20 Years of Orphan Drug Policy Evolution in the Netherlands: The Role of Institutional Entrepreneurs

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List of abbreviations

Abbreviation	Description
ACP	Adviescommissie Pakket, an advisory body on policy around the basic package
CBG, or MEB	College ter Beoordeling van Geneesmiddelen, or Medicines Evaluation Board, an independent organisation that assesses medications, monitors side effects and risks, and encourages proper use of medications.
EMA	European Medicines Agency, a EU agency that protects and promotes human and animal health by evaluating and monitoring medicines
EU	European Union, an economic and political cooperation of 27 European countries
KNAW	Koninklijke Nederlandse Akademie van Wetenschappen, an advisory body to the government in the field of science
NPZZ	Nationaal Plan Zeldzame Ziekten, a national plan outlining the prerequisite actions needed to ensure that rare disease patients benefit
ODAP	Orphan Drug Access Protocol, a pilot designed to make orphan drugs more readily available to patients.
RWE	Real-World Evidence, the clinical evidence on the use and potential benefits or risks of a medical product
VSOP	Vereniging Samenwerkende Ouder- en Patiëntenorganisaties, the association of collaborating parent and patient organisations in the field of congenital and inherited disorders
WGM	Stuurgroep Weesgeneesmiddelen, or the 'Dutch Steering Committee Orphan Drugs', an intermediary organization that aims to stimulate the development of orphan drugs and to improve the treatment and care of patients with rare diseases.
ZN, or CVZ	Zorginstituut Nederland, a public health care institute that advises the minister on the content of the insured basic package. Note: between 1999 and 2014, the name of this organization was CVZ, College voor Zorgverzekeringen. However, for the sake of consistency, this thesis refers to ZN.
ZonMw	Zorg Onderzoek Nederland en Medische Wetenschappen, an independent administrative agency that promotes and funds health research and encourages the use of knowledge developed in the field of health care

Abstract

Introduction: This master's thesis examines the historical development of orphan drug policy in the Netherlands, particularly the role of institutional entrepreneurs in shaping these changes. It notes the unique challenges of rare diseases, which affect millions of people across the European Union, and the complex, tailored responses required due to economic constraints and differences in health care systems, patient demographics, and organizational capacity across nations. **Theory**: This study draws on institutional theory and institutional entrepreneurs. It contextualizes these concepts in health systems, and highlights the significant influence of enabling conditions in bringing about institutional change. **Methods**: A qualitative grounded theory approach is employed, using a literature review and semi-structured interviews. Data collection included a literature review, document analysis of orphan drug regulations and media articles, and semi-structured expert interviews. A thematic analysis approach, supported by NVIVO software, was used to analyze and code the interview data in conjunction with the literature and document and media findings, allowing for the identification of patterns and relationships within the data. **Results**: Institutional entrepreneurs played a significant role in disruptions, catalyzed by public debates on drug costs and access, changing the policy landscape, integrating promising orphan drugs into basic health insurance, and reevaluating traditional drug evaluation and pricing mechanisms. Despite progress, challenges remain, highlighting the need for continued vigilance and collaboration to address affordability and access issues in the complex field of orphan drug policy. **Discussion and Conclusions**: Both the social status of institutional entrepreneurs and enabling field features such as public discourse and high-profile cases contribute to institutional change. It presents unique findings, such as the substantial impact of individual institutional entrepreneurs with high social status in initiating change within existing institutions, improving patient access, and reducing drug prices. It emphasizes the importance of innovation in policy making, international cooperation and societal engagement in driving institutional change towards a more patient-centered, economically viable and internationally collaborative healthcare landscape in the Netherlands.

