply forgot to mention it.

All in all, the main actors involved in the discussions show a large degree of convergence on demands, and sometimes also underlying assumptions, regarding the topic of orphan drugs reimbursement.

2b. What strategies does the WGM deploy in the different interfaces with other relevant actors?

First, this research sub-question deals with the different types of interfaces through which the intermediary organisation communicates with other parties. The methods used within these interfaces are diverse and range from promotional activities, such as brochures and a website, to interviews, meetings and scenario studies. The most prominent ones include meetings, sending out letters, producing plans and reports, and organising symposia or workshops.

Table 29 shows the interface types most often deployed. Moreover, the table shows which types of methods were used within these interfaces.

Turning to the interface strategies used, in Table 30 we present for every period the interface types used for and the characteristics of the three major starting points for strategies, i.e. access, empowerment and impact. Based on this, interface strategies are explorative and inductively constructed. As was stated at the start of this section, a clear distinction between actors A and B could not be made here as the WGM is an example of a coordinating intermediary user organisation (the represented actors are mostly the same as the other

Table 29 - interface types used and relating methods deployed.

Interface type	Times applied	In reimbursement event theme	Methods used (only prominent ones)
Consultation	23	2	Interviews, letters
Education	7	1	Meetings, letters
Presenting, advocating	39	6	Letters
Mediation	9	0	Meetings
Coordination	8	5	Meetings
Deliberation	26	7	Meetings
Anticipation	5	1	Conferences, meetings, workshops
Co-production	29	0	-

Table 30 - induced interface strategies per period for the WGM reimbursement event theme.

Period	Interface types used	Characteristics	Proposed interface strategy
I	Presenting/ advocating (letter)	• Access: regarding CVZ full, input was asked • Empowerment: internal knowledge sources • Impact: letter as part of formal consultation; CVZ appreciated input and WGM evaluated it favourably	Representation of other's interests/ consultative presentation
II	Deliberation (meetings), presenting/ advocating (letters)	• Access: regarding CVZ full, input was asked • Empowerment: internal knowledge sources • Impact: letter as part of formal consultation; CVZ appreciated input and WGM evaluated it less favourably (WGM's voice not heard as most important actor)	Representation of other's interests/ consultative presentation
III	Anticipation (workshop), presenting/ advocating (petition)	• Access: forced access to parliament • Empowerment: through aligning with range of actors • Impact: parliament used the petition, the Ministry of Health was forced to react	Anticipative alignment/ unasked advocacy
IV	Presenting/ advocating (letter)	• Access: forced access to parliament • Empowerment: using external sources; plans and documents did not show finalised version • Impact: role of this document in parliamentary debate was not large	Deliberation/ unasked advocacy
V	Deliberation (meetings), consultation (questionnaires)	• Access: full, parliament and Ministry of Health requested it • Empowerment: through consulting and deliberating • Impact: mediocre, input to ministry was part of many documents	Creative consultation/ consultative presentation

interested parties). Still, the interaction with other actors is becoming bi-directional; this is reflected in the strategies shown in the following table.

The prominent strategies used by the WGM during its demand articulation exercises as a coordinating intermediary user organisation included anticipative alignment and unasked advocacy. In Chapter 8 we combine these tentative versions of interface strategies with those found in the other case studies into a more robust set.

2c. *To what extent can the joint construction of demands by the WGM and their interacting partners be attributed to the interface strategies used? And how effective were those interface strategies?*

We followed the shifts in Figure 49 and looked at whether the interface strategies used contributed to those shifts. The first shift from period I to II showed two shifts. First, CVZ moved from a state of 'congruent' to 'shared' demand. This occurred because CVZ had changed its underlying assumptions somewhat by explicitly emphasising the solidarity issue while backing up their first-order statements. One of the reasons for this shift could be the WGM's input to the CVZ report in period I, in which it also stressed this solidarity

issue. This claim is substantiated by the fact that CVZ evaluated its experiences with participation as useful.

The second shift was that of the Ministry of Health VWS from 'congruent' to 'conflicting' demand. The WGM had no influence on this shift because the WGM had only articulated its demands indirectly, namely through participation in the CVZ reports. It appeared that VWS disagreed on the first-order level with CVZ, and thus also with the WGM.

The transition from period II to III/IV yielded one interesting change made by parliament. It shifted from 'untuned' to 'shared' demand, i.e. the first-order level demand statements began to agree with the WGM. The WGM petition was one of the reasons for this.

The last substantial shift occurred during the transition from period IV to V: VWS moved from a state of 'conflicting' to 'congruent' demand. The ministry agreed that finances for intramural orphan drugs should be managed on the basis of a special reimbursement rule but still disagreed on the reasons why. The WGM contributed to VWS's decision-making process by participating in their consultations. In this way, while the WGM's strategy of consultative presentation (Table 30) was effective, it was probably not decisive.

All in all, the WGM deployed a wide range of interface strategies. Some of which were effective in causing shifts in the joint construction states of demand (Figure 49). Especially the combination of anticipative alignment and unasked advocacy was a strong one (period III). Other strategies exerted only partial influence because of the set-up of the participation, e.g. in the periods I, II and V, or had little effect (period IV).

6.4 Preliminary conclusions

In the context of the reimbursement event theme, the number of demand statements of the WGM rose steeply and converged on one particular problem related to reimbursement. During this process the ideas for solutions narrowed down even further in one specific direction, and the WGM did not change its orientation (propose versus oppose) towards the options for reimbursing orphan drugs. The event theme showed a constant iteration between the problems and ideas proposed by the WGM. This is illustrated by the upward spiralling of problems and ideas in Figure 44. It can be concluded that first-order learning occurred.

Analysis of first-order and second-order learning in the reimbursement theme produces two other conclusions. Firstly, learning on both levels is interrelated. Secondly, as could be expected from the nature of these types of learning, second-order learning progresses at a less rapid pace than first-order learning. Second-order learning only pertained to developing objectives, whereas norms and preferences remained unchanged. The way in which underlying assumptions, including the tasks and functions of an organisation, are outlined, and the way in which issues that are placed on an organisation's agenda may reflect the stage of development ('maturity') of an intermediary organisation. In later stages, reflecting on the underlying assumptions becomes more important, e.g. when confronted with an evaluation and a reconsideration of objectives in the light of achievements so far. One major accomplishment is that actors in the Dutch health care sector are now more aware of the WGM's presence, partly because of their provision of information.

Moreover, the hypothesised order of event categories in the first-order learning loop, i.e. agenda-setting – synthesis – expression – evaluation, was found to be in place, but not in all

periods. The same goes for the second-order learning loop (self-position – other-position). These first-order learning loops were characterised as demand articulation mechanisms, such as 'administrative consultation' cycle, 'active case building' cycle, 'knee-jerk reaction' cycle, and 'network building' cycle.

The other event theme, on orphan drug R&D, also showed an increase in the number of demand statements, but far less sharpening in terms of content or orientation. In the R&D theme the major focus lay on putting problems on the agenda, but ideas to solve these problems were either lacking or proved to be too complex. Accordingly, in the reimbursement event theme, the articulation of demands is clear, while in the R&D event theme demands are voiced and put on the agenda, but no development and sharpening of ideas occurred.

Concerning the first-order and second-order learning in the R&D event theme it can be concluded that the two are interconnected. Moreover, it appeared that despite slow first-order learning and a rather dispersed character of different topics, second-order learning occurred, mostly because the WGM needed to position itself on the subject of R&D. Furthermore, the hypothesised order of event categories was found but idiosyncrasies were also identified, mostly because of the dispersed nature of the activities. Demand articulation mechanisms included: 'network building', 'project stimulation', and 'testing the waters'.

Figure 49 illustrates that several parties concurred with one another at the beginning and the end of the reimbursement event theme. In the meantime, the demand statements became progressively more articulated and for two of the three interacting partners (CVZ and parliament) this implied a move to (more) shared demands. These two actors agree with the WGM on both first-order and second-order statements. At the same time, through articulation, the third actor (the Ministry of Health) moved away from a state of congruent demands to a state in which there was disagreement on both first-order and second-order issues (state of conflicting demands). Later on, the Ministry moved back to the former state. We conclude that the articulation of demands resulted in a temporary mounting disagreement on first-order and second-order level, followed by a state of increasing (congruent demand) agreement.

The WGM deployed a host of interface strategies. Some of them were effective, such as the combination of anticipative alignment and unasked advocacy. Other strategies had only a small or partial influence on the shifts in joint construction, e.g. because of the lacking impact of formal participation.

In general, the coordinating intermediary user organisation WGM has been heavily engaged in policy issues around rare diseases and orphan drugs such as reimbursement and R&D stimulation. The organisation took a rather neutral stance towards these topics and was able to influence them with differing degrees of success.

Chapter 7

Case study Dutch Breast Cancer Association

7.1 Introduction to the Dutch Breast Cancer Association

The Dutch Breast Cancer Association (*Borstkanker Vereniging Nederland*, BVN) is a representative intermediary user organisation that acts on behalf of (ex-)breast cancer patients, individuals who show hereditary susceptibility for breast cancer, relatives of breast cancer patients, and other interested parties. The central objective is to improve the well-being of breast cancer patients, e.g. by aiming at good medical and psycho-social care. The BVN regards breast cancer as a somatic disease with drastic psycho-social consequences. The organisation has around 6,000 members and is partially funded by the Dutch Cancer Society (KWF Kankerbestrijding). This Society is a charity fund that communicates cancer information to the Dutch general public and finances basic research.

The BVN and the Dutch federation of cancer patient organisations (NFK) regard both patient communication and representation as their main objective. Its advocacy efforts related to new technologies mostly covered the later stages of development, when they become available to patients. There is growing awareness though that a more anticipatory stance towards innovations might be beneficial as well. The BVN channels many topics through the NFK because these issues are more easily organised on the general level of all cancer types. Other organisations closely related to the BVN are Pink Ribbon, the Dutch version of a charity fund dedicated to breast cancer founded in 2003, and the European umbrella organisation Europa Donna, founded in 1993, which the BVN joined in 1999.

In the 1970s not a great deal of attention was paid to accompanying breast cancer patients. Nevertheless, in the US ex-patients and health workers began to visit patients to assist them emotionally and practically in the process of breast amputation, the then-state-of-the-art treatment for this disease, e.g. by helping in the search for the right prostheses. Dutch individuals began to follow this model and started to organise themselves around certain hospitals. These different regional groups decided to unite their efforts and founded the National Contact Body on Mutual Help Groups Breast Cancer (LCBB[48]). Growing recognition among medical professionals and hospitals led to the foundation of Breast Prostheses Information Centres situated inside hospitals.

Later, in 1992, it became possible for individual patients to become members of the LCBB, which had started to turn into a patient organisation. Mutual help and communication became even more important for the LCBB. Other actors, such as the government, began to position patient organisations as important players in policymaking within the health care policy arena: they were the so-called 'third parties', besides health care suppliers and insurance companies (Ministerie van Volksgezondheid, 2001). At the same time, this meant that the LCBB should modernise and professionalise its organisation, and strive for solid backing. In 2000 the LCBB internally deliberated about

48 Landelijke Contactorgaan Begeleiding Borstkankerpatiënten.

its position regarding interest representation and advocacy. This led to the LCBB 2000+ project that studied how these new developments should be taken into account. As a result major changes took place, including renaming the LCBB into the BVN. Furthermore, there was a shift in focus from mutual help to patients' interest representation. From 2002 onwards, the organisation consisted of a board that was controlled by the general meeting of members. The central body of the BVN was shaped by the Platform in which representatives of all other bodies took place, i.e. the regional departments, and working groups on communication, representation, support, and special target groups (on hereditary, tiredness), and an advisory committee. Moreover, the reorganisation of the internal structure coincided with furnishing the organisation with a national office consisting of a professional secretariat and a managing director.

Main achievements since then have included aiming at multidisciplinary diagnosis and treatment teams in hospitals, the October promotional month (the first was held in 2003) in association with Pink Ribbon, assisting in drafting the medical guidelines on breast cancer, and advocating reimbursement for expensive drugs, which is the subject of this case study. Another topic that the BVN actively took up in 2005 was organising information meetings about DNA micro arrays and breast cancer, in cooperation with the Dutch Cancer Genomics Initiative and a small gene expression analysis-based diagnostics company called Agendia. The BVN did this because it wanted to inform its members on the promising new genomics technologies and because the Dutch Cancer Genomics Initiative wanted to inform the public about its research work.

Opening up the organisation for individual members increased the democratic character of internal decision-making, which expressed itself during the annual general meeting for members. Since 1999, the organisation's policy plans have been discussed and approved here. The board prepares these plans, consulting the organisation's working groups and committees, which also consist of members. These groups propose ideas which are then weighed and prioritised by the BVN board. The BVN has a large number of volunteers at their disposal, although due to the severity of breast cancer or recovery, members are not always interested in becoming actively engaged in the organisation.

The BVN maintains contacts with a wide range of actors. Figure 50 illustrates these interactions. Most of these relations were already explained above and some of them will become clear when describing the event theme on reimbursement in the next section. However, one interaction should be mentioned explicitly: interaction with the pharmaceutical industry. The BVN receives finances from eight pharmaceutical companies and in return provides space for their messages in the BVN's magazine. Nevertheless, the BVN tries to maintain an objective and neutral stance towards these companies by always negotiating and contacting them as a single entity or a 'league' of equal companies.

This case study focuses on one event theme concerning the reimbursement of expensive breast cancer drugs in hospitals. This topic was discussed for more than a decade (from 1995 onwards) and led to unequal access to therapy. The problem was a major topic in health care policy debates. The breast cancer drugs Taxol and Herceptin are two major examples in this event theme, which had prompted the BVN to become heavily involved. There are several reasons why we selected this event theme on which to concentrate in this case study. Interviews and reflexive remarks in documents show that the BVN and other actors in the field regard the BVN's role in these discussions as substantial. This is also one of the few occasions in which the BVN was engaged in advocacy efforts

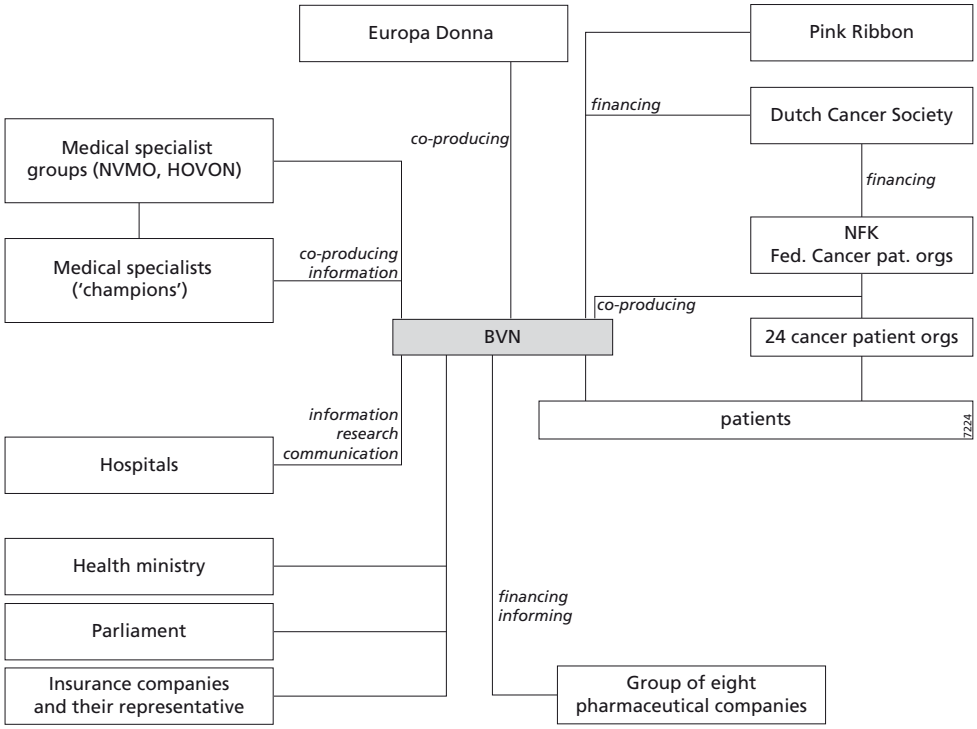

Figure 50 - social map of the Dutch Breast Cancer Association and its interacting partners.

related to pharmaceutical technologies. For this thesis the discussions on reimbursement are topical because we regard reimbursement as an integral part of the drug innovation process (see 2.2.1 and 2.2.2). Furthermore, the breast cancer drug that dominated the latter stages of this debate, Herceptin, is a frequently-mentioned – even archetypical – example of pharmacogenomics (see section 3.3). The event theme concentrates on the Herceptin saga. This narrative is recounted in the next section and also includes a prelude about the reimbursement issues related to Taxol.

7.2 Demand articulation processes inside BVN (research question 1)

This research question is divided into the three sub-questions dealt with below.

1a. Does first-order learning take place inside the BVN?[49]

New medicines can (formally) be introduced in medical practice after registration. Only then are physicians allowed to prescribe them and insurance companies reimburse them. For each registered drug a separate decision is required about its reimbursement by the Dutch Health Care Insurance Board (CVZ). Each hospitalised patient has the right of access

49 We wish to thank dr. Marta Kirejczyk for her help on the Taxol part (period I). This narrative is also part of a forthcoming article by Boon and Kirejczyk.

to medically-necessary treatment, including administration of the appropriate drugs. Each hospital has an assigned budget that it can allocate to different forms of treatment and care at its own discretion. The cost of these treatments must be covered by the hospital's budget. Taxol and Herceptin are relatively expensive drugs that can be administered in hospitals only. Their reimbursement in this context became a problem during the 1990s and 2000s as the narrative below recounts[50].

I. April 1995 – December 2001: Taxol and the temporary solution.

Ia. April 1995 – November 1995: What is the problem? Is there a problem? In 1993-1994 Taxol had been registered for two indications: metastasised ovary cancer and metastasised breast cancer. In spring 1995 organisations of patients suffering from ovary and breast cancer published the fact that some hospitals did not provide treatment with Taxol to their patients because of the difference in hospital budget distribution. They wrote a letter to and discussed the issue with the Ministry of Health (VWS), demanding a guarantee of equal access to Taxol treatment for all patients with relevant medical indication. They lobbied the MPs and instituted legal proceedings demanding equal access.

The issue was taken up by parliament. MPs reiterated that unequal access to treatment with Taxol should not occur and redefined the problem in general terms. In cases of financial deficit the government, together with parliament, should decide on priority-setting in the provision of drugs to all patients that needed them. MPs also asked what the causes for unequal access to Taxol were and why the drug had not been assessed according to the outlined reimbursement procedure.

The health minister questioned the occurrence of inequality and stated that the current system regulating the use of drugs in hospitals guaranteed equal access of all patients to adequate treatment. She suggested that differences in medical judgement regarding adequate therapies might be the problem. She requested the Sick Fund Council (ZfR; the predecessor of CVZ) and the Association of Integral Cancer Centres (VIKC) to investigate the provision of Taxol by hospitals. In November 1995 the investigation confirmed the existence of inequalities. In their report the ZfR and the VIKC argued in favour of a system in which the registration of expensive drugs would be tied to a directive for their use and to a decision regarding adequate financing. The Breast Cancer Association (LCBB; later called BVN) wrote a letter to the Ministry of Health demanding equal treatment.

Ib. January 1996 -February 1997: Recognition of the problem and search for solution. The health minister commissioned the VIKC and the Dutch Society of Internists (NIV) to draft a directive for Taxol treatment. The observance of this inequality, she hoped, would eliminate it. The LCBB and the Dutch federation of cancer patient organisations (NFK) wanted to be on the board that drafted the directive. In May 1996 medical professional and patient organisations endorsed the directive but unequal access to treatment with Taxol persisted. In October 1996 the minister requested the Sick Fund Council to investigate the VIKC's directive, devoting special attention to the process of priority-setting for medical conditions to be treated with Taxol, and to the actual impact of Taxol treatments on hospital budgets. Around the beginning of 1997 the LCBB demanded to be heard by the investigating committee of the Sick Fund Council and wrote letters to the Council protesting against financial grounds for denying Taxol treatment to patients. In February 1997 the Sick Fund

50 In contrast with the previous two case studies, here the narrative is already woven around eight distinct periods for the sake of clarity. How this was done is described after the presentation of the narrative (after Figure 51).

Council approved the VIKC's directive, but pointed to a (partial) shortage of data regarding the effectiveness of Taxol treatment for different indications. The Sick Fund Council thought these effectiveness considerations should be a part of the reimbursement decision-making. The LCBB formed a coalition with the medical doctors in lobbying against the proposal for a phase III-trial for Taxol aimed at investigating the drug' effectiveness.

Ic. March 1997- April 1999: More research and broadening of the debate. The minister instructed the hospitals to register data on the use of Taxol, and commissioned research into evaluating the consistency of Taxol practice with the directive. The research should also provide insight into the effectiveness of Taxol therapy. The VIKC and the NIV, represented by the Netherlands Society for Medical Oncology (NVMO) were to carry out the research. The LCBB was also included in the supervisory committee after a certain amount of pressure had been exerted. During this evaluation, up to 90% of the costs of treatment with Taxol was subsidised by the Sick Fund Council (April 1997 – April 1999).

In the meantime the debate shifted from the problem of reimbursement of the Taxol costs to the reimbursement of expensive drugs in general. The Health Care Insurance Board (CVZ, the successor of the Sick Found Council) stated that the current reimbursement system could not cope with the introduction of expensive drugs in hospitals without problem. It recommended that treatments with expensive drugs should be regulated by protocols, accompanied by additional financing and registration of the drug. Evaluation research should be deployed to measure treatment results. In June 1997 MPs demanded that the minister designed a comprehensive policy framework for the introduction of expensive new drugs in health care.

Id. May 1999- 2002: A temporary closure of the debates in search of a permanent solution. Upon the expiry of the research subsidy in April 1999 the costs of treatment with Taxol had to be covered by the hospitals' budgets. The Health Care Tariffs Board (CTG) began to work on a directive for the reimbursement of expensive drugs. Renewed suggestions concerning the unequal access to Taxol treatment appeared in the media and were taken up by MPs. In June 2000 the minister rejected these suggestions and confirmed her policy to finance the drugs through hospital budgets. She also rejected a suggestion to earmark a portion of hospital budgets for expensive drugs. The registration research had shown that both the number of patients treated with Taxol, and the impacts of the costs on a hospital's budget were much smaller than expected.

The NVMO set up a Committee for the Assessment of Drugs used in Oncology (BOM) to assess the added therapeutic value of new drugs according to fixed criteria comparable to those developed in the evaluation of Taxol. In 2002 the Health Care Tariffs Board introduced a temporary regulation, which allowed for the reimbursement of up to 75% of the cost of expensive drugs used in hospitals by public and private health insurance. Taxol was one of the drugs covered by this temporary regulation. The regulation expired at the end of 2003.

II. 2002 – September 2004: Medical professionals and patients pressure. Two medical professional groups (NVMO and HOVON) put pressure on the Ministry of Health, later assisted by the BVN and NFK, in two parallel ways: by sending letters and holding meetings, and by attracting media attention. They claimed that despite the then-current reimbursement rule (a non-uniform percentage up to 75% was financed by public and private insurance), problems still existed with financing expensive drugs in hospitals. These problems would lead to inequality of health care, and this was something that was regarded as totally unacceptable. Other parties such as the representatives of hospitals and insurance

companies also reacted. The Ministry of Health denied these problems of reimbursement, also during direct deliberations with the opposing stakeholders. The BVN put the topic firmly on its internal agenda and started to prepare an advocacy document.

III. September 2004 – February 2005: Clashes in the House. Many actors wrote letters to Members of Parliament about the subject, which led to passionate debates in parliament. The health minister promised to investigate the problems, taking into account the viewpoints of a wide range of stakeholders, such as representatives of insurance companies, hospitals, pharmacists, pharmaceutical companies, and patients (NFK and others).

IV. February 2005 – May 2005: Consultation. The Ministry of Health entered into deliberations with these actors and wrote letters asking for specific information.

V. May 2005 – August 2005: Enter Herceptin, Ministry of Health: "there is no problem". Medical specialists returned from the annual meeting of the American Society of Clinical Oncology (ASCO) during which Roche had revealed data of the HERA-study. It was found that, apart from metastasised breast cancer, Herceptin also worked for early-stage breast cancer patients. Meanwhile, the BVN published a report in which they showed that many patients who should be treated with Herceptin were not receiving the drug and that there were differences in treatment between regions, which was billed as "postcode care". This led to fierce reactions in the media and in politics. Furthermore, the health minister reported the results of their consultation. He claimed that there were no concrete figures and cases found that would prove that a reimbursement problem existed. Nevertheless, he was aware that stakeholders, e.g. patient and hospital representatives, had problems with the reimbursement rule and promised to change it into a uniform, fixed 80% financing through insurance companies. He also wanted these drugs to be tested for cost-effectiveness before including them on the expensive drugs list. The BVN entered into an exchange of letters with the Ministry of Health in which the government expressed the wish for concrete evidence of patients who were undertreated.

VI. August 2005 – January 2006: Preparation of the new reimbursement rule and the adjuvant Herceptin gap. The medical specialists included Herceptin for early-stage breast cancer in their guidelines, although it had not yet been registered for this indication. This meant that it could not be included in the reimbursement scheme and the expensive drugs list. Hospitals and physicians were faced with a "devilish dilemma": because of the inclusion in the guidelines there was a medical claim to use Herceptin. On the other hand, it could not be financed properly, which might lead to rationing, exclusion from treatment, and inequality between hospitals. In the meantime, several parties, e.g. hospital, industry and patient representatives, engaged in the design of procedures for determining cost-effectiveness. Furthermore, the BVN presented the Ministry of Health with fourteen concrete, but anonymous cases of undertreated patients.