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1. Introduction

Up to 36 million people in the European Union (EU) suffer from a rare disease (European Commission, 2022a). These diseases are defined as those affecting five or fewer people per 10,000 inhabitants in the EU (European Commission, 2022b). Orphan drugs, which are designed to treat these rare diseases, are often among the most expensive on the market (Luzzatto et al., 2018). Historically, access to orphan drugs for people with rare diseases has been limited due to the lack of a profitable strategy in funding orphan drugs caused by small market sizes (Kacetl et al., 2020). These economic constraints, or the economic logic, lead pharmaceutical companies to focus on more profitable opportunities (Douglas et al., 2022; Simoens, 2011). Hence, the rare disease field faces significant challenges in terms of innovation, including the need to balance market driven demands with addressing societal needs (Gaudillière, 2019; Hanlin & Andersen, 2016; Kim, 2016). To address these challenges, policies offer incentives for pharmaceutical companies to develop drugs for these conditions (EMA, 2023a). These policies span the spectrum of drug development, from research and development (R&D) to market approval. However, the implementation and effectiveness of these policies vary considerably between countries, reflecting differences in healthcare systems, patient demographics, and organizational capacity (Callenbach et al., 2022; European Commission, 2022b; Stadhouders et al., 2016). The complex environment of the field of rare diseases therefore requires a multifaceted, tailored approach that considers the institutional dynamics and their capacity for change. Institutions, as emphasized by various sociology and innovation scholars (DiMaggio & Powell 1983; Geels, 2004; Meyer & Rowan, 1977; Scott, 2013), can be understood as a mix of formal and informal rules, values, norms, and established behaviors that not only regulate social relations and legitimate actions, but also profoundly shape the functioning and decision-making within a system or society. This master's thesis takes a particular interest in the changing institutional field of rare diseases in the Netherlands, a country that has navigated unique institutional dynamics to promote orphan drug innovation and availability over the past two decades.

The Dutch healthcare system is characterized by a patient-centered approach and a strong commitment to equity of access (Daley et al., 2013). However, the high costs and specific challenges associated with orphan drugs have required distinct policies and collaborations to address the discrepancy between ensuring access and maintaining financial sustainability (Caso-González, 2022; Jeyaprakash, 2023; Kanters et al., 2014; Slusna et al., 2023). Institutional change in this area has not occurred spontaneously, but rather as a result of deliberate strategies by actors who have managed to leverage the strengths of the Dutch healthcare system while introducing new practices and norms to accommodate the specificities of orphan drugs. Understanding institutional changes therefore requires a closer look at the key actors and processes involved in the evolution of orphan drug policy. These actors include, among others, researchers, policymakers, patient organizations, pharmaceutical companies, healthcare providers, and insurance companies, all of whom are motivated to find common ground for the rare disease community, but may not all have the same incentives. Over the past two decades, these actors have innovatively shaped the field of rare diseases, embodying the concept of institutional entrepreneurs.

According to Battilana et al. (2009), institutional entrepreneurs are essential in changing institutions and implementing multiple mechanisms of change. Particularly, these actors can challenge established norms and practices, create a sense of urgency for change, create new institutions that better serve their needs or the needs of society, or change the core characteristics of existing institutions to better serve all actors involved (Battilana et al., 2009; Yildirim et al., 2022). This ability to challenge and adapt institutional norms is especially relevant in the field of orphan drug policy, where the typical economic logic of the market does not apply (Horgan et al., 2022; Simoens, 2011). Thus, institutional entrepreneurs play a critical role in this field, driving policy and institutional changes that enable more effective responses to the complexities of rare disease treatment.

Building on the existing literature on institutional entrepreneurship, this master's thesis seeks to explore this phenomenon specifically in the context of Dutch orphan drug policy. While previous research has provided valuable insights into the role of institutional entrepreneurs in other sectors, there is a lack of knowledge about their influence on rare disease health policy in the Dutch context. Related literature on institutional entrepreneurs specifically in the Netherlands includes institutional entrepreneurs in the platform economy (Pelzer et al., 2019), policy entrepreneurs in transformative smart mobility (Gironés et al., 2020), sustainable entrepreneurs in the biomass industry (Thompson et al., 2015), and institutional entrepreneurs in the context of temporary work in the labor market industry (Koene & Ansari, 2013). Furthermore, the Netherlands were mentioned several times in the literature on institutional entrepreneurs in the health sector, such as institutional entrepreneurs in health reform (Tuohy, 2012) and institutional entrepreneurs in health education (Varpio, 2017). However, the Netherlands has not been the focus of the latter studies. Therefore, this master's thesis is a contribution to this literature through an in-depth examination of the role of institutional entrepreneurs in relation to rare diseases in the Dutch healthcare system over the past two decades. The dynamics of institutional change are likely to be different in this unique context, given the specific challenges posed by rare diseases and orphan drugs. Moreover, the pharmaceutical industry and the health sector in general is highly institutionalized and regulated, meaning it has well-established pathways for innovation (Douglas et al., 2022). Therefore, research on the role of institutional entrepreneurs in this highly regulated sector and in the specific context of orphan drugs in the Netherlands could provide new insights into institutional change and potentially offer innovative solutions to the universal problem of access and affordability of rare disease treatments.

1.1 Research question

The proposed research question of this master's thesis is as follows: "*What has been the role of institutional entrepreneurs in the orphan drug policy field in the Netherlands between 2000-2023?*"

A qualitative grounded theory approach was used to address this research question. First, by conducting a literature review, 18 orphan drug regulations, 39 news articles, and seven interviews from 2012 were analyzed. In addition, six semi-structured interviews were conducted with experts involved in the institutional change processes.

1.2 Societal and scientific relevance

This research sheds light on the mechanisms through which access to orphan drugs has been expanded, thereby improving the lives of rare disease patients. Understanding these processes can also guide future policy decisions and institutional adaptations to further improve healthcare for these patients. From a theoretical perspective, this study contributes to the existing literature by exploring the role of institutional entrepreneurs in the context of orphan drug policy in the Netherlands. Despite a rich literature on institutional entrepreneurship, the specificities of orphan drug policy present unique challenges and opportunities that can deepen our understanding of institutional entrepreneurship in the health sector.

This thesis consists of four main sections. First, the theory section explores institutional theory with a focus on institutional entrepreneurs. Second, the methods section describes a qualitative literature review, policy document and media analyses, and expert interviews. Third, the findings section provides an in-depth history of orphan drug policy in the Netherlands and the dynamics of this institutional landscape. Finally, the conclusion and discussion section synthesizes the findings, evaluates the effectiveness of the policy, suggests reasons for changes in the landscape, and discusses implications for innovation scholars and relevant actors.

2. Theory

2.1 Institutional theory

The foundations of institutional theory were developed by Meyer and Rowan (1977), who emphasized the profound influence of broader institutional forces, such as norms, values, and unquestioned beliefs, on organizations. Extending this understanding, DiMaggio and Powell (1983) described institutions as the accepted patterns of behavior that regulate social relationships and dictate acceptable and legitimate actions in particular contexts. This view underscores the role of institutions in determining the behavior of actors within a given field and highlights the process by which organizations conform to prevailing norms and practices.

In addition, Geels (2004), building on the work of DiMaggio and Powell, further developed the concept of institutions by conceptualizing them as formal and informal rules, norms, and decision-making routines that shape the functioning of a system or society. Scott (2013) further contributed to this perspective by conceptualizing institutions as a mix of informal rules (such as norms, values, and mental frameworks) and formal rules (such as laws, regulations, and technical standards) that coordinate and structure activities. This study adopts the perspective developed by DiMaggio and Powell (1983), which emphasizes the role of institutions in determining behavior and the process by which organizations conform to prevailing norms and practices, combined with Scott's (2013) perspective on the formal and informal rules that shape institutions, while focusing on the transformative role of institutional entrepreneurs as outlined by Battilana et al. (2009).

2.2 Institutional entrepreneurs

Despite their essential function in maintaining organizational structure and promoting efficiency, institutions can have a homogenizing influence that, while beneficial in certain contexts, can potentially hamper innovation (Battilana et al., 2009). The authors suggest that actors can initiate change within these institutional systems. These actors can be individuals or organizations (Hoogstraaten et al., 2020). Battilana et al. (2009) highlight the role of key actors in institutional change as institutional entrepreneurs. These are actors that introduce new ideas, practices, or norms into existing institutional contexts, driven by an ambition to effectualize change.