VII. January 2006 – June 2006: Herceptin approval in early-stage breast cancer. Herceptin was registered and thus admitted for inclusion on the expensive drugs list. In this way the specific problems surrounding Herceptin reimbursement were alleviated. Several stakeholders kept trying to influence the setting up of procedures for cost-effectiveness testing. The government took into account all these issues and included them in the final testing guidelines.

VIII. June 2006 – April 2007: Administrative deliberation and new lobbying leading to a patient manifesto. The Ministry of Health evaluated the reimbursement rule and was quite satisfied with the results, all the more so because they had found no concrete indication of problems. At the same time, patient advocacy and medical professional groups continued to

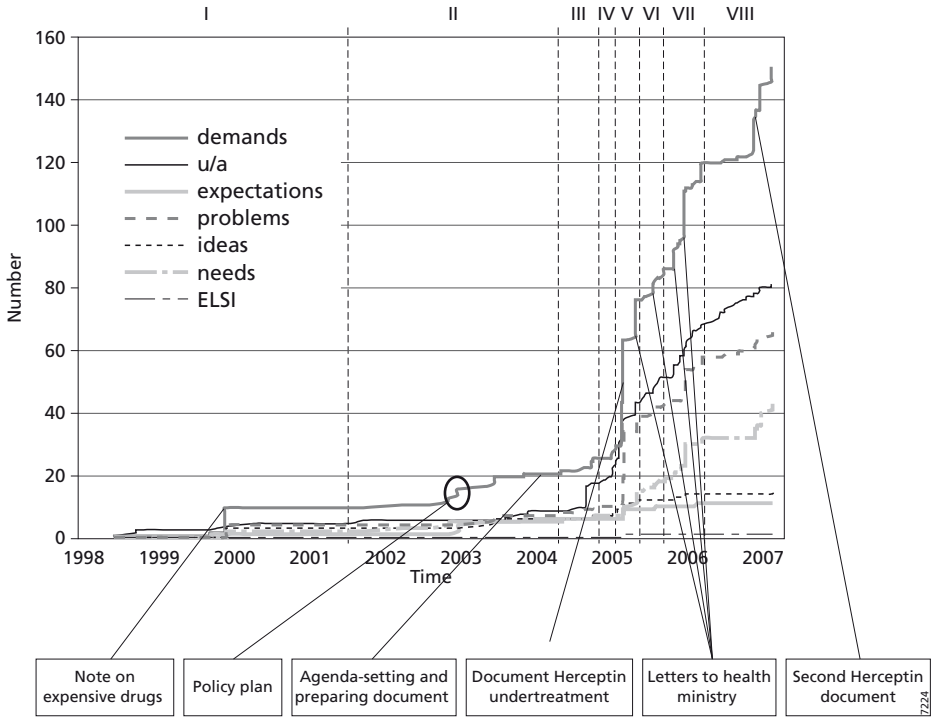

Figure 51 - cumulative number of demand and underlying assumption statements in the Herceptin event theme. Striking demand periods are denoted with numbers I to VIII. Only the most prominent events are mentioned in the boxes on the horizontal axis.

see the reimbursement arrangements as problematic, and decided to bring it to the fore by producing a patient manifesto. This manifesto was accompanied by a renewed version of the Herceptin undertreatment report and a document in which the mutual dependencies between stakeholders were analysed. These dependencies explained why stakeholders, such as medical specialists and hospital boards, were not eager to come forward with concrete figures and cases of undertreatment.

The number of expressed demands increased rapidly during the Herceptin event theme, as is shown in Figure 51. This figure shows the number of demands, underlying assumptions, and different types of demands over time. It illustrates that the expressed demands consist mostly of identifying problems and stressing needs. Other demand subcategories, such as ideas and expectations, were less frequently expressed. The Herceptin event theme is subdivided into different periods (I to VIII in Figure 51). These periods are the result of leaps in the number of BVN statements, substantiated by the logic of the narrative. These eight periods return in Table 31. This table illustrates the content of the periods and describes whether the level of concreteness of the demand statements increased and whether the BVN's orientation towards the topic changed.

Apart from the growing number of demand statements, Table 31 illustrates that in most periods the demand statements increasingly sharpened over time. This applies in particular

Table 31 - changes in concreteness and direction of demand statements (Herceptin event theme).

Period	Context	Topics of demand statements	Content more/ less concrete	Change in direction
I	Note on expensive drugs	Patient was dependent on hospital board's budget choices.	No change	No
		The situation was the same as some years ago with Taxol.	No change	No
II	Policy plan	Evaluation of past Taxol events and expectations about future problems.	More	No
	Support of NVMO-HOVON letter	Problems with hospital drug financing and need for higher percentage (at least 75%). More specific viewpoint and problem definition.	More	No
	Meeting with VWS (with others)	Guaranteeing a good quality of care, a higher reimbursement percentage and long-term solutions. More specific demands (for the future).	More	No
	Agenda-setting and preparing Herceptin document	Take on lack of access to Herceptin. Research question centred on comparisons made with other countries and cause of the problems (reimbursement, indolence on the part of medical specialists or the organisation of diagnosis). Look for cases for legal follow-up. Focus on Herceptin.	More	No
III	BVN acted through NFK; preparation of Herceptin document	Put on the agenda and analyse problems, e.g. about lack of Herceptin access. Not all patients were given the medicines they needed because of financial problems in hospitals: they should still get it. Re-emphasise problems, no articulation.	No change	No
IV	BVN acted through NFK; preparation of Herceptin document	Analyse problems, e.g. about lack of Herceptin access: causes included culpable behaviour physicians, or hospital budget problems. Problem: patients were ill-informed. Causes of problems were sought.	More	No
V	Document on Herceptin undertreatment	Proved undertreatment of patients; differences between regions; unflattering comparison with other European countries. Making use of a case of an individual patient and the recent ASCO results.	More	No
		Probable causes: reimbursement rule, weak patient groups and patients who did not claim treatment, physicians who did not stick to guidelines, bad hospital management.	More	No
	Letter to Senate	New health care system and the related increased power of insurance companies was not the best solution. Examples included Herceptin report in which patients were victims of a situation where stakeholders involved "constantly positioned others as being responsible". Divergence of demands by putting them in the context of the new health system.	Less	No

Period	Context	Topics of demand statements	Content more/ less concrete	Change in direction
	Letter to Ministry of Health	Gratitude because of Ministry's firm position: reimbursement of expensive drugs in hospitals was guaranteed. Nevertheless, why not more concrete cases received. Warning to all stakeholders: match prescription with financing or BVN would make move towards the legal system or the media.	No change	No
VI	Letter to Ministry of Health	Answered call by VWS to provide concrete cases by presenting fourteen examples of women made anonymous who did not receive proper Herceptin treatment.	No change	No
	Letters to Europa Donna	Asking to put pressure on Roche to register Herceptin for early-onset use. Specific demand for arrangement for Herceptin reimbursement.	More	No
VII	Letter to Ministry of Health/ Inspection for Health Care	The fourteen cases had been solved, but problems remained; BVN was not eager to provide privacy data.	No change	No
	Reaction to CVZ draft report	100 instead of 80% reimbursement would not lead to inefficient drug use as examples from the past showed; concerns about "overregulation" that would slowdown uptake of medicines.	More	No
	Reaction to positive Herceptin decision EMEA and CVZ	BVN happy with decision but worried about undertreatment of Herceptin caused by 80% (instead of 100%) reimbursement and poor her2/neu diagnosis. BVN thought that this was part of the same problem: if patients did not know whether Herceptin would be efficacious in their case, then the hospital would not be compelled to finance the expensive drug.	More	No
VIII	Second Herceptin document	Availability increased; still differences between regions and in comparison with other countries; 100% coverage wanted; concerned about financing and validity of her2/neu testing. Viewpoint: 100% reimbursement and more attention to quality of her2/neu testing (now also worries about underdiagnosis).	More	No

with regard to the early period (II), and in the build-up towards and during the publication of the first Herceptin document (period V). The immediate reactions on this document failed to provoke more articulated views, which goes without saying since the brunt of the BVN's message had already been conveyed in the Herceptin document. When the BVN tried to link the Herceptin discussion to the then looming national health care reforms (V), the demands became even less concrete for the moment. Later, the BVN began to look for the precise causes of the reimbursement problems and to substantiate the signals that the Herceptin document picked up by presenting concrete, though anonymous, cases. Besides this general, sharpening trend, there were no changes in direction as the orientation of the

BVN's demand statements remained unchanged. All in all, we could say that first-order learning occurred to a large degree in this event theme.

1b. Does second-order learning take place inside the BVN and how is this connected with first-order learning?

The first strand of this research sub-question concerns whether second-order learning occurred inside the BVN in the context of the Herceptin event theme. There were no alternations in one dimension of the second-order level: the ultimate preferences. The unacceptability of inequality in health care and the equal access of medicines remained the prominent rationales behind the BVN operations.

Nevertheless, what did change was the way in which the BVN learnt to deal with patient advocacy, particularly in the context of reimbursement. For example, the second Herceptin document was produced much faster, and the BVN did not have to repeat the long period of agenda-setting in which no articulation took place (leap II, III, IV) that had preceded the production of the first document. On the other hand, the second document was not very different from the first one. Also, its impact might be less as well because other parties had learnt how to react to document of this nature, e.g. the Ministry of Health immediately attacked the way in which the investigation had been carried out.

The BVN learnt about its underlying assumptions on other occasions as well, e.g. during the evaluation of its expectations about patient advocacy, and its role as 'third party' in health care. Given this importance of patient advocacy, the BVN also developed ideas about how to gain access to policy debates, how to collect data, and how to use that data in an effective way. Therefore, it is concluded that second-order learning took place in this event theme.

The second part of this research sub-question is about the interaction between first-order and second-order learning. Figure 52 illustrates the cumulative growth in demand statements (first-order) and underlying assumptions (second-order statements).

The figure shows that the first-order and second-order statements are intertwined in this event theme. The interactions are numbered and can be explained as follows:

1. Increasing emphasis on advocacy and patient groups as 'third party' in health care results in seeking action. A known problem is chosen, namely the financing of expensive drugs. Also this problem aligns with the organisation's ultimate preferences, such as equality and justice concerning access to expensive drugs.
2. Demands are legitimised by the ultimate preference of best treatment for all; thus accessibility for all must be guaranteed.
3. Evaluation: data collection was hard and bringing problems to the attention of policymakers proved to be difficult.
4. Agenda-setting is accompanied by questions about the BVN's 'power' to put issues on the map, and the expected benefit of the advocacy efforts: it would have to be a learning process.
5. Reflection on data and data collection includes the need to focus on articulating problems, the causes of these problems, and short-term vs. long-term action. These causes were put forward.

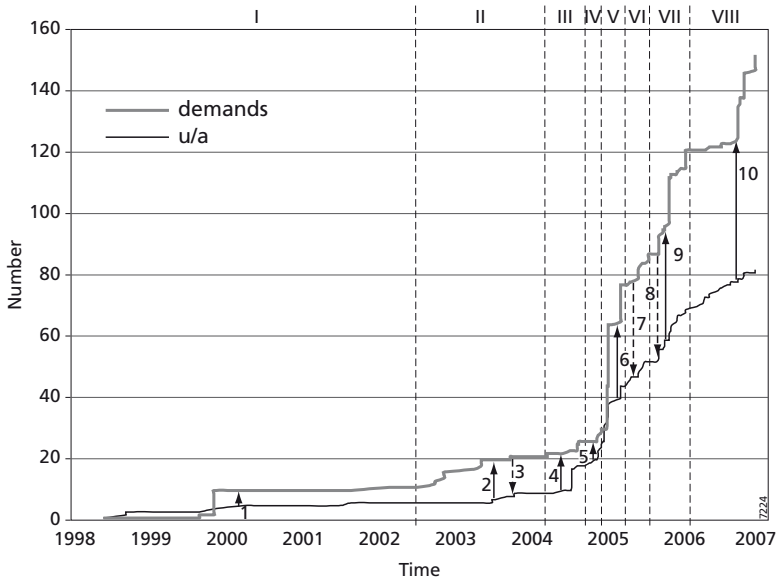

Figure 52 - the influence of demand statements on underlying assumptions (dotted arrows) and vice versa (solid arrows) related to the Herceptin event theme.

6. Expectations and hopes for short-term action by actors. It is emphasised that the document should contain short messages, no causes and nuances. The causes of the problems are now linked to the roles of different stakeholders. These roles are anchored in the ultimate preferences of the BVN, such as upholding the autonomy of physicians.
7. Evaluation: satisfied with the Herceptin report, but continuing with advocacy through monitoring and influencing politics, as well as pursuing legal action. More support is needed on a strategic and legal level.
8. Evaluation: learning points include identifying target groups, increasing support by patients, cooperating more, looking at what other actors are doing, taking care of follow-up.
9. Emphasise role of patients as important and capable of cooperating in policy issues, in this way underlining the need for participation in setting up procedures for cost-effectiveness.
10. Ultimate preferences of equality of medicines and unacceptability of unequal access are emphasised.

All in all, the interactions between the first-order and second-order learning levels described above illustrate that these levels are intertwined and in this case take the form of legitimisation of demands and evaluation of demand efforts. Furthermore, it can be concluded that second-order learning took place in the BVN in this event theme.

1c. What 'demand articulation mechanisms' can be discerned studying these learning processes?

This research sub-question refers to the two learning loops and whether the event categories were found in this event theme. Starting with the first-order learning loop, the order of event categories (agenda-setting – synthesis – expression – evaluation) in this event theme was investigated. Figure 53 illustrates this.

The figure above illustrates the order in which the event categories took place in this event theme. It can be deduced that in period I the advocacy efforts on Taxol were evaluated. The BVN concluded from these evaluations that the solution proposed in the Taxol case was only temporal and new reimbursement problems were just around the corner. This led to agenda-setting and the synthesis of data and ideas about problems, solutions, etc. This continued for the next few periods with increasing articulation of demands. Running parallel to these content-related developments was the building up of a network of stakeholders with whom – and sometimes through whom – the BVN organised their efforts. We return to the subject of cooperation when answering the next research question about the joint construction of demands.

The next four periods (II-IV) are characterised by a proactive stance towards the topic of reimbursement: continuous agenda-setting and evaluation was spurring the synthesis of demand statements. This synthesis was achieved by aligning with other actors, which led to collaborations, some of which resulted in jointly-stated demands. In period V this culminated in a large expression of demand by the BVN: the first Herceptin undertreatment report.

A string of letters, reactions and evaluations in period VI and VII followed this report. In these periods there was little time to produce new information and the demands that were issued were mainly reactions to questions that other actors raised after the publication of

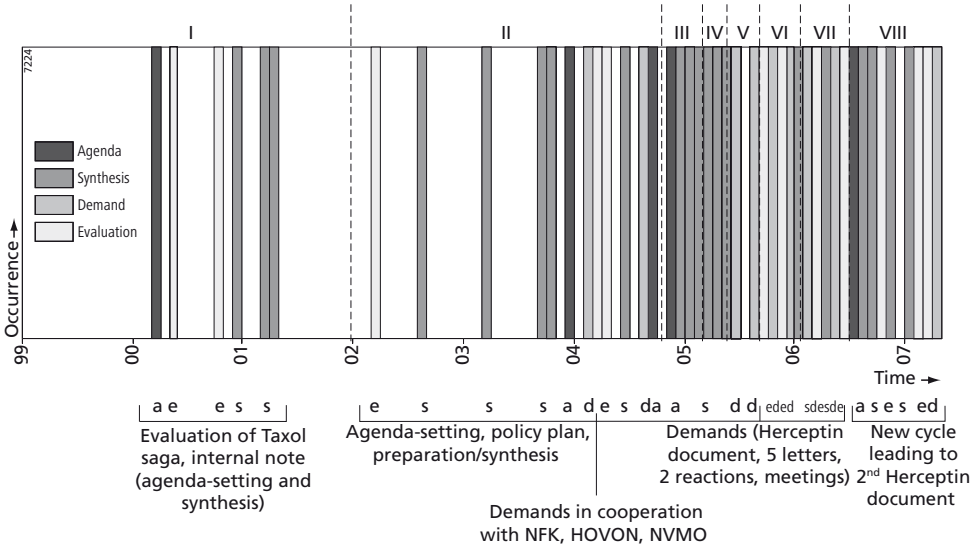

Figure 53 - occurrences of the event categories (agenda – a, synthesis – s, demand expression – d, and evaluation – e) over time in the Herceptin event theme.

the Herceptin report. These demand expressions were alternated with evaluations by the BVN of its large advocacy operations.

The last period (VIII) comprises a complete cycle of event categories in roughly the same order that was hypothesised in the conceptual model (agenda – synthesis – expression – evaluation). It concerns the production of the second Herceptin report. The BVN put it on its agenda proactively, but during the synthesis of the report it became part of a larger advocacy initiative led by the NFK, including other (cancer) patient groups and medical professional organisations. In this period, again, there is room for continuous evaluation by the BVN.

The loops that were found in Figure 53 are characterised in an explorative way in Table 32.

Concerning the second-order learning loop during the Herceptin event theme, a string of other-positions and self-positions that influenced each other was formed. The Ministry of Health stimulated the third party role of patient groups (*other-positioning*, period I). The BVN accepted this role, despite the fact that it saw problems in executing it (*self-positioning*, I). This led the BVN to co-produce an advocacy effort (*self-positioning*, II). Other parties did not approve of how the discussions took place (*other-positioning*, II). Here the chain of influence was broken, because in spite of this other-positioning, the BVN did not change its intentions to continue with these activities (*self-positioning*, III). Another group of actors later thought that the BVN should continue to take action on Herceptin (*other-positioning*, IV). The BVN substantiated the causes for Herceptin undertreatment with its own underlying assumptions (*self-positioning*, V). This led others to believe that patient groups should be involved in setting up the new reimbursement rule (*other- positioning*, VI). The BVN was satisfied with this influence (*self-positioning*, VI). Others saw the BVN as an important advocacy actor, but wondered whether the BVN was the right party to perform such extensive, supporting investigations (*other-positioning*, VI/VIII). The BVN sensed this and was somewhat unsure about its competence and resources (*self-positioning*, VIII). Over the eight periods self-positioning and other-positioning seem to influence each other, forming a loop. The only exception occurred when the other-positioning in period II failed to influence the self-positioning in period III.

Accordingly, in this event theme several demand articulation mechanisms that characterise the first-order learning loop could be discerned, as well as the existence of a second-order learning loop consisting of mutual interactions between self-positionings and other-positionings.

7.3 Demand articulation processes in interaction with others (research question 2)

The BVN interacts with many actors from different levels (international, national, regional) and backgrounds. These different kinds of organisations (Bs) feature in Figure 50 presented above and include representatives of medical specialists, companies, health insurance companies, and the government. At the same time, the BVN was founded as a representative organisation of breast cancer patients (their families, individuals who have a high susceptibility for breast cancer, etc.), and in this capacity also interacts with these actors (As).

Table 32 - induced demand articulation mechanisms per period for the BVN Herceptin event theme.

Loop	Event category order	Characteristics				Proposed demand articulation mechanism
		Agenda-setting	Synthesis	Expression	Evaluation	
I	Agenda–evaluation–synthesis	Proactive	Internally-powered	No	Yes, reflecting on previous events	Reflection
II-V	Evaluation–synthesis–agenda–demand/evaluation–synthesis–agenda–synthesis–demand	Proactive; continuous	Internally-powered and aligning external actors	Yes (single issue)	Yes; continuous	Active case building
VI-VII	Agenda–synthesis–demand/agenda–evaluation	Reactive	Little new information	A few times	Extensive	Knee-jerk reaction, administrative consultation
VIII	Agenda–synthesis–evaluation–demand	Proactive	Internally-powered and aligning external actors	Yes (as part of bigger advocacy effort)	Yes; continuous	Active case building

In interaction with actors A and B the BVN acquired many tasks, the most important of which are communication, mutual help and advocacy. These three main objectives are organised on both national and regional levels in the Netherlands. Active departments are located in all regions which take care of communication and mutual help by organising meetings, activities, and telephone help services. Moreover, in the contact they maintain with hospitals and integral cancer centres these regional departments also initiate their own advocacy efforts, e.g. by interacting with nursing staff dedicated to the care of breast cancer patients. These departments are characterised as having a low participation threshold. This means that members can become involved in the organisation quite easily. The same goes for the national level organisation, although these three objectives have increasingly professionalised in recent years. Communication is mostly one-way in the form of a public website, a magazine and conferences. Mutual help is given by means of a national telephone service and information on the public website. The advocacy efforts are organised through a special committee, but many responsibilities are also shared by the BVN board and the managing director. Although the board and the managing director have a large degree of power, members and volunteers, working in different committees, also have their say during the general membership meeting and through a central body of the BVN, in which representatives of all the committees meet: the Platform.

In this section we investigate demand articulation in interaction with external parties (Bs) and with the actors represented by the BVN (As). Again, we focus on the event theme that

deals with the reimbursement of expensive drugs in hospitals, most notably the discussions around the financing of Herceptin.

2a. Does demand articulation take place in a multi-actor innovation arena involving interactions between the BVN and its representing actors (As) and other relevant actors (Bs)? In other words, to what extent is convergence or joint construction of demands occurring?

The debates on expensive drugs reimbursement in hospitals involved many actors, like the Ministry of Health (VWS), parliament, medical professional organisations (HOVON, NVMO), other patient groups (NFK, CCUV on Crohn's disease and RPB on rheumatism), representatives of health insurance companies (ZN), the pharmaceutical companies (Nefarma), hospitals (NVZ), and the government agencies on health insurance (CVZ) and health tariffs (CTG). In Figure 54 we show to what extent these organisations agreed on the first-order and second-order with the BVN on the eight periods of the Herceptin event theme. The arrows indicate the shifts in these positions. They are explained in detail below.

Figure 54 exhibits that some actors strongly sided with the BVN in most of the periods of the event theme. The BVN had strong links with most of these actors. For example, the *NFK* founded a platform committee on drugs policy that aimed at patient advocacy on medicines. The BVN chairwoman was also a member of this committee, which shared the anxieties about access to expensive medicines, the problem characterisation, and ultimate preferences. Through the NFK, the BVN ended up in a coalition with other patient groups, including the patient group on Crohn's disease (*CCUV*) and rheumatism (*RPB*). Most prominently, the NFK took the lead in advocacy activities in periods VII and VIII.

Three other important actors who frequented and actually started this coalition were the medical professional groups on oncology (*NVMO*) and haematology (*HOVON*), and hospital representatives (NVZ). Through their network of medical specialists they identified the increasing potential problem of expensive drugs in hospitals. They sent a letter to parliament, discussed it in high-impact media and entered into discussion with the Ministry of Health. The NFK and the BVN latched on to these developments because they coincided with their own problem perception and the activities they were planning to organise. From period V onwards, the NFK and BVN took over this leading role in the coalition but the medical professional groups remained involved all the same. Only in period VII did the BVN and the medical specialists differ in their opinions on the necessity and benefit of determining the cost-effectiveness of (expensive) drugs (shift #1). The *NVZ* agreed on both levels as well: they foresaw the problems the after-Taxol reimbursement measures would pose and demanded a failsafe solution to the problem. Of course one of NVZ's reasons for expressing their opinion was out of self-interest, but equality of access was also a main motivation.

The BVN, NFK, NVZ, CCUV, RPB, NVMO and HOVON have in common that they all: 1) cooperated in coalitions during their advocacy activities; 2) substantiated their claims after conducting research, e.g. a consultation; 3) communicated their results both to the government and parliament, but also tried to take a second route via the media. On the first-order level they all fought against the unacceptability of unequal access to drugs ("postcode care"), interference with regard to the autonomy of physicians, the lack of a structural solution, and asking specifically for complete reimbursement. On the second-

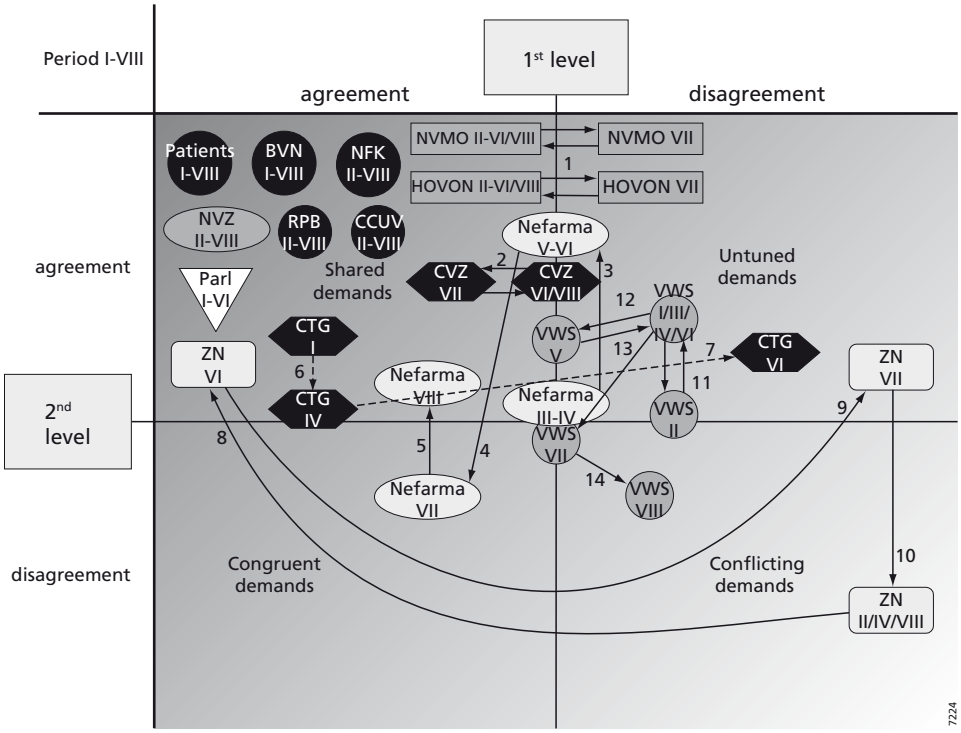

Figure 54 - shifts in the level of joint construction between the BVN and actors A (patients) and actors B (other relevant actors). Numbers in the boxes indicate the periods the actors feature in; the arrow numbers are dealt with when answering research sub-question 2c.

order level they agreed on the importance of equal access to optimal care, and the benefits of involvement in the policy debate.