To be classified as an institutional entrepreneur, actors must initiate changes that disrupt the institutional status quo and actively participate in the implementation of these changes (Battilana et al., 2009). Moreover, institutional entrepreneurs play a critical role in the implementation of the following three mechanisms of change. First, they can create disruption by challenging established norms and fostering a sense of urgency about the need for change. This can be done by stimulating public discourse about the inadequacies of existing institutions or by engaging in acts of civil disobedience that draw attention to the need for change. Second, institutional entrepreneurs can also create new institutions that better meet their demands or address unmet societal needs. This may involve designing new policies, creating new organizations, or formulating new norms as alternatives to existing institutions. Finally, institutional entrepreneurs can initiate change within existing institutions by modifying their core features to better meet the needs of all actors involved. This can be achieved by proposing new policies or working with key actors to change existing practices (Battilana et al., 2009).

Furthermore, Battilana et al. (2009) identify two conditions that enable institutional change: enabling field characteristics and a high social status of the actor. Enabling field characteristics refer to certain conditions in the institutional environment that make it receptive for change. These conditions often occur as shocks or jolts to the status quo, such as major crises or significant policy changes, which disrupt the established equilibrium and open up windows of opportunity for change. A high degree of heterogeneity in the field is another enabling characteristic, as the presence of diverse perspectives, values, and practices can catalyze discussions and debates that lead to shifts in prevailing norms. Finally, a low level of institutionalization is essential. This means that the rules and norms governing the field are relatively fluid, undefined, or contested, making it easier for actors to challenge them and bring about change.

The social status of the actor is the second condition identified for institutional change. On the one hand, high-status actors play a central role in the institutional field, making their potential influence great (Battilana et al., 2009; Hoogstraaten et al., 2020). However, because these actors can be invested in the current system, they are less likely to initiate or pursue change. Low-status actors, on the other hand, can afford to take risks and challenge the existing institutional regime without fear of significant negative consequences since they “are, generally speaking, less sanctioned when deviating from institutions” (Hoogstraaten et al., 2020. p. 116).

They can become catalysts of institutional innovation, often working from the periphery to the center. This perspective underscores the importance of understanding the position of the institutional entrepreneur within the field, and its implications for the dynamics of institutional change.

2.2.1 Institutional entrepreneurs in healthcare systems

Lockett et al. (2012) demonstrate how institutional entrepreneurs are at the forefront of advocating for new practices and ideas in the healthcare landscape, challenging the status quo and often trying to bring about healthcare reform through their actions. However, they show that the subject position, or "all socially constructed and legitimated identities available in a field" (p. 357), determines their capacity in effecting institutional change. In line with Hoogstraaten et al. (2020), Lockett et al. (2012) argue that institutional entrepreneurs vary potential to drive change depending on their social status within the field. On the one hand, institutional entrepreneurs at the center of the field, with high social status, are often well positioned within the status quo and tend to reinforce their existing positions rather than drive substantive change, as their position privileges them within the current institutional arrangements. On the other hand, institutional entrepreneurs at the periphery, with lower social status, are more likely to seek radical change, aiming to redistribute power and resources and develop innovative ways of working. However, while the social status of institutional entrepreneurs in healthcare is acknowledged by Lockett et al. (2012), the characteristics of the field are neglected.

While Lockett et al. (2012) focus on individual institutional entrepreneurs, Breton et al. (2014) and Hoogstraaten et al. (2020) suggest that healthcare organizations themselves can also serve as institutional entrepreneurs. Breton et al. (2014) suggest that healthcare actors, as collective entities, can use their resources, networks, and legitimacy to disrupt, create, or transform existing structures. Moreover, the authors emphasize the critical need to initiate collective action with influential actors in the field in order to gain sufficient legitimacy and resources to effect institutional change, underscoring the importance of institutional entrepreneurs as skilled actors. In other words, not only the social position of institutional entrepreneurs is recognized, but also the notion of a collective approach that points to institutional entrepreneur*ship*.