The (breast) cancer *patients* who are members of the patient organisations involved are in the same state of joint construction as the BVN. It is difficult to answer the question to what extent the opinion of all Dutch breast cancer patients has been represented by the BVN. Nevertheless, patients strongly influenced how the BVN put the reimbursement issue on the agenda and dealt with it. Through the mutual help telephone service and e-mails, patients expressed their worries about inadequate Herceptin treatment. This was underlined by the developments in the USA, where Herceptin became part of standard therapy in an earlier stage of treatment. Patients threatened to go to the USA or finance the treatment out of their own pockets. Later, the BVN and NFK encouraged patients to file their complaints and founded a special telephone service, assisting them to take legal action. Some of these cases were stored and used anonymously in advocacy efforts, such as a letter to the Ministry of Health. Moreover, medical specialists also influenced the agenda-setting by means of their representative groups. Through their daily contact with patients, the specialists claimed to have a good overview of their situation and stressed that patients were best off with accelerated access to medicines. Also the patient groups regarded the relationship between physicians and patients as problematic because oncologists might not wish to inform patients about the possibility of Herceptin treatment because they knew that the hospital could not afford it. This meant that only well-informed patients were able to

insist on Herceptin treatment. To avoid jeopardising this relationship and the physician's autonomy, the patient groups felt that government should not put doctors in such a position. Besides the bottom-up reactions, some patients became more active as volunteers in committees and boards of patient organisations. These 'patient champions' delved into their own experiences as a patient and, making use of this experiential knowledge, articulated a breast cancer patient's vision of the problem. Examples of statements include "the patient finds benefit in good, safe, effective, innovative drugs", "which should be available to them as quickly as possible". And: "every drug that is beneficial to treatment should be made available".

Other actors shifted between the different states of joint construction, such as the Ministry of Health (VWS), parliament, the representatives of health insurance companies (ZN) and pharmaceutical companies (Nefarma), and the government agencies on health insurance (CVZ) and health tariffs (CTG).

The *Ministry of Health* (VWS) was mostly situated in a state of untuned demand, i.e. the ministry disagreed on first-order elements with the BVN but agreed on the second-order level (underlying assumptions): during the first few periods (I-IV) the ministry did not regard the reimbursement situation as problematic and found that the regulation in force would be sufficient, i.e. using the research-related ("academic") budgets of hospitals for reimbursement. Like the BVN, it too underlined the importance of proper access to medicines. In period II the VWS moved closer (shift #11 in Figure 54) to a state of conflicting demands because it was displeased with the way in which the patients and medical professional groups approached the media while the issue was still under discussion. In period V the ministry partially agreed with the solutions that were proposed by the BVN and other organisations, e.g. a constant reimbursement percentage, and shifted more towards a state of shared demand (#12). Nevertheless, it repeated that it had not received any concrete cases of problems with reimbursement. In fact, during the entire Herceptin event theme the ministry would deny the existence of any known specific cases. Later it became apparent that the reasons for the solutions presented, including the fixed 80% financing by insurance companies, were not the same as those put forward by the BVN and other organisations. For example, the Ministry of Health felt that the cost-effectiveness testing of drugs was more important than quick access to drugs (#13). These differences intensified with regard to the publication of the second Herceptin report and related advocacy activities of the NFK. The Ministry of Health differed in its opinion about the extent of the solutions offered (the NFK wanted to see a 100% coverage), and the causes of the problem that the NFK had identified from an analysis of the mutual dependencies between stakeholders. This led to a shift (#14) to a state of conflicting demands.

Parliament has been engaged in discussions about the reimbursement of expensive drugs from the start. The majority of political parties agreed with the demands and underlying assumptions as proposed by the BVN and other organisations, although not all them were as vociferous as others, such as left-wing opposition parties. It became clear that all parties found inequality of access unacceptable, and therefore favoured priority-setting between drugs above rationing (second-order arguments). On the first-order level there was more heterogeneity but all parties agreed that problems did exist, and that there was a need to come up with a structural – instead of a temporal – solution.

The two government agencies that implement the reimbursement regulation, the CTG and CVZ, occasionally became involved in the policy debate. After the Taxol debate (period I) and on the Herceptin issue (period VI), *CTG* agreed with the BVN and notably the

hospital representatives NVZ, on how to organise the new reimbursement regulations (state of shared demands). In period VI this entailed the option of reimbursement if a drug had not yet been registered but was already included in the guidelines for medical specialists. Nevertheless, the Ministry of Health did not approve this version and the regulation was changed. CTG believed the then-new regulation would be adequate to solve the problems, something the BVN did not agree with (#6 and #7). *CVZ* only became involved when the Ministry of Health decided to change the regulation and the CTG requested the CVZ to assist in designing procedures to include cost-effectiveness testing as a criterion for inclusion on the expensive drugs list. The CVZ set up these procedures in an open manner: they consulted a wide range of actors to give them the opportunity to express their opinion, and were not insensitive to the second-order underlying assumptions of other actors, e.g. the BVN's wish to become involved in decision-making and the fact that insured persons should have sufficient access to health care. Most parties agreed on the necessity of cost-effectiveness criteria, but emphasised that these new procedures should not impede quick access to treatment. Therefore, the CVZ swayed between agreement and disagreement on the first-order level (#2).

The position of the pharmaceutical industry representative *Nefarma* is rather unclear in the first periods of the event theme, leading to an ambiguous position in Figure 54 for periods III and IV. Nefarma stressed that for pharmaceutical companies the elements of "enterprising, innovative and indispensable" are core values. Moreover, on the first-order level Nefarma did not touch upon the same issues as those that occupied the BVN. Later on Nefarma expressed their underlying assumptions, which proved to be more in line with those of the BVN. However, regarding the first-order level Nefarma only partially shared the same issues (#3): they were also in favour of treatment based on medical guidelines but at the same time kept stressing that the cost-effectiveness assessments were unclear, and that the pharmaceutical industry cannot be solely held responsible for these procedures. In period VII Nefarma shifted to a state of congruent demands (#4). Despite agreeing on the new reimbursement regulations they differed in opinion about how to organise health care: Nefarma is a proponent of market-based health care as opposed to central government steering. After the last shift (#5) Nefarma is back in the state of shared demands when they underline the importance of cost-effectiveness testing, complete reimbursement of expensive hospital drugs (first-order), and faster and more equal access to innovative drugs (second-order).

Finally, the representative of the health insurance companies, *ZN*, disagreed on all levels with the BVN in the first few periods (II/IV) and was in a state of conflicting demands. Most prominently it failed to see the situation as problematic because hospitals would have enough resources to deal with the expensive drugs, and it concurred with the Ministry of Health to solve the reimbursement problems by using the hospitals' research-related ("academic") budgets (first-order level about a proposed solution). Moreover, like the Ministry of Health, they too abhorred the way in which patient and medical professional groups addressed the problem by using the mass media (second-order level about how actors should behave in debates). Later, when the financing of Herceptin for an unregistered, early-onset breast cancer indication became problematic, they shifted to a state of shared demand (#8). ZN agreed that a drug which is included in medical guidelines should be reimbursed. It asked for a special subsidy for the specific Herceptin case. Then it dissented from how the BVN saw the organisation of the new reimbursement regulation (first-order differences; #9): ZN was not in favour of the temporal registration of new drugs.

Later the BVN and ZN also differed in opinion about the role of insurance companies in health care, and what this role means in terms of the quality of health care and for the patients involved (first- and second-order differences; #10).

In conclusion, the shifts in the joint construction of demands are very varied. The demands and underlying assumptions of some actors, such as the patient and medical professional groups, converge at an early stage with those of the BVN, mostly as part of forming coalitions. Other actors, such as the Ministry of Health, display divergent demands or a combination of divergence and convergence, and in this way decrease the demand articulation in interaction with other actors.

2b. What strategies does the BVN deploy in the different interfaces with representing actors and other relevant actors?

The interface types employed by the BVN and the related methods are presented in Table 33. It becomes clear that presentation and advocacy through, for example, letters, position documents and the mass media, formed the most prominent way of communicating with other interacting partners (actors B).

With regard to the aspect of communication with actors A (the represented actors) it was difficult to quantify the number of interface types and methods used because most of the time they were applied in a continuous way. Nevertheless, the interface types encountered most often in communication with the represented actors were presentation and advocacy. Methods included, for example, mutual help telephone and e-mail services.

The Table 34 tentatively and inductively constructs interface strategies applied by the BVN during the event theme in interaction with represented actors (As) and other interacting partners (Bs).

The strategies most often used by the BVN were based on the sudden anxieties of the represented actors, or a representation of their interests without direct interaction with them. In interaction with other actors, strategies such as agenda-setting, alignment of actors, unasked advocacy, forceful advocacy and consultative presentation dominated. We return to these constructed interface strategies in the final part of this thesis (Chapters 8 and 9) where they are combined with the strategies found in the other cases.

Table 33 - interface types used and relating methods deployed.

Interface type	Times applied	In Herceptin event theme	Methods used (only prominent ones)
Consultation	22	0	-
Education	2	0	-
Presenting, advocating	71	26	Letters, presentations, media, position documents
Mediation	0	0	-
Coordination	20	9	Meetings
Deliberation	136	6	Meetings
Anticipation	12	2	-
Co-production	17	6	Conference

Table 34 - induced interface strategies per period for the BVN Herceptin event theme.

Period	Interface types used	Characteristics	Proposed interface strategy
I			
Note on expensive drugs	A: – (signals not directly derived from patients)		A: representation of other's interests
	B: Presenting (internal)	• Access: N/A • Empowerment: N/A • Impact: none	B: agenda-setting
II			
Policy plan Agenda-setting and preparing Herceptin document	A: – (signals from specialists groups, hospitals and company)		A: representation of other's interests
	B: Presenting (internal)	• Access: N/A • Empowerment: N/A • Impact: none	B: agenda-setting
Support of NVMO-HOVON letter Meeting with VWS (with others)	A: -		A: representation of other's interests
	B: Deliberation (meetings)	• Access: forced by media attention; medical specialists felt "natural alliance" with patients • Empowerment: strong connections between physicians and patients yield information • Impact: strong alliance and dual track approach (deliberation and media attention) resulted in big impact	B: alignment of actors; forceful advocacy
III/IV			
BVN acted through NFK; preparation of Herceptin document	A: Presenting (phone calls, e-mails)	• Access: existing channels • Empowerment: not important • Impact: full	A: sudden anxiety
	B: Consultation (research)	• Access: through NFK • Empowerment: N/A • Impact: none	B: alignment of actors; agenda-setting
V			
Document on Herceptin undertreatment	A: Presenting (phone calls, e-mails)	• Access: existing channels • Empowerment: not important • Impact: full	A: sudden anxiety
	B: Presenting/ advocating (report)	• Access: forced • Empowerment: own research; high investments of efforts • Impact: due to 'catchy' message big impact on media and parliament	B: forceful advocacy

Period	Interface types used	Characteristics	Proposed interface strategy
Letter to Senate	A: -		A: representation of other's interests
	B: Presenting/ advocating (letter)	• Access: forced • Empowerment: making use of results of Herceptin report and other own research • Impact: none (Senate did not decide otherwise)	B: unasked advocacy
Letter to Ministry of Health	A: -		A: representation of other's interests
	B: Presenting/ advocating (letter)	• Access: administrative reaction to earlier advocacy (Herceptin report) • Empowerment: making use of results of Herceptin report and other own research; threatening with legal and media action • Impact: Ministry of Health kept denying problem (there were no concrete cases)	B: consultative presentation
VI			
Letter to Ministry of Health	A: Presenting (phone calls, e-mails)	• Access: existing channels • Empowerment: not important • Impact: full	A: sudden anxiety
	B: Consultation (research)	• Access: administrative reaction to request for information • Empowerment: making use of information patients had communicated over previous months • Impact: Ministry of Health not convinced; issue passed to Inspection for Health Care	B: consultative presentation
Letters to Europa Donna	A: -		A: representation of other's interests
	B: Presenting/ advocating (letter)	• Access: forced • Empowerment: none (just conviction that European level influence would be at the proper level) • Impact: low (Europa Donna did not have that kind of influence)	B: tentative advocacy

Period	Interface types used	Characteristics	Proposed interface strategy
VII			
Letter to Ministry of Health/ Inspection for Health Care	A: Presenting (phone calls, e-mails) B: Presenting/ advocating (letter)	• Access: existing channels • Empowerment: not important • Impact: full • Access: administrative reaction to request for information • Empowerment: making use of information patients had communicated over previous months; information anonymous • Impact: anonymity of data did not result in strong case	A: sudden anxiety B: consultative presentation
Reaction to CVZ draft report	A: -		A: representation of other's interests
Reaction to positive Herceptin decision EMEA and CVZ	B: Presenting/ advocating (letter)	• Access: administrative reaction to request for information • Empowerment: making use of information produced before • Impact: provided information is taken up	B: consultative presentation
VIII			
Second Herceptin document	A: Presenting (phone calls, e-mails) B: Presenting/ advocating (report), deliberations (meetings)	• Access: existing channels • Empowerment: not important • Impact: full • Access: forced • Empowerment: own research; high investments of efforts; aligning with others, such as the NFK • Impact: due to 'catchy' message big impact on media and parliament	A: sudden anxiety B: forceful advocacy

2c. To what extent can the joint construction of demands by the BVN and their interacting partners be attributed to the interface strategies used? And how effective were those interface strategies?

To answer this sub-question we scrutinised the shifts in Figure 54 and investigated the degree to which the interface strategies (Table 34) contributed to them and were indeed effective. These contributions can be characterised and categorised as follows:

- In a few instances the BVN failed to focus their strategies on specific actors and the statements and viewpoints only achieved some indirect impact. Examples of these are the shifts of Nefarma (#3-5).
- Actors moved in a direction of joint construction out of pure self-interest or opportunism, e.g. shift #8 of the health insurance company representative ZN. The BVN strategies had no major effect on these shifts.
- Whereas the BVN did interact with actors (e.g. through deliberation), differences in opinion still arose or prevailed. The interface strategies were not very effective. Examples include the shift during period VII of NVMO and HOVON (#1), and the correspondence with the Ministry of Health during period VI and VII (#13).

- The BVN tried to gain access to an organisation but despite these efforts still failed to make an impact, e.g. in the case of CTG (#6-7).
- The information produced by the BVN had a counterproductive effect, i.e. the information fuelled other actors to become antagonistic. Examples include later shifts of ZN (#9-10).
- The BVN sometimes articulated their demands as part of a wider consultation. This inevitably led to a wide range of opinions and a smaller impact. Nevertheless, in the case of the CVZ consultation the shift (#2) was in the direction of more shared demand.
- The BVN sometimes tried to force access to the debate, e.g. by using the mass media, while also being engaged in administrative negotiations. This led other parties to react unfavourably and question BVN's access to the debate (shift #11 by the Ministry of Health). It also led these other actors to better protect themselves from these 'attacks' by learning how to deal with them (the Ministry of Health's reaction to the second Herceptin report, #14).
- In some cases the BVN explicitly contributed to changes in actors' first-order and second-order opinions, e.g. of the Ministry of Health (#12). These cases were characterised by the forceful nature of the advocacy activities, and by using the 'natural alliance' between patients and medical specialists; this had an impact that was "undeniable" for media and parliament. Therefore, this strategy can be seen as quite effective, also because access to the debate had been difficult and the 'problem owner' (VWS) denied the existence of a problem throughout the event theme.

The large variety in contributions to demand articulation on the arena level illustrates the large degree of variation in effectiveness of interface strategies. The other research sub-question had already showed a diversity of deployed interface strategies and methods.

7.4 Preliminary conclusions

This chapter has described how a health policy problem, i.e. the reimbursement of expensive drugs in hospitals (a problem that involves a large number of different actors in health care) unfolds. It also uncovers the strategies these actors use to articulate their demands and attempt to influence others by doing so. This case concerns a reimbursement issue that was regarded as problematic by only some of the actors involved, including the BVN, other patient groups and medical professional organisations. These 'outsiders' were not a part of the health policy arena in which this issue was dealt with. The actors who did belong to the arena benefited by maintaining 'silence' in the debate, e.g. the Ministry of Health constantly denied that there was a problem. This led the outsiders to go into battle, or force access to the debates.

Viable and effective strategies for these outsiders were to seek linkages with other parties that shared the same objectives and underlying assumptions about the problem. Coalitions were formed between patient organisations, such as the BVN and medical professional groups. These coalitions worked well, especially because their motives were patient-driven. Other actors claimed that these coalitions were "undeniable". Overcoming silence and seeking entry to the policy arena was achieved through a combination of direct deliberation and seeking media attention. This was effective, although the impact

on the media and parliament can partially be explained because they were susceptible to the inequality that was resulting from the reimbursement problem. Nevertheless, not all actors appreciated this approach, as became clear when studying the second-order learning loop: actors like the Ministry of Health and the representative of the insurance companies condemned the combination of media attention and deliberation as 'furtive' or 'deceptive'. On the other hand it did comply with the idea of patients and patient groups as being a full member of the health policy arena. Patient groups were seen as the so-called 'third party'. This difference in positioning was the source of some friction in the policy debate about expensive drugs reimbursement. Secondly, the BVN and others tried to underpin their problems not only with ethical arguments and objectives, but also by producing figures. In this case, these figures considerably helped in communicating and defining the problem to other parties.

Furthermore, what should also be considered is the effort that patient and medical professional groups put into gaining access to the debate, e.g. regarding the figures and reports produced by them. Other stakeholders should be aware of the pressure these efforts put on mostly volunteer-based organisations. While these activities show the creative potential of organisations like the BVN, at the same time they raise questions as to whether such efforts should be left to this kind of organisation.

Besides this rather forceful form of advocacy, the BVN used other interface strategies, such as agenda-setting, advocacy preparation, unasked advocacy, and responding advocacy. The interface strategies in relation to the represented actors were driven by anxiety about a problem and the desire for assistance, or the creation of an idea of the patients' interests. The latter is not so much based on an empirical construction of what patients want, but rather the result of a constructed image of 'the' patient by the BVN. The validity of this image-building might be questioned because patients' interests are actually quite heterogeneous. However, it could be argued that the BVN, through its daily contact with patients/members, knows quite well how to articulate demands of the patients.

Furthermore, the BVN interface types were quite varied in nature and methods used, although the emphasis was on presentation/advocacy, and the associated approach of letters and meetings. The BVN maintained its contacts with the represented actors (the breast cancer patients) through mutual help devices, such as the telephone and e-mail services. Moreover, some patients/members actively took part in the organisation's committees.

Regarding the demand articulation processes within the BVN we can conclude that first-order learning did occur in the context of the Herceptin event theme because the number of demands grew over time, and the level of concreteness also increased. Second-order learning also took place, e.g. on the way in which the BVN deals with patient advocacy. Moreover, first-order and second-order learning had a reciprocal influence on several occasions, e.g. by legitimising and evaluating demands. Lastly, we tentatively identified some demand articulation mechanisms, such as the 'reflection' cycle, the 'active case building' cycle, and the 'administrative consultation' cycle.

In general, the BVN became engaged in the issues around the reimbursement of expensive breast cancer medicines like the pharmacogenomics drug Herceptin. They articulated their demands and learnt how to deal with advocacy efforts along the way. The interaction with other actors and the people they represent were significant. Again, the BVN developed strategies to include these parties in a more or less effective manner.

Chapter 8

Lessons from the case studies

The first chapter introduced two challenges that the health care and pharmaceutical sector currently face in the context of emerging technologies: 1) the decrease in pharmaceutical innovations; 2) the adoption and implementation of these innovations by society, e.g. questions about access to drugs, unmet medical needs, and inequity. It is assumed that involving users in debates and processes around these innovations has a beneficial effect on taking up these problems. This thesis focuses on a particular type of user in the health care innovation arena: intermediary user organisations. In this thesis they are defined as stakeholders that facilitate interactions between users and one or more other actors.

Within the context of emerging technologies, users should be engaged in iterative, inherently creative processes in which they try to address what they perceive as important characteristics of, and attempt to unravel preferences for these technologies. These activities together can be labelled as demand articulation. The aim of our study is to obtain a better understanding of the role of intermediary user organisations in demand articulation concerning emerging technologies. Accordingly, the central research question of this thesis is:

How to understand the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies?

By looking into this we aim to gain more insight into how the actions and interactions of the various actors shape, develop and change emerging technologies. We concentrate both on demand articulation processes within intermediary user organisations, and the demand articulation processes in which these organisations interact with other actors. Related to these two focal points, this chapter presents the main conclusions for the first two research questions:

1. *How to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies? (section 8.1)*
2. *How to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies? (section 8.2)*

A second objective of this study is to make recommendations for intermediaries, governments, pharmaceutical companies and other actors in the health care innovation arena about conditions to improve the quality of user-producer interaction, and by this alleviate the two major challenges described above. This refers to research question 3 that was introduced in Chapter 1. Chapter 9 focuses on answering this question.

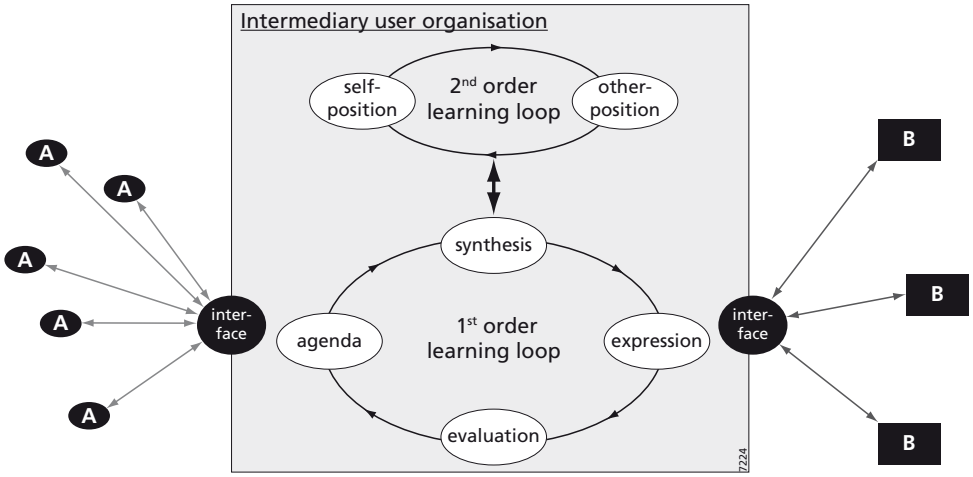

Figure 55 - central conceptual model as derived from theory in Chapter 2.

In this thesis a conceptual framework is proposed that contributes to understanding demand articulation processes of intermediary user organisations in the context of emerging technologies (see Figure 55).

The research questions were studied by focusing on three intermediary user organisations. These organisations are engaged in work on several issues. The sequence of events related to one topic is called an event theme. We studied those themes that intermediaries themselves regarded as significant and which were related to the emergence of a specific technology[51] (Box 8.1).

Box 8.1 intermediary user organisations, the event themes studied (in italics) and the most important activities

Dutch Neuromuscular Diseases Association (VSN)
gene therapy: following scientific developments, informing patients
stem cell therapy: following scientific developments, validating new therapies
exon-skipping: setting-up science networks, following scientific developments
enzyme replacement therapy: animal rights debates, clinical trials, reimbursement
idebenone: propagating clinical trials
TCH346: informing patients, propagating clinical trials
Steering Committee on Orphan drugs (WGM)
orphan drug R&D: stimulating science networks and programmes
reimbursement of orphan drugs: policy debates about financing expensive drugs
Breast Cancer Association (BVN)
reimbursement of breast cancer drugs: policy debates about financing expensive drugs used in hospitals, such as the pharmacogenomics drug Herceptin.

51 Pharmacogenomics or an analogy of this technology, such as orphan drugs, as was discussed in chapter 3.

8.1 Research question 1: Demand articulation processes inside intermediary organisations

This section concentrates on the following question:

How to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?

This question is divided into three more specific sub-questions.

1a. Does demand articulation or first-order learning take place inside intermediary user organisations?

Demand articulation processes inside organisations are conceptualised through two interlinked learning processes: first-order and second-order learning. First-order learning concerns developing demands by following the loop as described in Figure 55: agenda-setting – synthesis – expression – evaluation. This part of research question 1 concerns the issue whether first-order learning occurred.

First-order learning was measured on three aspects:

- Growth in demand statements, indicating that an intermediary appreciates the significance of an event theme; most themes showed an increase in demand statements.
- Convergence of demands, indicating the accumulation, i.e. gaining causative critical mass, and the sharpening of demands; most themes showed an increasing level of concreteness.
- Changes in direction of demands, indicating changes in the general opinion of an intermediary towards a topic, i.e. being positive or negative about a certain development or innovation project; most themes did not often show such changes.