2.3 The field of rare diseases

2.3.1 Dutch economics and policy challenges

The economics of rare diseases presents a unique landscape in terms of pricing and policy structures, shaped by a number of intrinsic challenges that distinguish this sector from more conventional pharmaceutical markets. Simoens (2011) argues that the concept of "economic logic" explains the unique characteristics of orphan drugs, which are characterized by high prices and low volumes. The higher costs associated with orphan drugs stem from the expensive, often lengthy development process, which must be offset by the price given the relatively small market for such diseases (Horgan et al., 2022; Simoens, 2011). In addition, the pricing mechanisms themselves further complicate this landscape. According to Simoens

(2011), orphan drug prices are often set at launch and lack transparency, obscuring the true cost of development and creating ambiguity in reimbursement. From a policy perspective, this lack of economic transparency creates difficult choices for health policymakers, who must balance the need for patient access, affordability, and incentives for continued innovation in the field of rare diseases. The need for greater transparency in the pricing and reimbursement of orphan drugs therefore underpins much of the discourse in this institutional environment.

2.3.2 European pricing strategies

Widening the scope to consider the broader implications of the above findings, Huttin's (1999) research provides a valuable lens at the time of her publication, especially since this was the year that the first orphan drug regulation was developed for the EU (EMA, 2023a). Huttin (1999) found significant variation in drug pricing across the EU, influenced by a variety of factors such as health policy objectives, market size, industry strategy, and socio-economic variables. These differences can lead to accessibility problems, especially for patients in countries with stricter pricing regulations. However, Huttin (1999) offered an optimistic outlook, pointing out that a shift towards unified pricing emerged. Increased European integration, efforts towards price transparency and a growing emphasis on evidence-based pricing all point to the potential for a more harmonized and equitable approach to orphan drug pricing in the future (i.e. the future perceived in 1999). These findings therefore point to the relevance of this research, not only in the context of rare diseases and their institutional environment, but also in a broader sense as a contribution to the ongoing developments regarding pricing and access to medicines in the EU.

2.3.3 Institutional changes through Dutch policy instruments

Cohen's (2007) study sheds light on the impact of the reformed Dutch health insurance system on pharmaceutical innovation. In line with the notions of institutional entrepreneurship and institutional change, the author highlights how the system change opened the way for innovative changes in the pharmaceutical sector. In particular, the intervention of the Dutch government played a key role in fostering an environment conducive to pharmaceutical innovation. Under the new system, health insurance became mandatory and included both private and public health insurers. This change led to increased competition among insurers and, as a result, more efficient healthcare delivery. It also stimulated demand for innovative, cost-effective pharmaceutical products. Cohen (2007) therefore emphasizes how these institutional changes, enacted through the policy instruments of the Dutch government, fostered a conducive environment for pharmaceutical innovation, supporting the role of policy instruments in facilitating institutional entrepreneurship and institutional change. In this light, Cohen's (2007) findings highlight the potential for policy changes to initiate transformational change in the healthcare sector, reflecting the mechanisms of change proposed by Battilana et al. (2009). This thesis therefore continues the search for the effects and consequences of such policy-driven institutional change in the Dutch rare diseases field, focusing on the complex processes, actors and mechanisms that have shaped its development over time.

3. Methods

3.1 Research design

This study uses a qualitative grounded theory approach to understand the ways in which institutional entrepreneurs have been agents of institutional change in the healthcare sector. Grounded theory is an inductive research method that involves developing theory from data by conducting systematic and iterative data collection, analysis, and categorization (Corbin & Strauss, 1990). The constant comparison of data is used to identify patterns, concepts, and relationships that lead to the development of a theory that is grounded in the data. As part of this inductive research method, this study combines a literature review and semi-structured interviews.

3.2 Data analysis

3.2.1 Literature review

As part of the grounded theory approach, a literature review was conducted. In particular, literature review on orphan drug regulation could prove beneficial in exploring the role of institutional entrepreneurs in transforming institutions and promoting institutional change within the field of rare diseases. This is because laws, regulations and policies provide structure and predictability, motivating entrepreneurs to dedicate resources to value creation (Lucas et al., 2022). The literature review consisted of five phases that are described below.