In the different event themes of the three case studies, first-order learning occurred in varying degrees (Table 35; second to fourth column).

Demands are subdivided into different types, e.g. visions/expectations, problems, ideas, and needs. Demand articulation processes in the event themes are dominated by one or several types, such as the mutual amplification of problems and ideas in the orphan drug reimbursement theme. Other themes revolve around more types of demand (Table 35, last column).

Answering this research sub-question, we can conclude that first-order learning took place in various instances inside these three intermediary user organisations. Moreover, when looking at the degree of first-order learning and the different event themes studied (Table 35), it may be concluded that first-order learning is also dependent on:

1) The stage of technology development. If the technology is in an early phase, such as was the case for gene therapy, stem cell therapy and exon-skipping, the possibilities to influence the course of development is low. The intermediary user organisation does not steer the course of development but plays a different role: in early stages it creates boundary conditions and visions, which may not be less significant but does result in lower levels of first-order learning. Later on in the development process, influencing the course of technology development and implementation is sought.

2) Sufficient support of the intermediary's position from other actors. For example, all three intermediary user organisations, being national-level groups, show a more prolific first-order learning curve, matching problems with ideas in the context of event themes dealing with national-level issues, like reimbursement. Here, access to national-level actors, the willingness of these actors to interact, and the resources to

Table 35 - summary of first-order learning over the cases.

Event theme	Demand increase	Convergence of demand	Direction in demand	Examples of content of first-order learning	Prominent types of demand
VSN					
I. Gene therapy	Moderate	No	Yes	Expectations about the gene therapy future	Visions dominate
II. Exon-skipping	First period more than in second	No	No	Building science for Duchenne; expectations about exon-skipping future	Visions and ideas dominate
III. Stem cell therapy	Yes	Yes	No	Expectations about stem cell therapy; dealing with alternative medicine	Problems dominate
IV. Pompe ERT	Yes	Yes	No	Animal biotechnology; setting up clinical trials; reimbursement; compassionate use	Problems dominate
V. Idebenone	First period moderate; second period yes	First period moderate; second period yes	No	Setting up and organising clinical trials	First period visions and facts dominate; second period ideas as well
VI. TCH346	Yes	Convergence followed by divergence and convergence again	No	Setting up and organising clinical trials	Visions, facts and ideas dominate
WGM					
Reimbursement	Yes	Yes	No	How to organise reimbursement, e.g. through special reimbursement rule	Problems and ideas spur each other on
Orphan drugs R&D	Yes	No	No	Inventories of rare disease research; ideas to set up research programme	Agenda-setting of problems; no ideas or follow-up
BVN					
Reimbursement Herceptin	Yes	Yes	No	Concretise extent of problem of reimbursement; calls for action	Needs and problems dominated

be a valuable partner are better matched by the intermediary as compared to trying to steer internationally-organised pharmaceutical companies[52].

3) The resources and level of professionalism of the intermediary.

1b. Does second-order learning take place inside intermediary user organisations and how is this connected with first-order learning?

The first part of answering this sub-question concerns whether second-order learning took place inside the three organisations during the event themes. Second-order learning concerns the development of strategies and objectives of an organisation, as well as its norms and underlying preferences.

We measured this second-order learning by explicitly recording objectives, strategies and norms mentioned in the documents concerning the event themes. Moreover, interviewing representatives of stakeholders, and asking their motives for certain actions resulted in uncovering the actor's underlying assumptions. Table 36 (third column) gives some examples of second-order learning in the three intermediary user organisations studied, such as the development and growing importance of objectives such as learning how to deal with clinical trials, science, and expectations; strategies; and normative concepts like 'solidarity' and 'the right of equal access to medicines'.

Second-order learning occurred in most event themes (Table 36, second column), although some of them showed slow development with regard to ultimate preferences[53]. Following the central conceptual model (Figure 55), second-order learning forces intermediaries to reflect on their own positions in interaction with how others position them. This loop of mutually-influencing self-position and other-positions was not found in all cases (Table 36, fourth column).

The second part of this research sub-question is about the linkages between first-order and second-order learning as proposed in the conceptual model. Table 36 (fifth and sixth column) shows that in all event themes of all cases there are interactions between the two learning types. As was hypothesised in Chapter 2, these linkages take many shapes and are attached to the different stages of the first-order learning loop. Underlying assumptions are proactively and reactively used during agenda-setting and weighing the entries, as well as legitimisation during synthesising demands. The organisation and set-up of demand expressions is not so much influenced by underlying assumptions, whereas during evaluation there is ample room for feedback on these assumptions.

The feedback mechanism is a pivotal element in the interactions between first-order and second-order learning. Organisations learn to tune their objectives to the kind of demands they articulate. Moreover, other actors position the intermediary user organisation and in this way influence how these intermediaries regard themselves (self-position). For example, when other actors want to place topics on the intermediary's agenda, they more or less impose their assumed thoughts about which issues the intermediary should be dealing with. Moreover, second-order learning results in the development of the objectives of intermediary user organisations. It could be claimed that these organisations have a course

52 Although this influencing sometimes occurred indirectly through internationally-organised patient groups, such as the International Pompe Association.

53 Which form a part of the organisation's underlying assumptions (see Table 1).

Table 36 - summary of second-order learning and interactions between first-order and second-order learning over the cases.

Event theme	Second-order learning?	Examples of second-order learning	Second-order learning loop?	Interaction first-order and second-order learning?	Characteristics of this interaction
VSN					
I. Gene therapy	Yes	How to deal with emerging technology, how to manage expectations, and why?	No	Yes	Legitimisation; self-positioning is partly influenced by first-order learning; reactive weighing
II. Exon-skipping	Moderate	Only in early stages when setting-up activities	No	Yes	Legitimisation of activities and proactive weighing
III. Stem cell therapy	Moderate	Only on how to manage expectations	No	Yes	Legitimisation; evaluation through feedback from others; pro/reactive weighing
IV. Pompe ERT	Yes	Constant and also articulated because it wanted to 'copy' the approach to other disease areas	Yes	Yes	Legitimisation; evaluation; timing; continue/discontinue decisions (proactive weighing)
V. Idebenone	Yes	Learning about dealing with R&D stimulation and steering; clinical trials; and policy regarding non-innovative drugs	No	Yes	Legitimisation; evaluation; reactive weighing
VI. TCH346	Yes	Learning how to deal with R&D stimulation when genetic origin of disease is unknown; learning about balancing representation of patients	Yes	Yes	Legitimisation; evaluation; pro/reactive weighing
WGM					
Reimbursement	Moderate	Slow learning; no changes in ultimate preferences (solidarity); maturing of organisation; in first periods others position WGM, later more self-reflection	Not in all periods	Yes	Legitimisation of demands; evaluation of activities (feedback); proactive weighing

Event theme	Second-order learning?	Examples of second-order learning	Second-order learning loop?	Interaction first-order and second-order learning?	Characteristics of this interaction
Orphan drugs R&D	Yes	Profound because of need for self-positioning (what do they find important?)	Yes	Yes	Underlying strategic choices made; evaluation (feedback); proactive weighing
BVN Reimbursement Herceptin	Yes	No changes in ultimate preferences (solidarity); learning about how to advocate	Yes	Yes	Choices underlined; evaluation (feedback); legitimisation of demands; reflection; proactive weighing

of life of their own, and that developing their underlying assumptions is part of a maturing process.

1c. What 'demand articulation mechanisms' can be discerned from studying these learning processes?

The first-order learning loop inside an intermediary user organisation constitutes four steps or event categories (Figure 55): agenda-setting – synthesis – expression – evaluation. Different intermediaries run through these loops in distinct ways depending on the characteristics of the issues at stake. In Chapter 2 these different learning loops are called demand articulation mechanisms.

These mechanisms were inductively and tentatively derived from the case studies in four steps: 1) coding the first-order demand statements in event categories, i.e. agenda-setting, synthesis, expression or evaluation; 2) recording the order of these event categories; 3) investigating whether the order of event categories was meaningful in relation to the content; 4) finding demarcating variations in the event categories that lead to the identification of different demand articulation mechanisms[54]. Examples of these variations are whether the agenda-setting was reactive or proactive, and to what extent the synthesis of demands originated from aligning with other actors. The mechanisms that were found in the event themes of the three case studies are summarised in Table 37.

Concerning research question 1, we can draw conclusions about demand articulation dynamics inside intermediary user organisations following the concept of the conceptual model (Figure 55). First-order learning often occurs, but variations are present because of differences in the degree to which intermediary user organisations are able to influence certain topics. We did find several patterns in the first-order learning loops. Most of these patterns followed the order of event categories as hypothesised in the conceptual model (agenda-setting – synthesis – expression – evaluation). Differences in order and characterisation of these event categories resulted in the distinct demand articulation

54 The names of these mechanisms are constructed in the same vein as producing names for scenarios.

Table 37 - demand articulation mechanisms of three cases combined.

Type of demand articulation mechanism	Characteristics of demand articulation mechanism	Found in event theme on
'Management of expectations' (realism/ enthusiasm)	Reacting on scientific news or proactively scanning scientific work leads to attempting to understand and validate the information in cooperation with scientists. Demands include disclaimers and balancing expectations with realistic views.	Gene therapy, exon-skipping, stem cell therapy, idebenone, TCH346
'Urging for action'	Scientific information is leading to proactively taking up a topic and to asking others to take action, e.g. start clinical trials. Intermediaries usually align with scientists in these efforts.	Stem cell therapy, TCH346
'Stay on track'	Proactively and continuously following developments, e.g. on the development of a drug, through information gathering and demand expression.	Pompe ERT
'Network building'	Proactively setting up a network of actors with a predefined goal and ideas. This is done by actively aligning and preparing other actors.	Exon-skipping, TCH346, WGM R&D
'Following others'	Reactively co-produce advocacy efforts initiated by others, e.g. in interaction with the international patient group.	Pompe ERT, TCH346, idebenone
'Active case building'	Proactively taking up an issue and building a case by gathering information and aligning with external actors, e.g. by producing facts and figures to support advocacy.	Pompe ERT, WGM reimbursement, BVN
'Administrative consultation'	Information is produced as part of a formal consultation in which the intermediary reactively participates. This consultation is mostly initiated by a governmental agency.	WGM reimbursement, BVN
'Project stimulation'	Setting up small projects as experiments to stimulate research on a more general level, e.g. for rare disease research.	WGM R&D
'Knee-jerk reaction'	Quick reactions to external events with virtually no synthesis or preparation, although preliminary work would certainly have been done in the context of other cases or general positioning.	Pompe ERT, WGM reimbursement, BVN
'Testing the waters'	Ideas are expressed in rapid succession to learn what others think about them. For example, how the WGM should stimulate rare disease R&D.	WGM R&D
'Reflection'	Issues are proactively put on the agenda but subsequent actions remain internal and are geared towards evaluation. E.g. over longer period of time it is decided whether to follow certain directions or topics.	BVN
'Unfinished business'	Issues are proactively put on the agenda but have not led to a follow-up (so far).	Pompe ERT

mechanisms illustrated in Table 37. The most prominent mechanisms include the 'management of expectations', 'network building', 'active case building', and the 'knee-jerk reaction' to issues. Furthermore, we may conclude that in all cases second-order learning is present, and that the mutual influencing of first-order and second-order learning can be observed in all event themes. In most of these themes this influencing takes the shape of weighing, legitimisation and feedback during evaluation.

8.2 Research question 2: Demand articulation in interaction with others

Moving from demand articulation inside intermediaries to demand articulation of these organisations in interaction with other actors, we answer the following research question:

How to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies?

Again, the answer to this question is broken down into three parts.

2a. Does demand articulation take place in a multi-actor innovation arena involving interactions between an intermediary user organisation and its representing actors (As) and other relevant actors (Bs)?

This part of the second research question focuses on how intermediary user organisations contribute to demand articulation at the level of the multi-actor innovation arena. While individual actors sharpen and articulate their demands in the same vein as the intermediary user organisation (see research question 1), they all try to influence demand articulation vis-à-vis other actors.

Here, we do not focus on the individual demand articulation of the various actors[55], but turn to look at the consequences it has on the joint construction of demands. This is measured by the extent to which first-order (demands) and second-order elements (underlying assumptions) of the various actors correspond, resulting in four different states of demand in which the actors can be placed (Figure 56). We compared the demands and underlying assumptions of the intermediary with the actors it represents (actors A; e.g. patient members) and other relevant parties (actors B; e.g. the Ministry of Health, parliament) for the distinct periods of one event theme per case[56]. The shifts in Figure 56 over the periods illustrate changes in the joint construction of demands per event theme.

The intermediary user organisations and their interacting partners showed various degrees of agreement and disagreement on the first-order and/or second-order level over the periods of the event themes as was illustrated by shifts in Figure 56 for each case[57]. In the *VSN* case, the patients, along with the scientists and medical specialists at the Erasmus Medical Centre, and the International Pompe Association remained in a state of 'shared demands'. There were also some parties that stayed firmly in a conflicting demands mode, e.g. the animal rights groups, and those that slowly moved to a state of shared demands, e.g. parliament and Genzyme.

In the case of the *WGM*, the other parties, i.e. parliament, the National Health Care Insurance Board (CVZ) and the Ministry of Health, quickly moved to a state of 'shared

55 Apart from demand articulation of the intermediary user organisation.

56 For the second research question we focused on one event theme per case study, i.e. the reimbursement theme for both the WGM and the BVN case, and the event theme describing the development of the enzyme replacement therapy for Pompe disease in the VSN case. See the methodology chapter for more information on the choices made.

57 See Figure 41 in Chapter 5, Figure 49 in Chapter 6, and Figure 54 in Chapter 7.

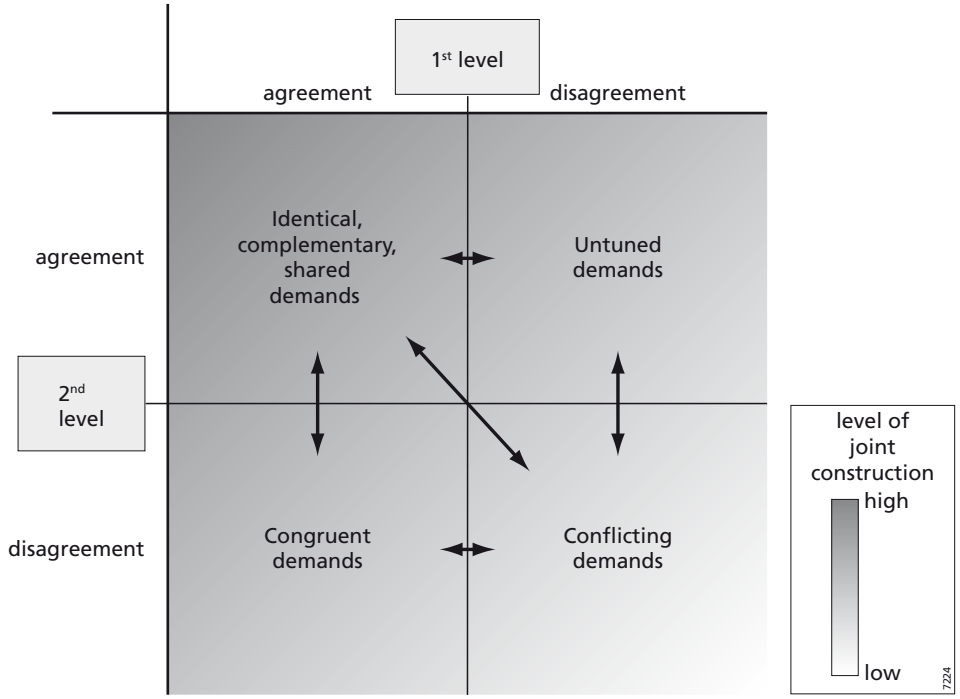

Figure 56 - four states of demand and related level of joint construction.

demands' with the WGM. The Ministry of Health remained dissenting from the WGM on the second-order level, and ended in a state of 'congruent demands'.

In the *BVN* case, most parties agreed with the BVN on the second-order level and frequently switched from agreement to disagreement and back again on the first-order level. There were also many actors who remained in a 'shared demand' state for most part or the event theme. Examples include other patient groups, parliament, the representatives of medical specialists and hospitals, and the represented actors.

Following these shifts in Figure 56 for each case, for some actors a development was seen towards converging demands being preceded by diverging demands. In the three cases the intermediaries and the other relevant parties (actors B) sometimes came to such a 'joint construction of demand'. On the other hand, some of these other relevant parties finished in demand states with a lesser degree of joint construction. Concerning the actors represented by the intermediaries (actors A), it can be concluded that in both the BVN and VSN cases[58] these actors remained in a state of 'shared demand'.

As was pointed out in Chapter 2, it should be emphasised that we do not envisage a state of 'shared demand' as a normative endpoint. In some stages of the debate it is necessary to broaden the perspectives instead of striving for convergence. Especially the earlier stages of technology development benefit from the broadening and enriching of demands. Later on these demands can converge again.

58 As was explained in Chapter 6 in the WGM case the distinction between represented actors and other relevant parties was difficult to make.

All in all, demand articulation takes place on the level of the multi-actor innovation arena. This implies that intermediary user organisations and the actors with which they interact, change regarding the level of agreement on first-order and second-order elements. More in general, the analysis of the (shifts in the) levels of agreement is a useful approach to describe the course of the debate, the changing positions of actors, and even the forming of coalitions. However, this analysis did not clarify the reasons behind the shifts, for example whether actors' strategies had any influence on demand articulation in an innovation arena. The next two sub-questions shed light on these aspects.

2b. What strategies do intermediary user organisations deploy in the different interfaces with representing actors and other relevant actors?

Interaction with other actors is organised through the interfaces of the intermediary organisation. We discern between interfaces that are applied during interaction with represented actors (A), and those used with other relevant actors (B). A classification of interface types is presented in Chapter 2, ranging from mediation and coordination to advocacy. We measured the occurrence of these interface types by coding the events in the database using well-defined indicators. Apart from this classification, different methods are used within these interfaces, e.g. writing letters, giving presentations and setting-up a questionnaire. These methods were inventoried as well.

Concerning the interactions with actors A there are two types of patients with whom the intermediary communicates. The first is the 'silent majority' of patients with which the organisation maintains contact more or less constantly. The most prominent types of contact with this category include presentation (using newsletters, the Internet, mutual help e-mail and telephone services, press releases), education (brochures), consultation (asking for opinions or data), and deliberation (annual patient get-togethers). The second category consists of 'patient champions': patients who are actively engaged in the intermediary organisation, e.g. by participating in working groups or committees. These patient members turned into this active mode through the information they received through the interface types and methods described above. At the same time however, they were also influenced by the media. Most of the times they became active as a result of a particular event, such as the public announcement of certain scientific or business results. Once these patients are part of the organisation, there is no longer the need for interface types or strategies because their communication turns into an activity internal to the organisation.

Concerning interactions with actors B, the intermediaries use a wide range of interface types as well. The most prominent of these include presentation/advocating, deliberation and coordination. Methods that are applied comprise letters, position documents and the mass media. To a lesser extent the intermediary user organisations use interface types that have a strategic, long-term focus, indicating lesser anticipation of future developments. Reasons for this might be that it would call for more resources and investments, and a certain amount of patience to pursue issues in the long term.

The intermediaries pursue different strategies in interactions with other actors B. In doing so, three processes are important: gaining access to debates, *access*; basing arguments on sufficient knowledge, *empowerment*; and influencing the debates, *impact*. Following the events and statements of the event themes in which the intermediaries are engaged, we combined the interface types, methods and the three types of strategies (access, empowerment and impact) into an explorative classification of interface strategies that are

Table 38 - constructed overview of interface strategies in interactions with actors A and B.

Interface strategies A	**Applied in organisation**			**Description**
	VSN	WGM	BVN	
Agenda-setting	X			Patients stress importance of certain developments and ask for a follow-up
Sudden anxiety	X		X	Sudden surge in stress or indignation of patients leads to full and quick access to organisation's agenda; also quick presentation of facts
Representation of other's interests	X	X	X	Interests of patients are constructed by intermediary without actual interaction
Advocate personal needs	X			Patient champions put their personal anxieties on the agenda and because of their inclusion have great impact
Anticipative alignment		X		Discussions with large and varied group of actors about future issues leads to agenda items and follow-up
Deliberation		X		Discussions with small and undiversified group of people about specific issues leads to agenda items and follow-up
Creative consultation		X		Other parties are asked to come up with input and small research projects are created to produce policy information
Interface strategies B	**Applied in organisation**			**Description**
	VSN	WGM	BVN	
Unasked advocacy	X	X	X	Unasked demands expressed, using own knowledge resources and yielding low impact
Anticipative alignment	X			Through contacts with others become better informed, and create mutual understanding
Forceful advocacy	X		X	Both aligning with others and using broad media coverage and parliament; producing information as well; aiming at high impact
Tentative advocacy	X			Tentative demand expression, through aligning with others and deliberation
Alignment of actors	X		X	Aligning with others creates critical mass
Consultative presentation		X		Input was asked as part of formal consultation, thus easy access and impact; producing information
Agenda-setting			X	'Just' express some points of interest that might be taken up later

applied by intermediary user organisations. Table 38 presents a summary of the interface strategies that were constructed following the different cases. We made a distinction between interface strategies used in interaction with represented actors (A) and with other relevant actors (B).

The table above provides the answer to the research sub-question concerned here. It shows that in interaction with actors A, a large array of interface strategies was deployed, ranging from representing patients without interaction to quick and passionate calls for action ('sudden anxiety'). These strategies mostly focus on ad hoc advocacy and also put a relatively large amount of effort into representing actors without actual interaction. Nevertheless, the

'advocate personal needs' and 'anticipative alignment' strategies ensure more longer-term commitment and focus.

Interactions with actors B were also varied and included interface strategies ranging from asked advocacy in the form of consultative presentation to unasked advocacy, and from forceful to tentative strategies. These strategies were most of the time not the result of ad hoc actions but had a proactive and long-term focus. They called for an elaborate preparation and direct interactions with stakeholders.

2c. To what extent can the joint construction of demands by the intermediary user organisation and their interacting partners be attributed to the interface strategies used? And how effective were those interface strategies?

The effectiveness of the interface strategies was investigated by looking at the extent to which diverging and converging shifts in Figure 56[59] were the result of interface strategies deployed by the intermediary user organisation, measured in general terms (negative – positive).

The interface strategies show a large degree of variation in effectiveness. In some cases *no effort* was made to influence a particular actor, apart from the indirect, unintended impact of statements and viewpoints which the intermediary produced. Also, some other actors changed their position out of sheer self-interest, without taking into account the intermediary, e.g. they changed their demands or underlying assumptions because of pressure coming from their own supporters. In other instances, the strategies deployed had a *negative* impact on the positions of others: the information produced or interface strategy chosen led others to be antagonistic, i.e. demands statements are articulated revealing stark contrasts that were hitherto less clear. Sometimes, despite advocacy efforts there was no impact because demands were not heard, e.g. simply because of the lack of proper communication. *Moderate* impacts were mostly the result of an organised consultation round in which the voice of the intermediary was only one of many. Lastly, intermediaries sometimes *positively* influenced other actors, mostly by aligning with like-minded parties, in that way forming a 'natural alliance' with an 'undeniable' message. Examples of these alliances are between patients and medical professionals, and between patients and scientists. The impacts not only influenced the contents of decisions, but also the opinions others had about input coming from intermediary user organisations, and (structural) changes in management and policy procedures.

The variation in effectiveness is easily related to the different types of interface strategies as presented in Table 38. Consultative presentation often leads to moderate effectiveness, whereas forceful advocacy, implying a high degree of alignment and application of resources, is linked to high access to debates or the agendas of other actors, empowerment of the intermediary, and high impact on the debate. The communication with actors A was in all three studied cases also effective. A large variety of interface strategies was observed, ranging from active to passive involvement of represented users, and from a short-term to a longer-term focus. Ideally, intermediary user organisations refrain from only using 'representation of other's interests' and also focus on 'sudden anxiety', 'advocate personal needs' and 'anticipative alignment' strategies.

59 See Figure 41 in Chapter 5, Figure 49 in Chapter 6, and Figure 54 in Chapter 7.

To answer research question 2 about how to understand the demand articulation dynamics of intermediary user organisations in interaction with other actors, we conclude that demand articulation takes place between intermediaries and other organisations in the health care innovation arena. The represented actors (A) mostly agreed on demands (first-order learning) and underlying assumptions (second-order learning), and thus being in a state of shared demands with the intermediary. The other interacting partners (B) sometimes differed in opinion on these two aspects, causing diverging and converging demand articulation dynamics, both leading to coalitions of actors within the innovation arena.

The intermediaries effectively used several strategies aimed at access to debates or agendas, empowerment through resources, and impact on decisions. The use of a combination of interface strategies in interactions with represented actors, such as embodiment of needs and aligning with end-users to work out their needs, should form an effective combination for effective interactive demand articulation. Interface strategies concerning other relevant parties should first and foremost focus on those strategies incorporating alignment of efforts, a high degree of resource application, as well as strategies that are geared towards a proactive and long-term orientation.

The next chapter adopts the conclusions that were presented here to draw lessons for stakeholders in the health care and pharmaceutical innovation arena, such as governments, pharmaceutical companies, and intermediary user organisations themselves. Furthermore, we discuss to what extent the findings and conclusions of this thesis contribute to user involvement literature and practice. The latter to produce conditions and recommendations to improve the quality of user-producer interactions.

Chapter 9
Evaluation and conclusions

In this last chapter we draw more general conclusions on demand articulation processes in and with intermediary user organisations in the context of emerging technologies. We first present the lessons various stakeholders can learn from our analyses, which form the answers to research question 3 (9.1). The methodology is then reflected on (9.2), and section 9.3 offers the final concluding remarks.

9.1 Research question 3: Lessons for stakeholders involved in user-producer interactions

In this section the answers to the four sub-questions comprising research question 3 are discussed.

3a. In what way did intermediary user organisations influence technology development and vice versa?

This thesis started from the perspective that user involvement in drug innovation processes is beneficial to all parties involved because it has a positive impact on the quality of innovation processes. When studying emerging pharmaceutical technologies we not only focused on the early stages of the drug R&D process but also took into account issues in the implementation phase. The reason for this is that we believe that all phases of the innovation process, both early and late, iteratively influence each other. For example, market conditions and reimbursement practices often influence early-stage developments, as was the case with the pharmacogenomics drug Herceptin.

The three studied intermediary user organisations, i.e. the patient organisations for neuromuscular diseases (VSN) and breast cancer (BVN), and the steering committee on orphan drugs (WGM), influenced several phases of the innovation process. The VSN dealt with emerging technologies, such as gene therapy and stem cell therapy, as well as with reimbursement issues in the later stages of the drug innovation process. The same applies to the WGM, which prominently engaged itself with the reimbursement of orphan drugs, but also tried to influence rare disease R&D in the Netherlands. Lastly, the BVN primarily focused on issues at stake in the later stages of the innovation process, such as the reimbursement of drugs.

In contrast to the benefits of user involvement in innovation processes, in recent years some authors have been less enthusiastic about this premise, especially in the health and pharmaceutical context. First and foremost, instrumental counterarguments include the substantial financial investments and time needed to set-up meetings, and overcome potential knowledge gaps to organise proper user involvement (Caron-Flinterman, 2005). Especially while the biomedical subject matter is rather esoteric and might call for the education of user participants. Moreover, these interactions imply discussions between

actors with different norm systems or underlying assumptions (Vos et al., 2004), and dealing with potentially inflated expectations and requirements about new technologies (Gilbert et al., 2000). Furthermore, the current structural and institutional settings, such as protocols and regulatory frameworks that govern clinical trials, are complicating proper public involvement in health care decisions (Tait, 2007). Moreover, it is claimed that more participation is not always better. It would not always make sense to include the public in basic scientific disputes: the legitimacy of expertise in these issues needs to be recognised (Collins and Evans, 2002). Lastly, as was mentioned in the introductory chapter, some scholars were rather suspicious about the role pharmaceutical companies might play through involved and organised users.

These objections are balanced with the five reasons to involve users in pharmaceutical innovation processes as introduced in Chapter 2. These reasons are applied to structure the answer to this research sub-question.

1. *Overcoming market failure:* intermediary user organisations articulated demands concerning research and development stimulation for orphan drugs in general (WGM), and drugs for neuromuscular diseases in particular (VSN), in order to cover ground that is not claimed by other actors, such as the government and industry.
2. *Employing knowledge of the users and their creative potential:* the VSN tried to gain access to the agenda-setting of scientific research by creating and maintaining international networks of researchers and organising workshops. Moreover, in the development phases of drugs the VSN articulated their choice for a specific manufacturing procedure during the development of an enzyme replacement therapy for Pompe disease by Pharming and Genzyme. The impact hereof, however, was small. The other cases did not show an impact on agenda-setting of drug research and development. However, intermediaries do utilise users' knowledge to put issues on the health care and drug policy agenda.
3. *Enhance effectiveness (and speed) of the innovation process:* all three organisations under study provided boundary conditions that contributed to the effectiveness of innovation processes. Some of their efforts focused on creating awareness and communicating information about new technologies. They also included assisting with and initiating clinical trials, the management of expectations, supporting companies in their claims to regulatory agencies (VSN), and creating research projects (VSN and WGM). Moreover, the intermediaries also organised conditions relevant to the marketing phase after regulatory approval, e.g. on the subject of reimbursement (WGM and BVN). Quick market introduction is also valued by the intermediaries themselves; if choices between alternatives had to be made, the intermediary would often express their preference for the most expeditious solution (VSN).
4. *Ethical and social debates in society:* this is achieved by addressing contested issues around a technology and in this way making sure that the interests of users of pharmaceutical products have an impact. Both the range of disputed topics and the opinions voiced in the health care innovation arena are broadened and enriched by the interference of intermediary user groups. One example from the VSN case referred to the debate on animal biotechnology, using transgenic animals to manufacture pharmaceuticals. Apart from the interests of animal rights groups also those of patients were taken into account during the debate.
5. *Increase democratic value of the innovation process:* the VSN and BVN patient groups actively tried to involve patients in their activities and organisations. Legally these

associations are governed by their members, but in practice only some of them, the 'patient champions', penetrate decision-making of the organisations.

Following the abovementioned drawbacks of user involvement and confronting them with the five positive impacts found in the case studies, the intermediary user organisations' influence on the course of corporate strategy varies. On the one hand, intermediaries failed to be involved in the agenda-setting of drug development of pharmaceutical companies. This might be because of the size of these companies, their international focus, and the fact that the Netherlands does not accommodate many large pharmaceutical companies. Also, the intermediaries might not be empowered enough to be taken seriously.

On the other hand, a wide variety of small Dutch biotechnology companies showed a lower threshold for contact. The VSN case featured Pharming, and in the case of the BVN a small DNA micro array company, Agendia, should be mentioned. These companies were eager to interact with the patient groups and exchange information. Moreover, they were open to deliberation on conditions, such as inclusion in clinical trials, and on ethical issues. The results from the three case studies reveal that intermediary user organisations influenced the innovation process in several ways following the five reasons to involve users mentioned above. Intermediaries have a notable impact on the effectiveness of the innovation process, following several efforts to enhance and alter the innovation processes, and are often involved by the government in issues to overcome market failure. They also broaden and enrich societal and ethical debates.

The second part of this research sub-question concerns the influence of technological developments on intermediary user organisations. This impact can be regarded as considerable. Emerging technologies create significant promises for patients, which not only have the potential to change their lives, but also pose great expectations for the progress of drug development. Intermediaries are influenced as well. In some instances because of the characteristics of the technology, e.g. the growing importance of diagnostics in pharmacogenomics might prompt changes in who to include in interactions, but in other cases because they need to introduce new ways of coping with contested issues. The demand articulation mechanisms are good examples of this, such as the development of management of expectations after claims about novel therapies. It might even be the case that the patient organisations landscape becomes more scattered because of the influence of pharmacogenomics and the related hypothesised stratification of patient populations. This might lead to a decrease in resources and attention for every single organisation. Nevertheless, rare disease patient organisations already deal with small patient groups, and most of the time they are regarded as highly empowered[60].

All in all, access to and the impact of patients on intermediary user organisations is fairly good, certainly for patients that are highly empowered (in terms of capabilities, opportunities, interests and in some cases pure stamina) to join the committees and boards of these organisations. In turn, these intermediaries influence technological development by ensuring boundary conditions that facilitate innovation processes, by articulating their

60 This is partially explained by the inherent drive these patients have ("if they don't do it, nobody else will") and because sometimes a group of related, smaller diseases are organised in one association, e.g. the VSN.

demand, and by broadening and enriching debates on contested drug-related issues. Technological developments also have an impact on users' lives and the way intermediary user organisations deal with these new innovations, e.g. by adjusting their objectives, ultimate preferences, and positioning (second-order learning).

3b. What lessons can intermediary user organisations learn from the analysis of demand articulation processes and to what extent are the 'demand articulation mechanisms' and 'interfaces' (strategies and organisation) of use for these intermediaries?

Intermediary user organisations are defined in this thesis as 'stakeholders that facilitate interaction between users and one or more other actors'. Here five insights of demand articulation in intermediary user organisations are drawn from our analysis. These aspects are based on the theoretical analysis in Chapter 2 and supported by the empirical findings of the cases.

1) Intermediary organisations have changed their tasks from transferring knowledge to also adding value to knowledge, and instigating efforts to influence the innovation process.
This claim is substantiated by literature on intermediary organisations, explorative interviews with the representatives of several stakeholders in the Dutch health care innovation arena, and reviewing policy documents about patient advocacy organisations. These combined sources indicate a shift in emphasis from mutual help groups and communication to representation of interests.

Nevertheless, only one of our case studies, the BVN, showed this shift, whereas the others had already taken the representation of stakeholder interests on board from the start. The BVN started out as an organisation of decentralised mutual help groups that later joined forces and included the provision of information in their tasks. At the start of the 2000s, the BVN consciously professionalised and transformed their activities to include advocacy efforts. This broadening of objectives largely followed pressure exerted by Dutch politics and government. The WGM was founded after this pressure had started and therefore the organisation immediately included advocacy in their objectives. The VSN had already stimulated research pertaining to neuromuscular diseases from its initiation onwards. It could be argued that advocacy efforts towards actors other than scientists and companies only started properly later on.
2) Intermediary organisations have no well-defined roles and therefore need to carefully position themselves within multi-actor innovation arenas.
The BVN presents an example of this unclear-defined positioning, which dominated several periods of the reimbursement event theme. The BVN, together with medical professional groups, strived to gain access to the policy arena. They effectively adopted a strategy of direct deliberation and seeking media attention. The Ministry of Health, amongst others, did not appreciate this approach. On the one hand their condemning of this approach as 'furtive' is understandable because they thought direct deliberation would suffice and seeking media attention reeked of blackmail. On the other hand it does comply with the idea of patients and patient groups being full members of the health care policy arena: in policy documents they have been called the 'third party' (in addition to health care suppliers and insurance companies). This difference in positioning of the BVN was the source of friction in the policy debate. Some actors positioned the BVN as an activist group that primarily takes care of patients' interests. This was at odds with the position the BVN would have liked to have

taken, i.e. to maintain a certain degree of impartiality. One could say that the BVN struggled with its neutrality. Although the BVN might represent certain actors, and therefore are 'on their side', it must remain a trusted and credible partner for the external actors and constantly needs to make its internal goals and criteria explicit. A certain level of neutrality is essential to play such a role effectively.

When comparing the BVN with the WGM, we see that the latter organisation deliberately emphasised its neutrality. The WGM is a committee consisting of people that represent a heterogeneous range of organisations. Therefore, its demands should be more balanced than those of (single topic) activist groups. It took the WGM some time to arrive at this point after deliberate second-order learning. This type of learning may reflect the stage of development ('maturity') of an intermediary user organisation.

The VSN often took an activist position as well, but in contrast to the BVN, the organisation did not have to enforce access to debates. When the VSN sided against the animal rights groups in discussions about transgenic animals, the organisation articulated their demands, taking into account their position as a patient representative. While the other parties disagreed with the VSN's demands, they still acknowledged its position. The position of the VSN was not neutral but at the same time clear.

In conclusion, intermediary user organisations are by definition in interaction with a heterogeneous array of actors. In this context, intermediaries might articulate demands that are disagreeable to some of them. Other actors in the health care policy arena expect intermediary organisations to maintain a certain degree of impartiality: although they might represent certain actors and therefore side with them, they need to remain a trusted and credible partner for the external actors and constantly need to explicate their internal goals and criteria (self-positioning). If they fail to overcome this "neutrality paradox" (Klerkx, 2007), other actors will be less favourable to see them as a trusted and capable interaction partner (Burt, 1992; Fernandez and Gould, 1994). At the same time, other actors should not change their positioning towards an actor because of opportunistic, strategic reasons. For example, on one occasion acknowledging the importance of intermediary user organisations and on other occasions denouncing them. Apart from aiming for neutrality and transparency, another way to increase acceptability of their positioning is by broadening the number and diversity of actors with which they interact. For example, balanced, transparent interaction and financing from a diversified group of pharmaceutical companies might alleviate the abovementioned problems (or doubts) surrounding a pharmaceutical company's influence on patient advocacy groups.

3) Intermediary user organisations are one of the most prominent actors in the health care (innovation) arena.

Firstly, the explorative interviews conducted as a preamble to this study showed that intermediary user organisations played a prominent role in interactions in the health care innovation arena. The findings of the three case studies are in line with this assumption. The intermediary user organisations studied had in some instances a large impact on the debates. Apart from these organisations, other intermediaries representing users of drug innovations also played a role. Examples include medical professional groups, representatives of insurance companies and hospitals, and international patient groups.

Secondly, the representation of users by intermediary organisations poses questions about the validity of the demands that intermediaries articulate: do they really represent the demands of their members? There is evidence from other cases (Parthasarathy, 2003) that a wedge is driven between the interests of represented actors, e.g. patients, and those of an

intermediary, e.g. patient group. This split is partly due to the patients' or organisations' difficulties in communicating or extracting demands, and partly by the fact that the patients form a heterogeneous group. This became evident in the TCH346-event theme in which the VSN regarded itself as the guider of the interests of neuromuscular disease patients in general, whereas the position of the VSN did not exactly match the specific interests of individual patients.

A large variety of interface strategies vis-à-vis the represented actors were pursued (see research sub-question 2b), ranging from active to passive involvement of represented users, and from short-term to longer-term focus. We roughly discern three inroads that intermediaries use as a way to solve this 'representation problem'. These include: 1) representation of others' interests without interacting with them, 2) direct user representation through 'patient champions' or the 'silent majority' speaking out, for instance at committee meetings, conferences or via telephone services, and 3) attempts to hear a wide range of users. The best way to solve the representation challenge is to combine these three solutions, and in doing so make sure that the access, empowerment and impact of the end-users is optimal. This means that intermediaries should abandon forming ideas about what their members want based solely on images or examples they have encountered. For example, they should consult a broader range and higher number of members, e.g. by using questionnaires and deliberations, although such solutions often call for more resources and professionalism.

4) Intermediary user organisations can learn from the demand articulation mechanisms that were found.

Classifying the mechanisms with which first-order learning processes[61] proceed inside intermediary user organisations revealed that some of these mechanisms are more dominant than others. This might create awareness within these intermediaries of what their prominent activities are or could be. By further reflecting on these mechanisms, intermediaries can become aware of how they function and what lessons they can learn. We do this for the four demand articulation mechanisms that were found in most event themes.

- *'Management of expectations':* emerging technologies induce enthusiasm, promises and expectations. As we encountered in the case studies, such as the study on stem cell therapy, expectations and promises can be 'performative' when they turn into requirements and in this way result in a self-fulfilling prophecy (Van Lente, 1993; Borup et al., 2006). Patients with no hope of recovery intensify this prophecy in their despair. Patient advocacy groups and other intermediary user organisations are aware of the risks of being ahead of the pack: their respectability is at stake and it might jeopardise scientific developments because too much resistance is created. They need to determine whether a technology is intrinsically novel and emergent or merely advertised as such as part of rhetoric efforts (Brown and Webster, 2004). On the other hand, constantly downplaying new developments might result in less (financial or scientific) attention. Therefore, these organisations aim to strike a balance and do this by aligning with scientific advisors or internalising the ability to assess scientific knowledge (empowerment). Hereto they continuously keep track of

61 First-order learning concerns the development of demands as a result of a loop that includes agenda-setting, synthesis, expression and evaluation. Different filling-out of these loops are characterised as demand articulation mechanisms.

scientific developments, annotate them, try to clarify them, and report on them using disclaimers. They always leave the choice to the patients, and if patients, despite the warnings, want to adopt a new therapy, they encourage measurement of safety and efficacy data. In this mechanism, visions about emerging technologies are created and maintained. Therefore, intermediaries can be loci for the development of future-oriented visions about technologies.

- *'Network building':* this mechanism revolves around the fact that in some cases intermediaries do not have the capabilities to tackle a problem or pursue an opportunity. In other instances these intermediaries have an overview of the field and the problem at hand, and envisage that some actors need to be brought together in order to work on the problem. This mechanism largely concerns aligning other actors to achieve some short-term or longer-term solutions. Implementing this mechanism not only requires these intermediaries to have an abstract idea of which route to take and which topic to handle, but also calls for excellent contacts and interaction skills.
- *'Active case building':* intermediaries start to build a case on a certain topic because they themselves put an issue on the agenda, e.g. taking up the aspect of inequality in Herceptin prescription. Case building requires a thorough preparation or synthesis of demands that includes in some cases even producing full-blown consultations, reports and figures. This usually involves cooperation with other actors. On the one hand, case building results into demands that are not easy to dismiss, but on the other hand it requires a lot of resources (knowledge, professionalism) that secure empowerment to produce these results.
- *'Knee-jerk reaction':* the mechanism in which represented actors anxiously call for quick action and the intermediary user organisation responds to that call. The impact of these quick actions is mostly large, depending on the intermediary's ability to react to the agenda-setting in a quick way, and whether it concerns topics that attract media attention. The downside is that there is little time to prepare a proper demand statement or align with the organisation's underlying assumptions. In most instances this did not appear to be a problem because the organisation could have prepared itself in the context of other activities and had already developed their underlying assumptions in such a way that they were not faced with huge problems in expressing their demands quickly.

In general, most demand articulation mechanisms are based on reactive as opposed to proactive agenda-setting. It could be that the full potential of the intermediaries' creativity could not be realised and, because the intermediaries are too late in reacting, they have trouble in accessing or impacting debates. However, it might also be the case that intermediaries themselves lack the ability or creativity to proactively take up certain issues.

Nevertheless, these demand articulation mechanisms illustrate how intermediaries articulate their demands in specific situations and can be applied to more intermediary user organisations in order to describe or prescribe how first-order learning is or should be organised. The next point discusses strategies that the intermediaries can employ in interaction with others.

5) Intermediary user organisations can learn from the interface strategies that were found in this study.

The strategies applied in interaction with other relevant actors (actors B[62]) with the most impact are based on close alignment between the intermediary and these other actors. The three cases illustrate this by stressing the prominence of coalitions. By this, alliances are meant between the intermediary user organisation and, for example, a university department (as in VSN case) or medical professional groups (as in the BVN case). These partnerships gain from the strong linkage between medical and scientific expertise and the actors who are thought to have the strongest and purest of interests: the patients themselves. These coalitions were characterised as 'undeniable' and 'natural alliances' by both insiders and outsiders. The impact of these alliances can even increase when they address issues with high media impact, such as topics that imply inequality or dishonesty. In other instances, intermediaries had less impact because they were unable to form coalitions or attract media attention.

Making an impact is not the only hurdle intermediaries should overcome. Major difficulties are also in place regarding access and empowerment. Intermediary user organisations often need to fight for access. This is mostly the problem when an issue is proactively put on the agenda and requires a significant increase in synthesis activity, e.g. in the form of producing solid analytical foundations.

Especially for the uncertain and controversial aspects of emerging technologies, like the orphan drugs future or ethical aspects of stem cell therapy, it would be useful to take a longer-term perspective and provide room for discussion with other stakeholders in a proactive way, without necessarily having a predefined agenda or specific problems. In this way, visions of and ideas about the future can be exchanged and discussed. This might even lead to learning on first-order and second-order elements, and the creation of a shared vision. Strategic intelligence methods, such as (constructive) technology assessment, are helpful in this regard (Roelofsen et al., 2008; Van Merkerk and Smits, 2008). These exercises require a certain degree of resources, long-term commitment and professionalism.

3c. What role can the government play in order to improve the conditions under which intermediary user organisations function in the context of user-producer interactions?

As was discussed in the first chapter of this thesis, the pharmaceutical and health care innovation arenas struggle with the adoption and implementation of drug innovations in society. Problems like access to (new) medicines will probably become the major challenges in these sectors in the future. Moreover, governments seek to organise their national innovation systems in such a way that they support innovation and can drive economic growth. The government is legitimised to take on such issues concerning societal interests. Furthermore, in some cases – such as rare diseases – there is a question of market failure, and the government is the only party to take on the problem (or become the problem owner).

Governments themselves sometimes become not only the problem owner but also a party with certain interests. In the health care sector they also need to maintain certain

62 Under point 3) above we already discussed the interface strategies pertaining to the represented actors (A).

guarantees for safe and efficacious medicines. At the same time, pharmaceutical companies try to earn money and strive after standards and norms that create a stable environment. In this battle or fog of conflicting values and interests, intermediary user organisations can prove to be beneficial (not only by transferring but also by adding value to knowledge) and to some extent independent or neutral (patient care is undisputed). Moreover, their contribution – both in relation to the content of their demands and their enthusiasm or resistance – might be essential to broaden and enrich debates about new technologies. Intermediaries should be invited to independently counterbalance actors who tend to dominate the innovation arena by articulating an alternative voice.

Therefore, governments should provide financial support these intermediary user organisations because other origins of resources would make these organisations vulnerable. Moreover, the government should also give them enough room to manoeuvre. Although it sometimes acted otherwise (see the BVN case), the Dutch government had intended to do both for several years already, billing patient groups the 'third party' in health care policy.

3d. What lessons can other stakeholders, such as the pharmaceutical industry and actors in other countries, learn from the analysis of demand articulation processes?

The five reasons to involve intermediary user organisations in innovation processes (see research sub-question 3a above) make it clear how these organisations can be beneficial to the pharmaceutical industry as well. Examples include contributing with their specific creative potential and enhancing the effectiveness of the innovation process.

Therefore, it would be in the interests of the industry to support intermediary user organisations that lack resources. At the same time, in aiding intermediaries the pharmaceutical companies should avoid investing one-sidedly or opportunistically, i.e. by only financing those groups that work on reimbursement for a company's specific drug. This stifles the freedom of action, and therefore the beneficial creativity of these intermediaries to put topics on the agenda proactively. It might also hint at direct-to-consumer marketing, which is illegal in the European Union.

Accordingly, others can position both pharmaceutical companies and intermediaries as biased. The intermediary's neutrality would be in dispute, which might render its demands meaningless and powerless. It is recommended to maintain both transparency and distance between decision-making, and/or even encourage the financing of one intermediary by more than one company through a portfolio of industry support.

The case study selection was discussed in the methodology chapter, which resulted in focusing on three Dutch intermediary user organisations. The context and functioning of intermediaries in other countries was also discussed. We believe that the developed conceptual framework is also helpful in the context of other countries, because this model contains concepts that are rather country a-specific, such as first-order and second-order learning and the linkages between these learning loops. Nevertheless, the filling-in of the demand articulation mechanisms and interface strategies might vary because of differences in, for example, political arenas, constitutional openness of the system, levels of democracy and levels of knowledge, cultural differences, and resources. For instance, African NGOs might have difficulties in accessing the decision-making of large pharmaceutical companies and charity funds, and might also lack the level of knowledge needed to approach drug innovation processes.

To conclude, intermediary user organisations are engaged in influencing the boundary conditions of innovation processes, and the broadening and enriching of debates. Sometimes their activities may even result in influencing, for example, R&D agenda-setting. For them to play their role in an effective way input would be required from government and industry, and the efforts of the intermediaries themselves, as we have illustrated in this section.

9.2 Reflection on case selection and methodology

The objective of the case selection was to include intermediary user organisations that varied on two characteristics, namely the stage of the innovation process they focus on and the type of intermediary. The first characteristic resulted in a rich and varied picture of user involvement through intermediaries. The significance of also including later-stage event themes in studying emerging technologies was discussed at the start of this chapter. Moreover, concerning the type of intermediary user organisations, we chose to focus on those that are part of the same social world as the users (see 2.2.4)[63], which is sensible in the context of studying user-producer interactions in the health care innovation arena (see 2.2.1). The intermediaries that were studied included one of a coordinating type, mostly focusing on all phases of the innovation process, and two of the representative types, focusing on the R&D and marketing phase respectively.

After discussing the case selection, we then turn to the analysis of the cases. The event history analysis was used as a starting point because of its emphasis on the process character of demand articulation. Especially the methodology proves useful to unravel and sharpen the dynamics of demand articulation inside intermediaries in the emerging phase of a technology, and reveals how these learning processes take place on the first-order and second-order level (see Table 35 and Table 36 in Chapter 8). Also the descriptive parts, the narratives, are based on the structured and balanced way of recording the event themes and the related processes as they developed.

The major downside of the presented methodology is the huge investment in terms of research resources: the archival work, conducting interviews and maintaining the database (including coding) is time consuming. Future research could be directed at setting up a quick scan of dynamics, i.e. an event history analysis that maintains scientific rigour but at the same time requires fewer resources. For example, this could be achieved by performing data collection, selection and analysis in constant interaction with key informants of the event theme or the intermediary. This could accelerate the data selection and assessment parts.

More detailed issues concerning the case selection procedure and methodology are discussed below, following the steps as described in Chapter 4.

1. *Selection of intermediaries*: the geographical delineation of the selection was discussed in the previous section. Concerning the time delineation we chose to study the

63 Following the typology of Fernandez and Gould (1994) this came down to selecting representative and coordinating intermediary organisations. We did not perform an elaborate comparison between these two types because that was not the objective of our studies. Still, this might again be an interesting point for further research.

emergence of a technology following events in the recent past instead of in real-time. The recent past was chosen because it allowed the events and demands to be brought into perspective, more data becomes available, the dynamics are richer, and unexpected sources of events and demands could be taken into account.