3.2.1.1 Identification of the research question

This phase involved mapping the research area to identify key concepts and theories relevant to the research question. To this end experts were consulted in the process to ensure that the review is relevant and applicable to the area. For this study, this will particularly mean consulting my supervisor expertise. Furthermore, I actively participated in the Social Pharmaceutical Innovation Global Conference on nine and ten March 2023, where more experts were consulted. In addition, I attended a lecture given by Prof. Carla Hollak, Professor of Metabolic Diseases, who spoke at a conference on June 19, 2023, organized by the Royal Netherlands Academy of Arts and Sciences (KNAW) on the topic of academic-driven drug development, which focused on orphan drugs.

3.2.1.2 Search for gray literature and scientific studies

Gray literature was used to identify the relevant policy documents and media articles for orphan drugs in The Netherlands. 18 relevant documents, such as laws, regulations, and guidelines related to orphan drugs, were collected from the National Health Care Institute (Zorginstituut Nederland, ZN), Medicines Evaluation Board (MEB, or CBG), ZonMw, and the VWS (see Appendix F for an overview of the policy documents). The documents were analyzed to identify the developments of orphan drug regulation in The Netherlands.

Relevant media articles were consulted through the Nexis Uni, a comprehensive online news database research tool. Search criteria were: "orphan drug" OR "rare disease") AND ("policy" OR "rules" OR "law" OR "governance" OR "practice" (translated "weesgeneesmiddel" OR "zeldzame ziekte") AND ("beleid" OR "regels" OR "wet" OR "bestuur" OR "handelwijze"). Due to time limitation, in consultation with the supervisor, it was decided to shorten the time period to 10 years, meaning that news articles were selected ranging from 01/01/2012 until 31/12/2022. The search resulted in 358 news articles, after which 122 duplicates were excluded through a filter provided by Nexis Uni. The remaining 236 articles were downloaded as Microsoft Word files (.dox), analyzed by a script that I wrote in R (version 4.2.0) to extract the relevant article text, the published year, to identify possible remaining duplicates, and to further explore the data to identify preliminary patterns (see Appendix A for the complete script with a step-by-step explanation, and illustrative Figures). Through both the use of the algorithm and careful verification of actual duplicates, 51 additional news articles have been excluded.

After reading the remaining 185 news articles, it was determined whether the article was actually about the regulation of orphan drugs in the Netherlands. As a result, 39 articles remained and 146 were excluded. The 146 news articles were excluded for various reasons. The majority of these articles were not relevant to the topic as they did not mention orphan drug policy. Although some articles touched on health-related topics such as political debates, rising health costs, and the organization and financing of hospital care, they did not specifically address orphan drug policy. Several articles were personal stories or accounts of living with a rare disease or disability, fundraising efforts for research or treatment, or personal experiences with the healthcare system. While these articles provided insights into the challenges faced by people with rare diseases, they did not provide information or analysis relevant to orphan drug policy. In addition, some articles discussed pharmaceutical companies or new drugs, including pricing, mergers and acquisitions, and manufacturing, but did not explicitly discuss orphan drug policy. Finally, a few articles covered unrelated topics such as book reviews, personal interviews and stories about technology, politics or social issues, which were irrelevant to orphan drug policy.

Finally, scientific literature was consulted to search for the current debate on institutional entrepreneurs in healthcare. This includes searching databases (e.g. PubMed, Scopus, and Cochrane Library) and tracking citations. These studies included peer-reviewed journal articles, books, literature reviews that provided insights into the skills that institutional entrepreneurs use to innovate in this context.

3.2.1.3 Quality assessment

The quality of the scientific studies, policy documents, and news articles were assessed, looking at their accuracy and relevance to the research question.