2. *Quick scan for event theme topics*: for each organisation we scanned the events they were involved in over the time period under study. Using a mixed set of sources and selection criteria we selected which event themes would be studied for all intermediaries. These selection criteria included the degree of relevancy concerning user involvement and emerging technologies. Regarding the latter, some technologies were archetypical examples of pharmacogenomics (Herceptin) or were related to pharmacogenomics (such as gene therapy, stem cell therapy and exon-skipping in the VSN case) because of their emergent character. Moreover, following the metaphor analysis performed in section 3.4, orphan drugs can be seen as a predecessor or analogy-to-some-extent for the pharmacogenomics future. At least this analysis illustrated that the comparison holds true for certain aspects of drug innovation processes, such as reimbursement and the economic impacts for the health care system. For example, in the event themes covering reimbursement of orphan drugs (WGM and VSN) several aspects, such as small patient populations and the centralisation of expertise, seem to indicate that this comparison with pharmacogenomics is valid. The metaphor analysis showed only a partial, mixed level of agreement between pharmacogenomics and orphan drugs on other aspects of drug innovation, such as the stimulation of orphan drug basic research and clinical trials. This means that the conclusions on some event themes (of the WGM and VSN cases) might only be applicable to fields that are 'orphanised' along the lines of what would be expected of the pharmacogenomics future.
3. *Collecting raw data inside intermediaries*: we made sure that the data collection was conducted in a valid way through triangulation of sources and data collection methods.
4. *Collecting raw data from the 'interacting partners'*: selecting the 'interacting partners' was done by assessing their importance in documents and by interviewing people from the intermediary organisation. A representative range of actors was involved in nearly all cases because a review of the archival documents and asking interviewees for suggestions for important actors yielded the same suggestions. Nevertheless, it was inevitable that not all actors were scrutinised as thoroughly as, for example, the intermediary or some important other actors (such as the proclaimed 'problem owner'). This was partly due to the lack of access to archival data, and also because of limitations regarding the method of interviewing. Interviewees might have had biased views on the past or were reluctant to admit unfavourable opinions on past behaviour. One solution is to discuss these issues in a more interactive way and in a multi-actor setting, for example in the context of focus groups. Focus groups can also be used to tackle the problem of 'not-articulating articulations': demands that are deliberately not mentioned by actors.
5. *Enter raw data into a database in the form of incidents*. The most problematic issue here was the precise definition of discrete database entries. An archival document contains several demand statements that could be entered in the database as separate or as one datum. This influences the significance of the report when measuring the number of demand statements over time. Through the standardisation of the data entrance, based on inclusion criteria, such as including one message per datum, this was taken into account. This does not prevent some entries from being more important than

others. However, the importance of entries was not measured separately. This could be a subject for further research, although this exercise might call for more triangulation of sources and materials.

6. *Identifying events from incidents*: the events were identified through coding using precisely defined indicators. Two raters participated in the coding of events, compared their codes, and iteratively changed these codings or the definition of the indicators. The interrater reliability increased in all cases to above the acceptable percentage of 80% (Poole et al., 2000). It would have been better to include more coders in these exercises but resources were insufficient to carry out this laborious task.
7. *Analysis*: the analytical part involved a large number of descriptive steps, which were mainly built upon the narratives of the event themes and the aforementioned coding exercises. Other steps concerned systematically framing the processes in the perspective of certain concepts, such as learning and shifts in joint construction. Both research question 1 and 2 resulted in statements on the appropriateness of the central conceptual framework, as well as constructing demand articulation mechanisms and interface strategies. The external validity of these outcomes is difficult to assess because they are based on the findings of three case studies. Nevertheless, as was proposed in the methodology chapter it should be possible to replicate the results in order to support theory. The next section provides some general conclusions about the theoretical replication of the presented theory.
8. *Triangulation of results*: the results were checked by confronting the intermediary representatives, and in some cases also people from outside these organisations, with the resulting narratives and other results. In general, this yielded suggestions for improving the results and favourable comments about the usefulness of these results for their own organisation.

All in all, this methodology provides intermediary user organisations involved in innovation processes with insights and ideas to play a more effective role in this process. For example, the intermediary can increase the understanding of their demand articulation efforts by structurally recounting the narrative of an event theme, the related learning processes, and the positions of all the actors involved. Uncovering other actors' underlying assumptions, using illustrations like Figure 56 in Chapter 8, could be beneficial in preparing for policy debates.

9.3 Concluding remarks

Scientific and societal relevance

This thesis contributed to the science, technology and innovation literature about user involvement in several ways. First, it sheds light on user-producer interactions in health care arenas dealing with emerging technologies. Our case study findings substantiated the central conceptual model that was explicated in Chapter 2. In this way, the thesis contributes to a better understanding of demand articulation dynamics, regarded as learning processes, both inside intermediaries and in interaction with other actors in the health care arena. Moreover, we have provided insights into intermediary organisations as important actors that facilitate interactions between users and other actors in innovation arenas.

Second, the contributions of the methodology used were discussed in the previous section and can be summarised as providing a way to study demand articulation *as a process* in a systematic way following several important concepts related to demand articulation over time.

In terms of societal relevance, the increased understanding of demand articulation processes, together with the related proposed demand articulation mechanisms and interface strategies, might give pointers as to how to organise these learning processes. Moreover, the methodology used, with its systematic following of events and statements over time, and by this uncovering of demand articulation processes, might be a useful tool to provide insights into the functioning of intermediary user organisations. It also can work as a consciousness-raising exercise in anticipation of the actions and motives of other actors. It could ease discussions about the positioning of these intermediary user organisations and related discussions about their reliability and neutrality. Also other actors might benefit from these insights and methodology for the same reasons. By improving the understanding of demand articulation processes inside intermediary user organisations and in health care innovation arenas, this thesis also contributes to dealing with the challenges as sketched in the introductory chapter. Demand articulation processes in intermediary user organisations can increase the efficacy of the pharmaceutical innovation processes and can benefit the debates concerned with the adoption and implementation of new drugs.

Suggestions for further research

Based on these conclusions and the relevance of the study, we suggest some lines for future research:

- Future research can follow the suggestion that intermediary user organisations should be *more proactive and anticipatory*, e.g. by pursuing action-oriented research approaches. This means that methodological tools, such as focus groups and policy laboratory or group decision room sessions[64] are used to actively create awareness amongst people working inside and with these organisations on how to deal with emerging pharmaceutical technologies.
- More work could be done on investigating the approach used by intermediary user organisations in the light of their *heterogeneity*. Their underlying assumptions (norms, strategies and objectives) are largely dependent on the diseases they are dealing with. Influencing debates and innovation processes concerning common versus rare, or lifestyle versus chronic diseases result in differences in organising demand articulation processes in these organisations.
- As was pointed out above, intermediary user organisations could benefit from a *quick scan* of their demand articulation processes. It should be investigated in what ways the presented methodology could be adopted in order to include such a quick scan.
- Regarding the demand articulation processes, more attention could be paid to measuring the *impacts of interface strategies*. This might help the intermediary organisations in benchmarking their activities by comparing impacts with those of other (demand articulation) activities.
- The issue of *representation* could be taken up by delving deeper into developing methods to measure the demands of the represented actors. Especially uncovering

64 These are expert or evaluation meetings during which individual brainstorming is combined with group discussion and prioritising. All these exercises can be done using computers.

latent demands of these represented actors is significant in the context of emerging technologies.
- Lastly, it would be interesting to focus more on how intermediary user organisations can be engaged in the *agenda-setting of drug R&D* in pharmaceutical companies or public science programmes.

Answering the central research question

We now return to the central research question, i.e. how to understand the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies? The answer to this question is treated in the form of three major conclusions:

1) User involvement is important

The three cases illustrate that intermediary user organisations influence drug innovation processes and that other actors regard their input as valuable. Moreover, the findings evince that this influence is growing. Based on our case studies it can be shown that intermediary user organisations are primarily engaged in influencing the boundary conditions of innovation processes, e.g. in helping to organise clinical trials, creating awareness and communicating information about new technologies (management of expectations), supporting companies in their claims to regulatory and reimbursement agencies, and creating research projects. The intermediary user organisations contribute to these specific issues because they increase the speed and efficiency of the innovation processes, and express demands that would probably have been overlooked by other actors. These organisations did not influence the direction of R&D or the innovation agenda of companies or governments. This is substantiated by the findings of other scholars (Bal and Van de Lindeloof, 2005).

Furthermore, debates in the health care innovation arena in general benefit from the involvement of intermediaries. By articulating their demands and bringing in particular – sometimes idiosyncratic – insights, intermediaries broaden and enrich these debates. This might even take an unexpected form when cancer patient organisations take the initiative to talk about priorities for the reimbursement of therapies from collective resources, which is an issue other actors have not dared to touch. Intermediaries also help to legitimise eventual divergent movements in the debates.

Therefore, users – and in particular intermediary user organisations – influence and are relevant to drug innovation processes and policy. This holds for the context of emerging technologies in the health care and pharmaceutical sectors. Furthermore, as was concluded in Chapter 8, it is dependent on the willingness of at least a few other actors who play a dominant role in policy and management to acknowledge or reinforce the position of users (also depending on access to these actors); and on the resources and level of professionalism of the intermediary. The nature of the influence also depends on the development stage of the technology: in early stages the involvement is mostly about creating the right boundary conditions and visions, whereas later on this involvement extends to influencing the course of technology development and implementation.

2) Demand articulation processes play a large role

In user involvement in the context of emerging technologies demand articulation processes take centre stage. This thesis introduced a central conceptual model that hypothesised how this demand articulation is taking place. Chapter 8 illustrates that the outcomes of

the three case studies support the central conceptual framework. Inside intermediary user organisations both demands (first-order learning) and underlying assumptions (second-order learning) are developed by both sharpening and broadening out their demands and assumptions. These first-order and second-order learning loops are interlinked.

The intermediary user organisations ran through the first-order learning loops in several characteristic ways, in what we call demand articulation mechanisms. In other words, the intermediary user organisations organised their activities related to emerging technologies according to these mechanisms. Prominent examples include 'management of expectations', 'network building', 'active case building', and the 'knee-jerk reaction' (see section 9.1). The second-order learning loop refers to the confrontation between the underlying assumptions of an intermediary (self-position) with those that other actors assign to the intermediary (other-position). This loop reveals the positioning of the intermediary user organisation, which influences the effectiveness of their advocacy efforts.

The intermediary interacted with both the users they represent and other relevant parties. Actors develop demands and underlying assumptions in both a diverging and converging way compared to others, leading to demand articulation. This articulation occurs within innovation arenas in which intermediaries act. Converging movements cause the forging of linkages and even coalitions between actors, eventually followed by demand articulation on the arena level, such as was the case at the end of the WGM reimbursement debate.

The question remains whether the conceptual model is also applicable to sectors, technologies and arenas outside the health care and pharmaceutical innovation system. In other words, under which delineating conditions would the model be applicable? Apart from the fact that the content of the policy and management issues involved, and the related filling-in of the demand articulation mechanisms and interface strategies, is different for every case, we think that the model itself is rather robust. The concepts presented in the model, such as the first-order and second-order learning loops, are quite general and applicable to demand articulation processes in all sectors and technologies. Also for more incumbent technologies the model could be useful, although the development of and reflection on demands and underlying assumptions should be present in these technologies as well, in order for the model to provide insights into learning dynamics. The same applies to studying demand articulation in interaction with other relevant actors, although the analysis would become more interesting if converging and diverging dynamics are present. The assumption of this model being applicable to other technologies and sectors also depends on whether the political system can be characterised as democratic and is based on (consensual) deliberation, and that the issues engage the public and the media.

3) Intermediary user organisations are loci of demand articulation

This thesis opens the black box of intermediary user organisations engaged in demand articulation processes in the context of emerging technologies. Following the answers to research sub-question 3a, these organisations are involved in:

- Overcoming market failures: articulating demands that other actors do not take charge of.
- Developing and disseminating their creative potential: setting up scientific networks, and constructing visions of the future.
- Making innovation processes more effective: management of expectations, assistance with clinical trials, reimbursement and regulation.
- Addressing ethical and societal issues.

- Ensuring the democratic value of their demands, thereby representing the users properly.

The intermediary user organisations employ different types of interface strategies to follow these lines of involvement, related to access, empowerment and impact. In interaction with the represented actors, the intermediaries used interface strategies based on images of their interests ('representation of other's interests') and intensive interaction (e.g. 'creative consultation'), e.g. to ensure proper democratic value of their representation. When interacting with other relevant parties, the intermediaries used strategies such as aligning with allies and producing information that spurs coverage by the media and others, e.g. by addressing ethical and societal values ('forceful advocacy').

Furthermore, the five activity categories described above also point out the areas in which intermediary user organisations are currently underrepresented. These organisations might want to focus on these lacunae in order to increase their influence on drug innovation processes. Examples of these lacunae include: not being involved in agenda-setting and steering of (private and to a lesser extent public) drug research and development, and setting up future-oriented technology analyses to improve the articulation of visions of emerging technology futures.

These conclusions are applicable to intermediary user organisations in health care innovation arenas. Nevertheless, the tenability of the conclusions depends on the objectives and aspirations of these organisations, the resources they have at their disposal, and their age or maturity. The latter is especially prominent because second-order learning in the studied intermediaries illustrates that strategies and ways to do things always need to be developed in line with the organisation's objectives and aspirations.

Following this second-order learning and road to maturity, intermediary user organisations should take three dilemmas into account when striving after effective functioning in the innovation arena:

- Positioning: as was stated above, the second-order learning loop illustrates a confrontation between an intermediary's self-position and the position other actors assign to them. This confrontation reveals possible problems with the neutrality of intermediary user organisations. These problems were described above and, for example, included ambiguities about the role intermediaries should play and the degree to which they were taken seriously by others. The importance of proper positioning was substantiated by other authors as well (Hopkins and Nightingale, 2006; Klerkx, 2007). Intermediaries can alleviate this problem by being transparent about their interactions and by broadening the number and diversity of actors with which they interact. Especially in interactions with the pharmaceutical industry this is important. If intermediaries do not clearly position themselves, they will be seen as 'suspicious'. Moreover, blindly following pharmaceutical companies also decreases the creative potential of intermediaries, e.g. by avoiding non-pharmaceutical solutions. At the same time, this compels other parties to be consistent in their positioning of the intermediary organisation. It would be inappropriate to opportunistically change the opinion of another's position for strategic and short-term reasons. Nevertheless, it should be stressed that intermediaries could still choose as their strategy to be non-transparent, not-diversified in their interactions and strive after quick results through increased media coverage. The intermediaries should accept then, that this 'politics-based-on-incidents' leads others to position them as activists.

- Representation: for intermediaries it is essential to speak on behalf of their members and picture their demands in a representative way. Especially with emerging technologies, demands are not clear and for most users quite latent. The health care sector might appear a special case, because users have one homogeneous major need: they want to be healthy. But even here, there are various related needs involved, such as regarding safety, efficacy, and the organisational set-up of drug innovations. For example, in their hurry to gain access to new medicines, some patients are willing to use experimental drugs that are a long way off from being clinically tested. Therefore, it is not only problematic that represented actors do not have an idea of what their demands regarding emerging technologies look like, but they might also reveal contradictory demands. In the case studies we encountered several instances in which individual demands were strongly voiced but were in conflict with the general interest of the represented actors. We recommend the intermediaries to choose for the latter because this makes the organisations more credible as a representative actor. Moreover, when interacting with the represented actors, a mixture of interface strategies including both 'patient champions' and the 'silent majority', could serve as a starting point for achieving and enhancing the user representation by intermediary user organisations.
- The need to be proactive: reactive actions might call for less deployment of resources and may lead to quick success. Nevertheless, it is recommended to start as early as possible with proactively clarifying demands and underlying assumptions of the intermediary and those of other parties. In this way, intermediaries can better anticipate the course of the debate. Moreover, by creating a vision of future technologies in an early phase in a sense makes the intermediary empowered. The organisation claims the status of a locus of future-oriented technology analysis in the innovation arena and in this way is better able to steer the search for a shared vision on or demands for new technologies.

These three dilemmas show that intermediary user organisations play a precarious role in demand articulation in the context of emerging technologies. However, if these dilemmas can be overcome, these organisations will play a central and crucial role.

Closing

To conclude, this study claims that in the health care innovation arena user involvement leads to influencing drug innovation processes and policy debates. Demand articulation processes in organised users like intermediary user organisations can have beneficial effects on the two challenges that were mentioned in the introductory chapter – i.e. intermediaries can both influence the efficacy of the drug innovation processes, and broaden and enrich the debates on drug adoption and implementation. In this way, the health care innovation arena is made more robust and better equipped to meet future challenges, such as those related to emerging technologies, because it offers relevant actors in society better ways of coping with these challenges.

This thesis also contributes to the literature on user involvement in innovation studies. In the context of emerging technologies, this involvement is carried by demand articulation processes, which are learning processes about demands and underlying assumptions. The lessons that can be drawn from this study for user involvement literature in general are that

demand articulation processes are indeed influential, and that organised users, interacting with other actors in the innovation arena play an important role in these processes. Moreover, the concept of demand articulation itself is deepened and strengthened, linking it firmly with learning processes on several levels: inside the organisation in the form of learning loops and demand articulation mechanisms, and in interaction with other actors with interface strategies and as part of the joint construction of demands. Furthermore, the event history analysis method had been adjusted in such a way that the process character of demand articulation could be studied in full. By this a methodology is created that also in other technology fields may help to trace and study demand articulation processes.

Lastly, this thesis presents intermediary user organisations as having a precarious role, facing several dilemmas around positioning, representation and the need to be proactive. However, if these dilemmas are acknowledged and resolved, intermediary user organisations can be prominently and centrally engaged in demand articulation processes on behalf of users.

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Appendix A: key to abbreviations

Abbreviation	Long form
Actor A	Actor represented by the intermediary user organisation
Actor B	Other relevant actor that interacts with intermediary user organisation
AFM	Association Française contre les Myopathies (French Muscular Dystrophy Association)
ALS	Amyotrophic lateral sclerosis
AMDA	US Acid Maltase Deficiency Association
ASCO	American Society of Clinical Oncology
BioFarmind	Dutch Foundation of pharmaceutical biotechnology
BOM	Committee for the Assessment of Drugs used in Oncology
BVN	Dutch Breast Cancer Association
CBG	Dutch Medicines Evaluation Board
CCUV	Dutch patient organisation for Crohn's disease and Ulcerative Colitis
CG-Raad	Dutch Council for the Chronically ill and Disabled
CHMP	Committee for Human Medicinal Products Committee for Human Medicinal Products
CHO	Chinese hamster ovary
COMP	Committee for Orphan Medicinal Products
CTG	Health Care Tariffs Board
CVZ	Dutch Health Care Insurance Board
DMD	Duchenne muscular dystrophy
EAMDA	European Alliance of Neuromuscular Disorders Associations
EMEA	European Agency for the Evaluation of Medicinal Products
ENMC	European Neuromuscular Centre
EPPOSI	European Platform for Patients' Organisations, Science and Industry
ERA-Net	European Research Area Networks
Erasmus MC	Erasmus Medical Centre Rotterdam
ERT	Enzyme replacement therapy
EU	European Union
FA	Friedreich's Ataxia
FDA	US Food and Drug Administration
GAA	Acid alpha-glucosidase
HOVON	Dutch Haemato-oncology Association
IGZ	Inspection for Health Care
IPA	International Pompe Association
ISNO	Dutch Neuromuscular Research Support Centre
KWF	Dutch Cancer Society
LCBB	National Contact body on Mutual help groups Breast cancer (predecessor of the BVN)
LNV	Ministry of Agriculture
LUMC	Leiden University Medical Centre

Abbreviation	Long form
Nefarma	Dutch Association of innovative pharmaceutical companies
NFK	Dutch federation of cancer patient organisations
NHG	Dutch College of General Practitioners
NIV	Dutch Society of Internists
NPCF	Federation of Patients and Consumer Organisation in the Netherlands
NVMO	Netherlands Society for Medical Oncology
NVZ	Dutch Hospitals Association
OD	Orphan drugs
R&D	Research and development
RGO	Advisory Council on Health Research
rhGAA	Recombinant human acid alpha-glucosidase
RPB	Dutch rheumatic disease patient organisation
RVZ	Council for Public health and Health care
SMA Europe	European Spinal Muscular Atrophy Association
SONMZ	Dutch Foundation for Neuromuscular Research
STIGON	Dutch Stimulation programme for Innovative Pharmaceutical Research
TI Pharma	Top Institute Pharma
TREAT-NMD	TREAT Neuromuscular Network of Excellence
UPPMD	United Parent Project for Muscular Dystrophy
VIKC	Association of Integral Cancer Centres
VSN	Dutch Neuromuscular Diseases Association
VSOP	Dutch Genetic Alliance
VWS	Ministry of Health
WGM	Steering Committee on Orphan drugs
WHO	World Health Organisation
ZfR	Sick Fund Council (predecessor of CVZ)
ZN	Association of Dutch Health care Insurers
ZonMW	The Netherlands organisation for health research and development

Appendix B: references for the metaphor analysis

Pharmacogenomics references

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Appendix C: Event theme of the WGM concerning reimbursement of orphan drugs

Date	Event	Statement
20-9-2000	Health minister asks Health Care Insurance Board (CVZ) to look into reimbursement of orphan drugs	Rare diseases have small patient populations and therefore validation of efficacy and safety might be difficult.
15-2-2002	WGM reacts on concept version of CVZ report (letter)	The definitions and procedures have not been well defined yet: WGM fears bureaucracy and delays. WGM asks for direct stakeholders to be involved in the procedures. WGM calls for a European-wide reimbursement scheme.
28-2-2002	CVZ report	Reimbursement admission requirements for orphan drugs are the same as for non-orphan drugs, but allowances are made for the special characteristics of orphan drugs.
20-11-2002	WGM reacts on draft version of 2nd CVZ report (in an internal meeting)	The solution of paying intramural orphan drugs through the research budget of academic hospitals is seen as unwanted: soaring costs can lead to unwanted trade-offs between economic and health benefits. Transparency and continuous character of policy should be propagated, as well as advising role for various stakeholders in regulatory and reimbursement decisions. WGM advises to consult other parties as well (e.g. the academic hospital representative).
12-12-2002	WGM reacts on draft version of 2nd CVZ report based on the discussion in the internal meeting (letter)	Same as above.
30-1-2003	2nd CVZ report	Discusses necessity of pharmaco-economic studies for orphan drugs and details of reimbursement process of orphan drugs. CVZ recognises potential financial problems if rare diseases are treated in a few hospitals only and if these drugs are financed through their research budget. There should be a separate reimbursement rule for rare diseases that guides financing by national health reimbursement scheme instead of through academic hospital research budgets.
28-1-2004	Parliament discusses orphan drugs	MPs emphasise their preference for a separate reimbursement rule. The minister does not react, while the official response of the Ministry on the two CVZ reports is in preparation.
7-4-2004	Health minister reacts on CVZ reports	The minister's opinion in broad outlines corresponds with the proposed reimbursement strategy for orphan drugs. Notable difference: he refuses to deploy the separate rule and opts for finance through the more standardised codes and the research budgets of academic hospitals.

Date	Event	Statement
19-4-2004	WGM discussion meeting on minister's standpoint	Initially, other issues should have been discussed during the meeting, but just before the meeting it was decided to focus on the Health minister's reactions to the CVZ reports. It is discussed whether it would be useful to present a petition to parliament. WGM decides in favour of this.
8-6-2004	Petition	WGM supported by other organisations calls for a separate rule, more European collaboration on research, reimbursement and regulation, monitoring of benefits of orphan drugs, and more coordination of parties involved.
11-8-2004	Health minister reacts to petition (letter)	The minister rebounds a few points (monitoring and coordination can be a good task for WGM), dismisses the points on the separate rule, and indicates that European collaboration is organised through a special programme.
27-1-2005	Parliament discusses reimbursement orphan drugs	Again the separate rule and research budgets of hospitals are brought to the fore. The minister refuses to change his plans, but will investigate the matter in consultation with stakeholders.
4-4-2005	Consultation of WGM and other actors on reimbursement orphan drugs	WGM (and representatives of academic hospitals and insurance companies) are consulted. WGM and the academic hospital representatives perform additional investigations. It includes the notion that (bottom-up) centralisation of care for some rare diseases is taking place and that this can be beneficial to the quality of care (as appeared to be the case in the context of, for example, haemophilia and Gaucher's disease). In this context, the drawback of making use of the academic research budget is even more striking.
29-6-2005	Health minister reacts on parliamentary discussion based on consultation (letter)	The Health minister acknowledges the latter point, but more from an economic point-of-view and chooses for a separate reimbursement rule for orphan drugs.

Appendix D: Event theme of the WGM concerning R&D of orphan drugs

Date	Event	Statement
28-4-1997	Minister asks RGO for advice on orphan drugs	Coordination, prioritisation, stimulating research. Special attention to US Orphan Drug Act.
10-4-1998	RGO advice	National structure, European committee that prioritises orphan drugs (OD), financial stimulating measures
1999 and 2000	Preparation of national structure for orphan drugs (i.e. Steering Committee)	Coordinate and stimulate (infrastructure for) research, inventory of OD research, point of contact network, inventory is difficult, financial stimulation is necessary. The government does not support tax cuts for orphan drug R&D.
16-11-2001	Invitational conference	One of the six important objectives of WGM should be to pay attention to research and development of orphan drugs
24-11-2001	WGM subsidises projects	WGM decides to spend its total budget on its primary tasks. The remaining amount of money is then spent on projects that deepen patients' knowledge and stimulate scientific projects on orphan drug and rare disease research.
25-1-2002	Symposium	The results of the invitational conference and WGM's internal deliberation reinforce focus on stimulating orphan drug R&D.
11-11-2002	European programmes for 6th Framework	WGM participates in two initiatives (French and Italian) for the founding of Networks of Excellence for Orphan Drugs. These initiatives did not succeed.
14-11-2003	ZonMw and Ministry of Health give WGM money for projects on orphan drug R&D	Programme for the stimulation of innovative drug R&D in the Netherlands (STIGON) allocated some funds for stimulating orphan drug R&D. The health research-funding agency ZonMw and the Dutch Ministry of Health decide to fund two pilot projects set up by WGM. WGM chooses for a project on making an inventory of orphan drug R&D as a starting point for setting up a research subsidy programme, and a project that stimulates the development of orphan drugs proactively (an 'orphan drug developer'). Uncertainty on subsistance of WGM following the evaluation delays the start of these projects.
18-11-2004	WHO conference on 'Priority Medicines for Citizens of Europe and the world'	Objectives centre on the public prioritisation of drug research and development achievements. Orphan drugs become a cross-cutting theme. WGM contributes to the discussion by publishing a background paper.
22-11-2004	Evaluation of WGM	The gap between research and clinical application is one of the main problems with OD. WGM has emphasised the availability of OD, while R&D on these kinds of drugs is somewhat neglected. The Ministry of Health therefore indicates that WGM should pay more attention to this. This should lead to a subsidy programme for orphan drug research.
4-2-2005	WGM reacts on evaluation	WGM subscribes to the views as put forward in the evaluation report. It emphasises that stimulation and monitoring of R&D is important, while coordination is impossible.

Date	Event	Statement
1-12-2005	ZonMw and WGM co-apply for a part in an ERA-Net Project	The EU honours the ERA-Net Project on rare diseases (E-Rare). WGM is responsible for the work package on bridging fundamental and applied research.
23-2-2006	WGM deliberates with several boards of academic hospitals on a research programme for orphan drugs	Question marks are placed regarding national coordination of research, the viability of rare disease research, and the appropriateness of a research subsidy programme as the right innovation measure.

Summary

Demanding Dynamics
Demand articulation of intermediary organisations in emerging pharmaceutical innovations

The growing interest in the role of users in innovation processes is fuelled by a broad and diverse range of science, technology and innovation studies. Scholars in these fields claim that a better quality of interactions between users and producers enhances the innovation processes in which they are engaged. They might even lead to more successful innovations. This raises questions about what the role of different kinds of users might be and how user involvement may be effectively organised depending on the context and nature of the innovation process. This thesis focuses on intermediary user organisations that facilitate interactions between users and one or more other actors in emerging technologies in the health care and pharmaceutical sectors.

Innovations in these sectors currently face two challenges. Firstly, scholars have questioned the innovative capacity of pharmaceutical companies and they fear for a future decrease in pharmaceutical innovations. Secondly, the adoption and implementation of these innovations by society becomes more difficult because rising drug development costs inevitably lead to higher prices for drugs, spurring discussions about access to drugs, unmet medical needs, and inequity.

These challenges become all the more apparent against the backdrop of emerging pharmaceutical technologies, characterised by a large share of uncertainty, as well as great expectations and promises. Innovations are shaped as a result of the co-evolution of technology and society that spirals its way from early-stage to more established stages, leaning on several articulation processes. User involvement and user-producer interactions in emerging technological fields are carried by so-called demand articulation processes. These processes are defined in this thesis as iterative, inherently creative processes in which stakeholders try to address what they perceive as important characteristics of, and attempt to unravel preferences for an emerging innovation. Demand articulation takes place when thoughts of stakeholders, in terms of content and position (in favour or against), are made explicit, in such a way that other actors are prompted to (re-) act. It is a learning process that takes time. In the early phase of technology development stakeholders only have 'vague' ideas that become more concrete during the course of the demand articulation process. In this sense, these processes play an important role in clarifying needs for an emerging technology, and are especially prominent for stakeholders who are positioned on the user side of the innovation system, such as the intermediary user organisations. Moreover, they are also significant for actors who develop and produce these innovations, such as businesses.

In line with the emphasis on intermediary user organisations articulating their demands about emerging technologies, the ***central research question*** of this thesis is: *How to understand*

the demand articulation processes of intermediary user organisations in the context of emerging pharmaceutical technologies?

Chapter 2 first presents an overview of the role of user involvement in science, technology and innovation studies. Three strands of literature within innovation studies are discussed: the evolutionary economics theories, studies on the search for the origins of innovations, and the innovation systems literature. These illustrate that 1) users can be the 'locus' of innovative ideas (or at least needs), and in this way, have an important role in innovation processes and technology development; 2) user-involved demand articulation processes often play an important role in the concretisation of demands; 3) demand articulation is an interactive learning process involving all stakeholders in innovation systems; and 4) intermediary user organisations play a role in interactive learning in innovation systems.

Following this overview, the role of users and intermediary user organisations in the pharmaceutical industry is explicated. It is shown that the linear pharmaceutical innovation model or 'drug research and development pipeline' is under pressure and that there are several reasons to enhance interactions between phases, among others by involving external parties, such as users. A series of explorative interviews with representatives of actors in the Dutch health care field show that users in this sector are not as homogenously defined as in other sectors. Moreover, intermediary organisations take central stage as part of the demand side of the innovation system. An overview of the heterogeneity and structure of these intermediaries is presented. The focus in this thesis is on representative and coordinating intermediary user organisations. The representative intermediaries embody the interests of the users towards other actors. The coordinating type of intermediaries organise (part of) the interactions between actors without representing one of them.

In the second part of Chapter 2 the central conceptual model is developed in two parts running parallel to two sub-research questions derived from the central question:

1. How to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?
2. How to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies?

The first research question concerns demand articulation processes inside intermediary user organisations. Demand articulation dynamics consist of two intertwined learning processes:

- A first-order learning loop focusing on the development of demands, following a cycle of agenda-setting – demand synthesis – expression – evaluation.
- A second-order learning loop contributing to the development of underlying assumptions, objectives, ultimate preferences of the organisation itself (self-positioning) in relation with the position that is granted to the organisation by others (other-positioning).

It is hypothesised that these two loops are interconnected in such a way that underlying assumptions are influencing demands, and vice versa. Moreover, intermediary user organisations go through the learning loops in different ways, owing to distinct kinds of functions and tasks that intermediaries can fulfil, and depending on the issues at stake.

These differently-characterised learning processes are called 'demand articulation mechanisms'.

The second research question deals with the way intermediary user organisations interact with other actors in an innovation arena. Pharmaceutical companies, governmental and regulatory agencies, intermediary user organisations and other stakeholders articulate their demands, which results in either divergence or convergence of demands. Actors agree or disagree on first-order statements, i.e. demands such as needs and expectations. Moreover, they can agree or disagree on second-order statements, such as underlying assumptions.

Two types of partners are discerned with which intermediary user organisations interact: actors that are represented by the intermediary organisations, and other relevant actors with which the intermediary interacts on behalf of the represented actors. The communication between intermediary organisation and both types of interacting partners goes through so-called interfaces. There are differences in the organisation and strategies employed in these interfaces, concentrated on: 1) agenda access, 2) empowerment and provision of resources (knowledge) for the actors involved, and 3) impact on the agenda and decision-making.

Chapter 3 introduces pharmacogenomics as the emerging pharmaceutical technology this thesis focuses on. Pharmacogenomics is defined as the functional expression of genomics in pharmaceutical R&D associated with dividing patient populations into groups based on genetic or phenotypic tests. As such, pharmacogenomics paves the way for tailor-made medicines. This chapter also contextualises this emerging technology by showing trends and hot spots within the genomics science and technology field based on scientometric data like the number of patents and publications. We observe a general upward trend in scientific articles and patent applications in pharmacogenomics, which indicates a growing interest in this field. Patent and in the publication rankings reveal that subfields like anticancer drugs and medicines for disorders of the urinary system are prominent within pharmacogenomics field.

This chapter also gives an overview of the main characteristics of pharmacogenomics, especially regarding three aspects of drug response (pharmacokinetics, pharmacodynamics and disease stratification) and in relation to the drug R&D pipeline. It is shown that the introduction of the bulk of pharmacogenomics products still lies in the future. To study intermediary organisations, which most of the times have not been engaged much in this emerging technology, we use a metaphor analysis centring on orphan drugs to shed light on the possible future of pharmacogenomics. Orphan drugs, medicines for rare diseases with a low prevalence, and pharmacogenomics are compared on several aspects. This chapter analyses the (dis)similarities between these two fields. From this analysis it appears that – up to a certain degree – orphan drugs can be treated as an analogy for pharmacogenomics.

Chapter 4 provides the methodological background of this thesis. It first accounts for the case-study selection, design and delineation. The focus on emerging pharmaceutical technologies, on the Dutch health care setting, and the time scale of the study is explained. The selection of cases is illustrated based on two demarcating criteria: the type of intermediary (representative or coordinating) and the stage of the innovation process in which the intermediary is primarily engaged. Moreover, each case consists of several sequences of events centred on one topic, called event themes.

An analysis of demand articulation processes in intermediary organisations imposes the importance of the changes in and time-ordering of the topics and concepts that are studied over time. Therefore, in studying these processes we use the so-called event history analysis based on Van de Ven and colleagues. This methodology consists of a quick scan for event theme topics, collecting raw data inside intermediaries, collecting raw data from the 'interacting partners', enter raw data into a database in the form of incidents, identify/code events from these incidents, analyse these events, and triangulate the results.

Based on the incidents contained in the database for each event theme a narrative is constructed. The next step is to translate or code these incidents into qualitative event categories encompassing the different stages of the first-order learning loop (agenda-setting – demand synthesis – expression – evaluation), and second-order learning loop (self-positioning – and other-positioning).

For analysing demand articulation processes inside intermediaries, first-order learning is measured by looking at the growth in demand statements, convergence of demands, and changes in the direction of demands. Second-order learning is measured in the same vein, i.e. by looking at the number of statements about underlying assumptions, and whether its content and direction is converging or diverging. Moreover, it is investigated whether these two learning loops are interconnected. Lastly, the event categories are mapped over time. The discerned loops are then scrutinised and characterised in an explorative way. Different circumstances or types of demand might result in a distinct filling-out of the first-order learning loops, i.e. in different types of demand articulation mechanisms.

The second part of the analysis revolves around demand articulation processes of intermediaries in interaction with other actors. Here the analysis is about how intermediary user organisations contribute to demand articulation at the level of the multi-actor innovation arena. While individual actors sharpen and articulate their demands in the same vein as the intermediary user organisation, they all try to influence demand articulation vis-à-vis other actors. This is measured by the extent to which the first-order (demands) and second-order elements (underlying assumptions) of the various (represented and other relevant) actors correspond with the ones of the intermediary for the distinct periods of one event theme. This analysis results in four different states of demand in which the actors can be placed, i.e. agreeing on both first- and second-order, disagreeing on both first- and second-order, and the two situations in between.

Concerning the interface strategies we scan those strategies pursued by the intermediaries in interaction with other actors, mostly communicated through the interfaces. This scanning is done in an exploratory way, classifying the strategies found under the three hypothesised strategies (access, empowerment, impact), and later making an attempt to deepen this classification. A difference is made between communication with the represented actors and with the other relevant actors. Lastly, the effectiveness of the interface strategies is investigated by looking at the extent to which diverging and converging shifts in the demand articulation between the intermediary and the other actors is the result of interface strategies deployed by the intermediary user organisation.

Chapter 5 presents results of the first case study on the Dutch Neuromuscular Diseases Association, a patient representative organisation. This organisation is engaged in interaction with scientists, companies, governments and (international) networks. Influencing research and development in the field of neuromuscular diseases is one of their prime objectives. Event themes include gene therapy, stem cell therapy, exon-skipping,

enzyme replacement therapy for Pompe disease, and clinical trials for idebenone and TCH346.

Chapter 6 focuses on the Steering Committee on Orphan drugs, a committee founded by the Dutch government to support the situation of patients with rare diseases. It is made up of representatives of a diverse range of relevant stakeholders in the Dutch health care arena. Event themes include stimulating orphan drug R&D and the reimbursement of orphan drugs.

Chapter 7 concerns the case study on the Breast Cancer Association. This is a patient representative organisation that, together with a host of other actors, was engaged in discussions on the reimbursement of and access to expensive drugs used in hospitals, such as the pharmacogenomics drug Herceptin.

Chapter 8 presents the results from the three case studies in a more generalised way, and draws conclusions for the two research questions.

1. How to understand the dynamics of demand articulation inside intermediary user organisations in the context of emerging pharmaceutical technologies?

First-order learning takes place in various instances inside these three intermediary user organisations. It is dependent on the stage of technology development, sufficient support of the intermediary's position from other actors, and the resources and level of professionalism of the intermediary. Second-order learning occurs in most event themes of the three cases. Following the central conceptual model, second-order learning forces intermediaries to reflect on their own positions in interaction with how others position them. This loop of mutually influencing self-position and other-positions is not found in all cases.

All event themes of all cases show that there are interactions between the two learning types. These linkages take many shapes, such as weighing, legitimisation and feedback during evaluation. Organisations learn to tune their objectives to the kinds of demands they articulate, and vice versa. Second-order learning results in the development of the objectives of intermediary user organisations. It could be claimed that these organisations have a course of life of their own, and that developing their underlying assumptions is part of a maturing process of the organisation.

Several patterns in the first-order learning loops are found. Most of these patterns follow the order of event categories as assumed in the conceptual model (agenda-setting – synthesis – expression – evaluation). Differences in order and characterisation of these event categories result in the distinct demand articulation mechanisms. The most prominent mechanisms include the 'management of expectations', 'network building', 'active case building', and the 'knee-jerk reaction' to issues that come up.

2. How to understand the dynamics of demand articulation of intermediary user organisations in interaction with represented and other relevant actors in the context of emerging pharmaceutical technologies?

Demand articulation takes place in the multi-actor innovation arena. Intermediary user organisations and the actors with which they interact in this arena change regarding the level of agreement on first-order and second-order elements. In this context, the analysis

of the (shifts in the) levels of agreement is a useful approach to describe the course of the debate, the changing positions of actors, and even the forming of coalitions.

Concerning the interactions with the represented actors there are two types of patients with whom the intermediary communicates. The first is the 'silent majority' of patients with which the organisation maintains contact more or less constantly through newsletters, the Internet, mutual help e-mail and telephone services, press releases, etc. The second category consists of 'patient champions': patients who are actively engaged in the intermediary organisation, e.g. by participating in working groups or committees. To reach both groups a large array of interface strategies was deployed, ranging from representing patients without interaction to quick and passionate calls for action ('sudden anxiety'). These strategies mostly focus on ad hoc advocacy and also put a relatively large amount of effort into representing actors without actual interaction. Nevertheless, the 'advocate personal needs' and 'anticipative alignment' strategies ensure more longer-term commitment and focus.

Concerning interactions with the other relevant parties, the intermediaries use a wide range of interface types as well. The most prominent of these include presentation/advocating, deliberation and coordination. Interface strategies range from asked advocacy in the form of consultative presentation to unasked advocacy, and from forceful to tentative strategies. These strategies are most of the time not the result of ad hoc actions but have a proactive and long-term focus. They call for an elaborate preparation and direct interactions with stakeholders.

Lastly, the variation in effectiveness of intermediary organisation's demand articulation appears to be clearly related to the different types of interface strategies found. Consultative presentation often leads to moderate effectiveness, whereas forceful advocacy, implying a high degree of alignment and application of resources, is linked to high access to debates or the agendas of other actors, empowerment of the intermediary, and high impact on decisions. The communication with the represented actors is also effective in all three cases. A large variety of interface strategies is observed, ranging from active to passive involvement of represented users, and from a short-term to a longer-term focus. That is, ideally, intermediary user organisations refrain from only using 'representation of other's interests' and also focus on 'sudden anxiety', 'advocate personal needs' and 'anticipative alignment' strategies.

In Chapter 9 three major *conclusions* are drawn. Firstly, intermediary user organisations influence several phases of the innovation process. Although intermediaries failed to be involved in the agenda-setting of drug development of pharmaceutical companies, they have a notable impact on the boundary conditions and effectiveness of the innovation process. Moreover, they are often involved by the government in issues to overcome market failure, such as was the case in the orphan drug field. Debates in the health care innovation arena in general benefit from the involvement of intermediaries. By articulating their demands and bringing in particular – sometimes idiosyncratic – insights, intermediaries broaden and enrich these debates. Secondly, demand articulation processes play a large role encompassing intertwined first-order (characterised as demand articulation mechanisms) and second-order learning loops (consisting of self- and other-positions), and extending to other actors than the intermediary as well. By this, the findings substantiate the central conceptual framework that we regard as being also applicable to other sectors and technologies. Thirdly, intermediary user organisations are loci of demand articulations

including involvement in overcoming market failures, developing and disseminating their creative potential, making innovation processes more effective, addressing ethical and societal issues, and ensuring the democratic value of their demands.

Intermediary user organisations should take three dilemmas into account when striving after effective functioning in the innovation arena:

1) Positioning: the second-order learning loop illustrates a confrontation between an intermediary's self-position and the position other actors assign to them. This confrontation reveals possible problems with the neutrality of intermediary user organisations. Other actors in the health care policy arena expect intermediary organisations to maintain a certain degree of impartiality: although they might represent certain actors and therefore side with them, they need to remain a trusted and credible partner for the external actors and constantly need to explicate their internal goals and criteria (self-positioning).
2) Representation: for intermediaries it is essential to speak on behalf of their members and picture their demands in a representative way. When interacting with the represented actors, a mixture of interface strategies aimed at both 'patient champions' and the 'silent majority', could serve as a starting point for achieving and enhancing the user representation by intermediary user organisations.
3) The need to be proactive: it is recommended to start as early as possible with clarifying demands and underlying assumptions of the intermediary and those of other parties. In this way, intermediaries can better anticipate the course of the debate. Moreover, by creating a vision of future technologies in an early phase make intermediaries empowered.

These three dilemmas show that intermediary user organisations play a precarious role in demand articulation in the context of emerging technologies. However, this role could become central and crucial if the intermediary organisations can overcome the dilemmas mentioned.

Moreover, it is *evaluated what the different actors can learn* from this study. Intermediary user organisations can benefit from five insights following the findings of this thesis:

1) Intermediary organisations have changed their tasks from transferring knowledge to also adding value to knowledge and instigating efforts to influence the innovation process.
2) Intermediary organisations have no well-defined roles and therefore need to carefully position themselves within multi-actor innovation arenas.
3) Intermediary user organisations are one of the most prominent actors in the health care (innovation) arena.
4) Intermediary user organisations can learn from the demand articulation mechanisms that were found. These might create awareness within these intermediaries of what their prominent activities are or could be. By further reflecting on these mechanisms, intermediaries can become aware of how they function and how they can improve this.
5) Intermediary user organisations can learn from the interface strategies that were found in this study. For example, the three cases stress the prominence of coalitions, such as the partnerships between medical and scientific expertise and the actors who are thought to have the strongest and purest of interests: the patients themselves. These coalitions were characterised as 'undeniable' and 'natural alliances' by both insiders and outsiders.

The government should be aware of the fact that in health care it sometimes is not only a regulator but also a problem owner with certain specific interests and objectives. In the battle or fog of conflicting values and interests that might result from this situation, intermediary user organisations can prove to be beneficial by broadening and enriching debates about new technologies and by accepting, to some extent, an independent or neutral role. The government has already partly underlined this by billing patient groups to be the 'third party' in health care policy, but in some cases it should enhance this support rhetorically and financially.

The pharmaceutical industry could also back intermediary user organisations that lack resources, in this way supporting their beneficial impact on innovation processes and debates. At the same time, in aiding intermediaries the pharmaceutical companies should avoid investing one-sidedly or opportunistically. This stifles the freedom of action, and therefore the beneficial creativity of these intermediaries to put topics on the agenda proactively. It also might render the intermediary's demands meaningless and powerless in the eyes of other parties in the health care sector.

The *reflection* on the scientific relevance of this thesis reveals that this study sheds light on user-producer interactions in health care arenas dealing with emerging technologies. Our case study findings substantiated the central conceptual model. In this way, the thesis contributes to a better understanding of demand articulation dynamics, regarded as learning processes, both inside intermediaries and in interaction with other actors in the health care arena. The methodology proves useful to unravel and sharpen the dynamics of demand articulation inside intermediaries in the emerging phase of a technology, and reveals how these learning processes take place on the first-order and second-order level.

The lessons drawn above for various types of actors indicate the societal relevance of this thesis. The increased understanding of demand articulation processes, together with the related proposed demand articulation mechanisms and interface strategies, might give pointers as to how to organise these learning processes in intermediaries. The demand articulation model, mechanisms and strategies might be useful tools to provide insights into the functioning of intermediary user organisations, easing discussions about the positioning of these intermediary user organisations. Moreover, the findings of this study can be beneficial to pharmaceutical innovation processes and can benefit the debates concerned with the adoption and implementation of new drugs.

Samenvatting

Vragende dynamiek
Vraagarticulatie van intermediaire organisaties in opkomende farmaceutische innovaties

De groeiende belangstelling voor de rol van gebruikers in innovatieprocessen wordt gevoed door een scala van wetenschaps-, technologie- en innovatiestudies. Wetenschappers in deze velden beweren dat een vergroting van de kwaliteit van interacties tussen gebruikers en producenten zorgt voor verbeterde innovatieprocessen, en misschien zelfs voor succesvollere innovaties. Dit leidt tot vragen over wat de rol van verschillende soorten gebruikers zou kunnen zijn en hoe het betrekken van gebruikers effectiever georganiseerd kan worden, afhankelijk van de context en aard van de innovatieprocessen. Dit proefschrift richt zich op intermediaire gebruikersorganisaties die interacties faciliteren tussen gebruikers en één of meerdere andere actoren rond opkomende technologieën in de gezondheidszorg en de farmaceutische sector.

Innovaties in deze sectoren worden momenteel geconfronteerd met twee uitdagingen. Ten eerste staat de innovatieve capaciteit van de farmaceutische industrie ter discussie. Industrie-experts vrezen voor een afname in innovaties in deze sector. Ten tweede wordt de adoptie en implementatie van innovaties bemoeilijkt door de stijgende kosten van de medicijnontwikkeling die leiden tot duurdere medicijnen en discussies over toegang tot zorg, onbeantwoorde medische behoeften en ongelijkheid.

Deze uitdagingen worden steeds duidelijker tegen de achtergrond van nieuwe, opkomende nieuwe technologieën, die worden gekenmerkt door onzekerheid, maar ook grote verwachtingen en beloften. Innovaties zijn het resultaat van de co-evolutie van technologie en samenleving, van de prille naar de meer uitgemaakte fasen leunend op articulatieprocessen. Gebruikersbetrokkenheid en gebruiker-producentinteracties in opkomende technologieën worden gedragen door zogenaamde vraagarticulatieprocessen. Deze processen worden in dit proefschrift gedefinieerd als iteratieve, inherent creatieve processen waarin belanghebbenden adresseren wat zij belangrijke karakteristieken vinden van opkomende technologieën en waarin geprobeerd wordt de voorkeuren voor deze innovaties te ontrafelen. Vraagarticulatie vindt plaats wanneer de gedachten van deze belanghebbenden, omtrent inhoud en positie (voor of tegen), expliciet worden gemaakt, op een manier die ervoor zorgt dat anderen worden aangezet te reageren. Vraagarticulatie kan zo worden opgevat als een leerproces dat tijd kost. In de vroege fase van de ontwikkeling van een technologie hebben actoren slechts 'vage' ideeën die echter steeds concreter wordt gedurende het vraagarticulatieproces. Deze processen een belangrijke rol bij het verhelderen van behoeften rond een opkomende technologie, in het bijzonder voor actoren die zich bevinden aan de gebruikerszijde van het innovatiesysteem, zoals intermediaire gebruikersorganisaties. Ze zijn echter ook van belang voor partijen die nieuwe technologieën ontwikkelen, zoals bedrijven.

Met deze nadruk op intermediaire gebruikersorganisaties die vragen articuleren over opkomende technologieën is de ***centrale onderzoeksvraag*** van dit proefschrift de volgende:

Hoe kunnen we de vraagarticulatieprocessen van intermediaire gebruikersorganisaties begrijpen in de context van opkomende farmaceutische technologieën?

Hoofdstuk 2 begint met het presenteren van een overzicht van gebruikersonderzoek in wetenschaps-, technologie- en innovatiestudies. Drie lijnen in de innovatieliteratuur worden behandeld: de evolutionair economische theorieën, studies over de zoektocht naar de oorsprong van innovaties en literatuur over innovatiesystemen. Deze uiteenzetting toont aan dat: 1) gebruikers in sommige gevallen de bron kunnen zijn van innovatieve ideeën en op deze manier een belangrijke rol spelen in innovatieprocessen en technologieontwikkeling; 2) vraagarticulatieprocessen bijdragen aan de concretisering van vragen naar nieuwe technologieën; 3) vraagarticulatie een interactief leerproces is waarbij alle belanghebbende partijen uit het innovatiesysteem worden betrokken; en 4) intermediaire gebruikersorganisaties een rol spelen in interactieve leerprocessen in innovatiesystemen.

Naar aanleiding van dit overzicht wordt de rol van gebruikers en intermediaire gebruikersorganisaties in de farmaceutische sector bekeken. Het lineaire farmaceutische innovatiemodel, beter bekend als de 'R&D-pijplijn van medicijnen' staat onder druk. Redenen worden opgevoerd om het model aan te vullen met interacties tussen de verschillende fasen en met het betrekken van partijen buiten de farmaceutische bedrijven, zoals gebruikers. Een serie van verkennende interviews met vertegenwoordigers van de Nederlandse gezondheidssector laten zien dat gebruikers niet een homogeen te definiëren groep is. Intermediaire organisaties nemen bovendien een belangrijke plaats in aan de gebruikerszijde van deze sector. Een overzicht van de heterogeniteit en de structuur van deze intermediairen wordt weergegeven. De nadruk ligt in dit proefschrift op de representatieve en coördinerende typen intermediaire gebruikersorganisaties. Die eerste groep vertegenwoordigen de belangen van de gebruikers ten opzichte van andere actoren. Het coördinerende type organiseert een deel van de interacties tussen actoren zonder er één te representeren.