3.2.1.4 Data collection

Data was extracted from scientific studies using unique extraction forms for each document or source of data. In addition, rich descriptions, and details on the application of institutional

entrepreneurs mechanisms in the healthcare industry were sought. Simultaneously, semi-structured interviews were conducted (see section 3.2.2 Semi-structured interviews). In addition to the semi-structured interviews that were conducted, this thesis also used seven interview transcripts provided by the project supervisor. These interviews covered events regarding orphan drugs in 2012, providing unique insights into the experiences and outcomes of orphan drug policy at that time. However, unlike the more recent expert interviews, these historical transcripts were not coded in the same way. Instead, they were analyzed qualitatively in order to draw out the key experiences and lessons of that particular year. This approach was chosen because the context of a key event (described in section '4.3.1 year 2012') gave the interviews a unique situational perspective that required a different approach to analysis. These transcripts thus served as supplemental data that enriched our understanding of changes and continuities in the orphan drug policy landscape over time.

3.2.1.5 Synthesis of the data

In this phase, data from the scientific studies was juxtaposed, reviewed, reconciled, consolidated, and situated. The aim was to identify the mechanisms underlying the application of institutional entrepreneurs in healthcare in the context of institutional change for orphan drugs in the Netherlands. Along with the findings resulting from the policy documents, media analysis, and semi-structured interviews, the research question was answered.

3.2.2 Semi-structured interviews

Semi-structured interviews were conducted between March and June 2023 with seven experts with several backgrounds in the field of rare diseases in the Netherlands (see Appendix B). The participants were selected using purposive and network sampling to ensure that they have relevant knowledge and experience in the areas of interest. Moreover, the supervisor of this master thesis facilitated a list of candidates directly involved, underscoring the process of both purposive and network sampling. The interviews were conducted in-person or via videoconferencing and recorded for later transcription and analysis. The interview questions were designed to elicit information on the topics provided in Appendix C.

The data analysis for the interviews was conducted using a thematic analysis approach, as outlined by Braun & Clarke (2006). This method comprises several stages, including familiarization with the data, generating initial codes, identifying themes, reviewing themes, defining, and naming themes, and producing the report. To ensure coherence and consistency in the data analysis, the generation of initial codes and the development of themes was guided by the findings of the literature review. The overarching goal of this approach was to identify patterns within the data and to develop a comprehensive understanding of the underlying meaning and significance of the data in relation to the research question. These patterns served as focal points in the eventual analysis.

The software NVIVO was employed to facilitate the organization and analysis of the data. The first step involved importing the transcribed interview transcripts into the software. I then read through the transcripts and identify themes or categories that align with the identified themes of

the literature review. These themes were coded and organized within the software. Subsequently, the coded data was reviewed, searching for patterns and relationships within and between the themes (for a hierarchical overview of themes and codes, see Appendix D). Finally, the findings were interpreted and richly described in conjunction with the gray literature, including any quotes or examples from the data that were in support of the findings.

The analysis was conducted by one researcher, but was discussed with my supervisor, peers, and interviewees to resolve any discrepancies through discussion and consensus. It is important to note that the thematic analysis approach was an iterative process, meaning that the steps are repeated and refined as necessary to ensure a thorough and complete understanding of the data, in line with the grounded theory approach. This allowed for the identification of new themes or patterns that may not have been apparent initially, and the ability to further refine existing themes to better capture the nuances of the data.

3.3 Reliability and validity

Triangulation, or the combination of multiple methods to investigate a research question, was a crucial aspect of the research design of this study, as highlighted by Creswell et al. (2011). By combining the results obtained from the literature review and semi-structured interviews, a more comprehensive understanding of the actions and processes undertaken by institutional entrepreneurs in improving access to orphan drugs for patients with rare diseases was gained. The literature review provided an overview of the existing literature on the topic, including the outcomes of various studies and the quality of the evidence. The semi-structured interviews offered additional context and insights by allowing direct perspectives and experiences from actors involved in the institutionalization of the regulations. Through the triangulation of data obtained from both the literature review and interviews, the findings were confirmed or challenged, and any discrepancies or inconsistencies were identified. This approach enhanced the validity and reliability of the results, as they were supported by multiple methods leading to multiple sources of data.