In het tweede deel van hoofdstuk 2 wordt het centrale conceptuele model ontwikkeld in twee onderdelen die aansluiten bij vragen afgeleid van de centrale onderzoeksvraag:

1. Hoe kunnen we de dynamiek van vraagarticulatie begrijpen binnen intermediaire gebruikersorganisaties in de context van opkomende farmaceutische technologieën?
2. Hoe kunnen we de dynamiek van vraagarticulatie begrijpen van intermediaire gebruikersorganisaties in interactie met diegene die zij vertegenwoordigen en de andere relevante actoren in de context van opkomende farmaceutische technologieën?

De eerste onderzoeksvraag gaat over de vraagarticulatieprocessen binnen intermediaire gebruikersorganisaties. De dynamiek van vraagarticulatie bestaat uit twee, samengevlochten leerprocessen:

- Een eerste-orde leerlus ('first-order learning loop') die zich richt op de ontwikkeling van vragen en bestaat uit een cirkel met de stappen agendabepaling – synthese van vragen – expressie – evaluatie.
- Een tweede-orde leerlus ('second-order learning loop') die bijdraagt aan de ontwikkeling van onderliggende waarden, doelstellingen en ultieme voorkeuren

van de organisatie (de zelf-positionering) in relatie met de positie die andere actoren toekennen aan de intermediair (de ander-positionering).

We hypothetiseren dat deze twee leerlussen op elkaar ingrijpen: onderliggende waarden beïnvloeden de vragen, en vice versa. Daarnaast doorlopen de intermediaire organisaties de eerste-orde leerlus op verschillende manieren, afhankelijk van de verschillende functies en taken die deze organisaties hebben, en van de onderwerpen die onder behandeling zijn. Deze verschillend gekarakteriseerde leerprocessen worden 'vraagarticulatiemechanismen' genoemd.

De tweede onderzoeksvraag behandelt de manier waarop intermediaire gebruikersorganisaties omgaan met andere actoren in de innovatiearena. Farmaceutische bedrijven, overheids- en regulerende instanties, intermediaire gebruikersorganisaties en andere betrokkenen articuleren vragen, wat resulteert in divergentie of convergentie van vragen. De eerste-orde uitspraken van actoren, vragen zoals behoeften en verwachtingen, stemmen overeen of niet. Ze kunnen het ook eens of oneens zijn over tweede-orde uitspraken, de onderliggende waarden.

Twee typen van partners met wie de intermediaire gebruikersorganisaties omgaan worden onderscheiden: actoren die worden vertegenwoordigd door de intermediairen en de andere relevante actoren. De communicatie tussen de intermediaire organisatie en beide typen interactiepartners verloopt via zogenoemde interfaces. Deze interfaces worden verschillend georganiseerd en verschillende strategieën worden aangewend. Deze strategieën concentreren zich op: 1) toegang tot de agenda, 2) 'empowerment' en het beschikken over hulpmiddelen (kennis) en 3) impact op de agendabepaling en beslissingen.

Hoofdstuk 3 introduceert pharmacogenomics als de opkomende farmaceutische technologie waar dit proefschrift zich op concentreert. Pharmacogenomics wordt gedefinieerd als een functionele vertaling van genomics in farmaceutische R&D betreffende het verdelen van de patiëntenpopulatie in groepen gebaseerd op genetische tests. Op deze manier draagt pharmacogenomics bij aan het toekomstbeeld van geneeskunde-op-maat. Dit hoofdstuk onderzoekt ook de context van deze opkomende technologie door trends en zwaartepunten aan te tonen met behulp van scientometrische data zoals patent- en publicatieaantallen. We signaleren een algemene opgaande trend in patentapplicaties en publicaties betreffende pharmacogenomics, wat duidt op een groeiende aandacht voor dit veld. Dezelfde patent- en publicatiedata laten zien dat ziektegebieden zoals kanker en aandoeningen aan de urinewegen zwaartepunten zijn in dit veld.

Dit hoofdstuk geeft ook een algemeen overzicht van de karakteristieken van pharmacogenomics, in bijzonder met betrekking tot de drie aspecten van medicijnrespons (farmacokinetica, farmacodynamica en ziektestratificatie) en de relatie tot het R&D-proces van medicijnen. Dit overzicht geeft aan dat de introductie van het grootste deel van de pharmacogenomicsproducten nog in de toekomst ligt. Dit betekent dat intermediaire gebruikersorganisaties zich nog beperkt met pharmacogenomics hebben beziggehouden. Om toch empirische data te verzamelen rond de betrokkenheid van deze organisaties bij pharmacogenomics wordt een metafooranalyse ingezet om te bekijken in hoeverre weesgeneesmiddelen licht kunnen werpen op een mogelijke pharmacogenomicstoekomst. Weesgeneesmiddelen zijn medicijnen voor zeldzame ziekten, aandoeningen met een lage prevalentie. Deze geneesmiddelen en pharmacogenomicsproducten zijn vergeleken op verschillende aspecten. In dit hoofdstuk worden de verschillen en

overeenkomsten geanalyseerd tussen deze twee velden. Deze analyse brengt aan het licht dat weesgeneesmiddelen tot op zekere hoogte kunnen worden gezien als een analogie voor pharmacogenomicsmedicijnen.

Hoofdstuk 4 verschaft de methodologische achtergrond van dit proefschrift. In de eerste plaats verantwoordt het de selectie en de opzet van de cases. De nadruk op de opkomende farmaceutische technologieën, op de Nederlandse gezondheidssector, en de tijdsbeperking van de studie worden besproken. De selectie van de cases wordt geïllustreerd op basis van twee afbakenende criteria: het type intermediair (representatieve of coördinerend) en het stadium van het innovatieproces waar de intermediair primair bij betrokken is. Elke case bestaat bovendien uit verschillende onderwerpen, de zogenaamde activiteitenthema's.

Een analyse van vraagarticulatieprocessen in intermediaire organisaties vraagt om het analyseren van veranderingen in onderwerpen en concepten waarbij tijdsvolgorde van groot belang is. We hebben daarom gebruikgemaakt van de zogenaamde 'event history analysis' gebaseerd op werk van Van de Ven en collega's bij het bestuderen van die processen. Deze methodologie bestaat uit een snelle verkenning van de activiteiten van de intermediair om de belangrijkste activiteitenthema's te selecteren, het verzamelen van ruwe data binnen de intermediaire organisaties zelf, het verzamelen van ruwe data bij de actoren met wie die organisaties omgaan, het invoeren van deze ruwe data in een database in de vorm van incidenten, het identificeren/coderen van activiteiten op basis van deze incidenten, het analyseren van deze activiteiten en het valideren van de resultaten.

Gebaseerd op deze incidenten in de database wordt voor elk activiteitenthema een vertelling geconstrueerd. De volgende stap is om deze incidenten te vertalen ofwel te coderen in kwalitatieve categorieën van activiteiten, welke terugslaan op de verschillende stadia van de eerste-orde lerenlus (agendabepaling – synthese van vragen – expressie – evaluatie) en de tweede-orde lerenlus (zelf-positionering – ander-positionering).

De vraagarticulatieprocessen binnen intermediaire organisaties worden geanalyseerd door het eerste-orde leren te beschouwen aan de hand van de groei in uitspraken betreffende vragen, convergentie van de inhoud van deze uitspraken en veranderingen in de oriëntatie van deze vragen. Tweede-orde leren wordt op dezelfde manier gemeten: door te kijken naar het aantal uitspraken over onderliggende waarden, en of deze convergeren of divergeren wat betreft de inhoud en richting. Daarnaast is ook gekeken of deze twee leerlussen verbonden zijn. Tot slot wordt over de tijd het voorkomen van de activiteitencategorieën weergegeven. De volgorde van deze categorieën, al dan niet zoals is aangenomen in het conceptuele model, karakteriseert de leerlussen. Verschillende omstandigheden of typen vragen kunnen leiden tot een andere invulling van de eerste-orde leerlussen, ofwel verschillende vraagarticulatiemechanismen.

Het tweede deel van de analyse draait om vraagarticulatieprocessen van intermediaire organisaties terwijl deze in interactie zijn met andere actoren. Hier gaat het om de analyse van de bijdrage die de organisaties leveren aan vraagarticulatie op het niveau van de multi-actor innovatiearena. Terwijl alle actoren in deze arena hun eigen vragen intern concretiseren op een zelfde manier als de intermediaire organisaties, proberen ze ook hun vragen te articuleren naar andere actoren toe. Dit wordt gemeten door te beschouwen in hoeverre de eerste-orde (vragen) en tweede-orde elementen (onderliggende waarden) van de verschillende (representatieve en andere relevante) actoren overeenkomen met die van de intermediaire organisatie. Deze analyse resulteert in vier verschillende toestanden,

namelijk dat partijen overeenkomen op eerste- en tweede-orde met de intermediair, dat ze op beide orden niet overeenkomen, en de twee situaties daar tussen.

Met betrekking tot de interfacestrategieën scannen we de strategieën die de intermediaire organisaties hebben gebruikt in de interacties met andere actoren. Dit bepalen wordt gedaan op een exploratieve manier door ze eerst te classificeren naar soort strategie (toegang, 'empowerment', impact). Vervolgens wordt getracht verdieping aan te brengen in deze ordening. Een onderscheid wordt gemaakt tussen strategieën die worden gebruikt ten opzichte van de representatieve en de andere relevante actoren. Tenslotte wordt de effectiviteit van de interfacestrategieën onderzocht door te bestuderen in hoeverre de convergerende en divergerende bewegingen in vraagarticulatie op arenaniveau het resultaat zijn van deze strategieën.

Hoofdstuk 5 presenteert de resultaten van de eerste casestudie over de Vereniging Spierziekten Nederland. Deze patiëntenorganisatie is continu in interactie met wetenschappers, bedrijven, overheden en internationale netwerken. Het beïnvloeden van onderzoek en ontwikkeling op het gebied van spierziekten is één van hun belangrijkste doelstellingen. Activiteitenthema's betreffen gentherapie, stamceltherapie, exon-skipping, enzymvervangingstherapie voor de ziekte van Pompe en klinische trials voor idebenone en TCH346.

Hoofdstuk 6 gaat over de Stuurgroep Weesgeneesmiddelen, een commissie die opgericht is door de Nederlandse overheid met als doel het verbeteren van de situatie van patiënten met een zeldzame ziekte. De stuurgroep bestaat uit vertegenwoordigers van een groot spectrum van relevante actoren in de Nederlandse gezondheidszorg. Activiteitenthema's zijn het stimuleren van het onderzoek naar en de ontwikkeling van weesgeneesmiddelen en de vergoeding van weesgeneesmiddelen.

Hoofdstuk 7 heeft betrekking op de Borstkankervereniging Nederland. Dit is een patiëntenorganisatie die, samen met een groot aantal andere partijen, betrokken was bij discussies rond de vergoeding van en toegang tot dure geneesmiddelen die gebruikt worden in ziekenhuizen. Het pharmacogenomicsmedicijn Herceptin speelt hierbij een rol.

Hoofdstuk 8 vat de resultaten van de drie casestudies samen op een geaggregeerd niveau, en trekt conclusies voor de twee afgeleide onderzoeksvragen.

1. Hoe kunnen we de dynamiek van vraagarticulatie begrijpen binnen intermediaire gebruikersorganisaties in de context van opkomende farmaceutische technologieën?

Eerste-orde leren vindt plaats op verschillende momenten in de drie intermediaire gebruikersorganisaties. Het is afhankelijk van het stadium van technologieontwikkeling, de ondersteuning van de positie van de intermediair door andere actoren en de mate van beschikking die het intermediair heeft over hulpmiddelen en professionaliteit. Tweede-orde leren komt voor in de meeste activiteitenthema's van de drie cases. Net zoals in het centrale conceptuele model wordt voorgesteld, wordt de lus van elkaar beïnvloedende zelf- en ander-positionering gevonden in enkele – maar niet alle – cases.

Alle activiteitenthema's van alle cases tonen aan dat de interacties tussen de twee leerlussen aanwezig zijn. Deze relaties nemen vormen aan zoals weging van opties, legitimisering en feedback. Organisaties stemmen hun doelstellingen af op de soort vragen die ze articuleren en vice versa. Tweede-orde leren resulteert in het ontwikkelen van de

doelstellingen van intermediaire gebruikersorganisaties. Het kan worden gesteld dat deze organisaties een eigen levensweg hebben en dat het ontwikkelen van hun onderliggende waarden deel is van een rijpingsproces van de organisatie.

We hebben verscheidene patronen in de eerste-orde leerlussen gevonden. De meeste van deze patronen volgen de volgorde zoals die is gesteld in het conceptuele model (agendabepaling – synthese van vragen – expressie – evaluatie). Verschillen in deze volgorde en karakterisering van de activiteitencategorieën leiden tot de vraagarticulatiemechanismen. De meest prominente mechanismen behelzen de 'management van verwachtingen', het 'bouwen van netwerken', 'actief opzetten van een casus' en 'reflexreacties' op zaken die ineens opkomen.

2. Hoe kunnen we de dynamiek van vraagarticulatie begrijpen van intermediaire gebruikersorganisaties in interactie met diegene die zij vertegenwoordigen en de andere relevante actoren in de context van opkomende farmaceutische technologieën?

Vraagarticulatie vindt plaats in de multi-actor innovatiearena. Intermediaire gebruikersorganisaties en de actoren met wie ze omgaan in deze arena veranderen wat betreft de overeenkomst op eerste-orde en tweede-orde elementen. De analyse van de (verschuivingen in de) mate van overeenkomst is een waardevolle benadering om het verloop van een debat, de veranderende posities van actoren en zelfs de vorming van coalities te beschrijven.

Met betrekking tot de interacties met de gerepresenteerde actoren communiceert de intermediair met twee typen patiënten. De eerste vormt de 'stille meerderheid' van patiënten met wie de intermediair min of meer continu in contact staat door middel van nieuwsbrieven, persberichten, websites, en telefoon- en e-maildiensten ten behoeve van lotgenotencontact. De tweede categorie bestaat uit 'patiëntenkampioenen': patiënten die actief betrokken zijn bij de intermediaire organisatie, onder andere door deel te nemen aan commissies of werkgroepen. Om beide groepen te kunnen bereiken wordt een groot scala aan interfacestrategieën ingezet, variërend van het 'representeren van patiënten zonder met ze te communiceren' tot het 'beantwoorden van een snelle en gepassioneerde oproep voor actie'. Deze strategieën zijn meestal tijdelijk van aard en representeren vaak de patiënten zonder daadwerkelijke interactie. Andere strategieën die in deze context zijn gebruikt, zoals het 'bepleiten van persoonlijke behoeften' en het 'anticipatief afstemmen van belangen', beloven een focus op langetermijnverbintenis.

Met betrekking tot de interacties met de andere relevante partijen gebruiken de intermediaire organisaties ook een breed scala aan interfacetypen. De belangrijkste zijn het presenteren/bepleiten, overleg en coördinatie. Interfacestrategieën variëren van gevraagde belangenbehartiging in de vorm 'consultatieve presentatie' tot ongevraagde belangenbehartiging, en van krachtdadige tot voorzichtige strategieën. Deze strategieën zijn meestal niet het resultaat van tijdelijke acties, maar leggen de nadruk op een proactieve en langetermijnbenadering. Ze vragen om uitgebreide voorbereiding en directe interactie met andere belanghebbenden.

De variatie in effectiviteit van de vraagarticulatie van intermediaire organisaties hangt samen met het type interfacestrategie dat gebruikt wordt. 'Consultatieve presentatie' leidt vaak tot een matige effectiviteit, terwijl een 'daadkrachtige strategie met een hoge mate van afstemming met andere actoren en gebruik van hulpmiddelen' leidt tot betere toegang tot de agenda van debatten of andere actoren, empowerment en impact op beslissingen. De communicatie met de gerepresenteerde actoren is ook effectief in alle

drie de cases. Een grote variëteit van interfacestrategieën is waargenomen, van actieve tot passieve betrokkenheid van de gerepresenteerde gebruikers, en van een lange- tot een kortetermijnfocus. In het ideale geval zien intermediairen af van het slechts gebruiken van strategieën zoals het representeren van andermans interesses zonder interactie, maar concentreren zich ook op snelle, gepassioneerde oproepen voor actie, het bepleiten van persoonlijke behoeften en het anticipatief afstemmen van belangen.

In hoofdstuk 9 worden drie belangrijke *conclusies* getrokken. Ten eerste beïnvloeden intermediaire gebruikersorganisaties de verschillende fasen van het innovatieproces. Hoewel deze organisaties vaak niet in staat zijn om de agenda van de medicijnontwikkeling in de farmaceutische industrie te bepalen, hebben ze een noemenswaardige impact op de randvoorwaarden en de effectiviteit van het innovatieproces. Vaak worden ze door de overheid ook betrokken bij beleidsonderwerpen die gerelateerd zijn aan een falende markt, zoals het geval is bij weesgeneesmiddelen en zeldzame ziekten. Debatten in de gezondheidszorg hebben doorgaans profijt van de betrokkenheid van intermediaire organisaties. Deze organisaties verbreden en verrijken de debatten door het articuleren van hun vragen en het inbrengen van bepaalde – soms ongewone – inzichten. Ten tweede kan worden geconcludeerd dat vraagarticulatieprocessen een grote rol spelen en bestaan uit gekoppelde eerste-orde (gekarakteriseerd door vraagarticulatiemechanismen) en tweede-orde leerlussen (bestaande uit zelf- en ander-positionering), die ook toepasbaar zijn op andere actoren. Hierdoor ondersteunen de resultaten het centrale conceptuele model, welke ook van toepassing wordt geacht op andere sectoren en technologieën. Ten derde zijn de intermediaire gebruikersorganisaties plaatsen voor vraagarticulatie. Zij kunnen met het ontwikkelen en verspreiden van hun creatief potentieel met een zekere democratische waarde bijdragen aan het overwinnen van marktfalen, het effectiever maken van het innovatieproces, het adresseren van ethische en maatschappelijke issues, en dergelijke.

Intermediaire gebruikersorganisaties moeten rekening houden met drie dilemma's wanneer ze op een effectieve manier willen functioneren in de innovatiearena:

1) Positionering: de tweede-orde lerenlus illustreert de confrontatie tussen de zelf-positionering van de intermediair en de positionering van die intermediair door anderen. Deze confrontatie openbaart potentiële problemen met de neutraliteit van de intermediaire gebruikersorganisaties. Andere actoren in de gezondheidszorg verwachten dat deze organisaties een bepaalde mate van onpartijdigheid behouden. Hoewel ze bepaalde partijen vertegenwoordigen en daarom aan hun kant staan, moeten ze een vertrouwde en geloofwaardige partner blijven en continu hun interne doelstellingen en criteria (zelf-positionering) expliciteren.
2) Representatie: voor intermediaire gebruikersorganisaties is het essentieel om te spreken namens hun leden en hun vragen uiteen te zetten op een representatieve manier. Het gebruikmaken van een mix van interfacestrategieën en interacties met zowel 'patiëntenkampioenen' als de 'stille meerderheid' kan dienen als een startpunt voor het bereiken en verbeteren van het betrekken van intermediaire gebruikersorganisaties en gebruikers in het algemeen.
3) De aansporing om proactief te handelen: het wordt aangeraden om zo vroeg als mogelijk de vragen en onderliggende waarden van de intermediair en anderen te verduidelijken. Op deze manier kunnen intermediairen beter anticiperen op het verloop van het debat. Door het in vroeg stadium creëren van een toekomstvisie voor nieuwe technologieën worden deze organisaties bovendien beter 'empowered'.

Deze drie dilemma's tonen aan dat intermediaire gebruikersorganisaties een precaire rol spelen in de vraagarticulatie rond opkomende technologieën. Toch kan deze rol centraal en cruciaal worden als deze organisaties de dilemma's op een goede manier oplost.

Bovendien is in dit hoofdstuk *geëvalueerd wat de verschillende actoren kunnen leren* van deze studie. Intermediaire gebruikersorganisaties kunnen baat hebben bij de volgende vijf inzichten uit dit proefschrift:

1) Intermediaire organisaties hebben hun taken uitgebreid van het slechts communiceren van informatie naar het produceren van kennis en het initiëren van inspanningen om het innovatieproces te beïnvloeden.
2) Intermediaire organisaties hebben geen goed gedefinieerde rollen en moeten zich dus zorgvuldig positioneren in een multi-actor innovatiearena.
3) Intermediaire organisaties zijn één van de meest prominente actoren in de (innovatie) arena van de gezondheidszorg.
4) Intermediaire organisaties kunnen leren van de gevonden vraagarticulatiemechanismen. Deze kunnen inzicht verschaffen binnen de intermediairen over wat belangrijke activiteiten (zouden moeten) zijn. Intermediairen worden zich bewust van hun functioneren en hoe ze dat kunnen verbeteren door verder te reflecteren op deze mechanismen.
5) Intermediaire organisaties kunnen leren van de gevonden interfacestrategieën. De drie casestudies onderstrepen bijvoorbeeld het belang van coalities, zoals de samenwerking tussen medisch-wetenschappelijke experts en degenen waarvan wordt gezegd dat zij de sterkste en puurste belangen hebben: de patiënten zelf. Deze coalities worden gekarakteriseerd als 'onmiskenbaar' en 'natuurlijke allianties' door zowel actoren binnen als buiten deze samenwerkingsverbanden.

De overheid zou zich er bewust van moeten zijn dat zij in de gezondheidszorg niet alleen een regulator is maar ook een probleemeigenaar met bepaalde, specifieke belangen en doelen. In de slag rond deze conflicterende waarden en belangen die het gevolg kan zijn van de onduidelijkheid over de rol van de overheid, kunnen intermediairen waardevol zijn door het verbreden en verrijken van debatten over nieuwe technologieën en door het aannemen van een – min of meer – onafhankelijke of neutrale rol. De overheid heeft dit al deels onderkend door patiëntenorganisaties de 'derde partij' in de gezondheidszorg te noemen maar in sommige gevallen zou zij er goed aandoen dit nog meer te ondersteunen, in financiële en retorische zin.

De farmaceutische industrie zouden de intermediaire gebruikersgroepen die een gebrek aan hulpmiddelen hebben ook kunnen ondersteunen om op deze manier bij te dragen aan de waardevolle inbreng die deze organisaties hebben op innovatieprocessen en -debatten. Tegelijkertijd dienen de bedrijven te vermijden om al te eenzijdig en opportunistisch te investeren in de intermediairen. Dit verkleint de vrijheid van actie en daardoor de waardevolle creativiteit van deze organisaties om onderwerpen proactief te agenderen. Bovendien worden de vragen die de intermediairen articuleren betekenisloos of krachteloos gemaakt als andere partijen de organisaties te veel gaan zien als een verlengstuk van de industrie.

De *reflectie* op de wetenschappelijke relevantie van dit proefschrift laat zien dat deze studie bijdraagt aan het begrijpen van gebruiker-producentinteracties in de gezondheidszorg in de context van opkomende technologieën. De casestudieresultaten ondersteunen het

centrale conceptuele model. Op deze manier draagt dit proefschrift bij aan een beter begrip van de dynamiek van vraagarticulatie, te beschouwen als leerprocessen, zowel binnen intermediairen als in interactie met andere actoren in de gezondheidszorg. De methodologie blijkt waardevol in het ontrafelen en verscherpen van vraagarticulatieprocessen waar intermediairen betrokken bij zijn in de context van opkomende technologieën, en laten zien hoe deze leerprocessen worden doorlopen op eerste- en tweede-orde niveau.

De aanbevelingen die hierboven voor de verschillende actoren zijn opgesteld, duiden al op de maatschappelijke relevantie van dit proefschrift. Het verbeterde inzicht in vraagarticulatieprocessen geeft, samen met de voorgestelde vraagarticulatiemechanismen en interfacestrategieën, aanwijzingen over hoe deze leerprocessen beter georganiseerd kunnen worden in intermediairen. Het conceptuele model van vraagarticulatie, de mechanismen en de strategieën kunnen inzicht verschaffen in het functioneren van de intermediaire gebruikersorganisaties en discussies over de positionering van deze organisaties vergemakkelijken. De resultaten van deze studie kunnen daarnaast waardevol zijn voor farmaceutische innovatieprocessen en discussies over de adoptie en implementatie van nieuwe medicijnen.

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Curriculum vitae

Wouter Boon was born in Utrecht, the Netherlands, on 27 February 1980. He completed his secondary education at the St. Gregrius College in Utrecht in 1998. In 2002 he obtained his master's degree in Science and Innovation at Utrecht University (honour: cum laude), with a specialisation in mobility and infrastructure. In this context he conducted research at the National Institute for Public Health and the Environment (RIVM) on social impacts of transportation. After this he worked as a junior lecturer and researcher at the Transport policy and Logistics organisation section, faculty Technology, Policy and Management of Delft University of Technology, and Science and Innovation, Utrecht University. In June 2004 he started working as a PhD candidate at the Copernicus Institute for Sustainability and Innovation, Department of Innovation and Environmental studies, Utrecht University. The results are presented in this thesis. From the August 2008 onwards he will be at the Athena Institute for Research on Innovation and Communication, VU University Amsterdam, as an assistant professor.

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