3.4 Ethical considerations

This study adhered to ethical principles under the supervision of my supervisor. Informed consent was obtained from all participants before conducting the interviews and ensured that the participants' anonymity and confidentiality were maintained throughout the study (see Appendix C, informed consent).

4. Results

This section comprises five main sections. The first section provides a brief overview of the history of global orphan drug regulation since 1983, as well as the key orphan drug regulations in the EU. The second section focuses on the period from 2000 to 2011, during which efforts were made to stimulate orphan drug development, conduct research on facilitating networks,

and raise awareness. The third section covers the period from 2012 until 2016, highlighting the growing emphasis on collaboration, the establishment of facilitative networks such as synergetic expertise centers, and the horizon scanning of medicines. The fourth section covers the period from 2017 to the first half of 2023, demonstrating a shift towards cross-border collaboration through initiatives such as European Reference Networks (ERNs) and cross-border care. The final section offers an analysis on the Dutch rare disease field by placing it in the context of institutional change, with a focus on institutional entrepreneurship. An overview of the main findings of the Dutch orphan drug policy is presented in Table 1.

4.1 Orphan Drug Regulation

4.1.1 Global Orphan Drug Regulations

Orphan drugs are medicines developed to treat diseases that are so rare that it is usually not profitable for pharmaceutical companies to produce them because of the small number of patients who would benefit from them. To encourage research and development of orphan drugs, governments have established guidelines and regulations. The United States was the first to establish such guidelines with the Orphan Drug Act in 1983, followed by Japan and Australia in 1993 and 1997 respectively (Franco, 2013). In 1999, a common orphan drug policy was introduced in all member states of the EU (Appendix F, European Parliament, 1999; EMA, 2023a).

4.1.2 Orphan Drug Regulation in the EU

Regulation (EC) No 141/2000 is commonly known as the Orphan Regulation (EMA, 2023a). It established the criteria for designating a medicinal product as an orphan drug and the incentives for research, development, and placing on the market of orphan drugs. The Regulation was adopted in 1999 and came into force in January 2000. Its main objective is to ensure that patients with rare diseases have equitable access to high quality treatment in the EU. To achieve this goal, the Orphan Regulation aims to provide incentives for pharmaceutical companies to develop and market medicinal products for the diagnosis, prevention and treatment of rare diseases, including those affecting children. The rationale behind these incentives is to offset upfront investment costs that may not be covered by expected returns (EMA, 2023a).

Table 1: an overview of the orphan drug policies in The Netherlands, highlighting the policies implemented, media coverage, findings from policy documents, and pertinent insights gained from expert interviews.

Year	Policy Changes	Media Coverage	Policy Documents Findings	Expert Interviews Insights
1983 - 1999	World's first orphan drug policy in the US, stimulating orphan drug innovation.			Orphan drug policy lacking in the Netherlands.
2000 - 2011	Adoption of orphan drug regulation in the EU and harmonization in the Netherlands. Conditional reimbursement for high cost and rare disease drugs		Development of a national strategy by the Orphan Drug Steering Group. Building networks and improving access to orphan drugs. Guidelines and procedures for the reimbursement and administration.	Orphan drugs receive greater political attention. Growth in the number of high-cost orphan drugs. Enhancement of orphan drug development coordination.
2012 - 2016	Trial inclusion of promising orphan drugs in basic health insurance package. Publication of National plan for rare diseases by ZonMw. Introduction of stricter guidelines for orphan drugs evaluation and increased role of insurers in price negotiation. Shift towards proactive engagement with manufacturers to control costs.	Focus on high cost of orphan drugs for Pompe and Fabry diseases, and debates over ceasing reimbursement. Criticism of pharma companies for maintaining high drug prices. Political debate regarding the fight against rising cost of orphan drugs.	Policies triggered by coverage on Pompe and Fabry diseases and concerns over drug costs. ZN document emphasizes cost-effectiveness in healthcare, and introduces "Pakketbeheer Weesgeneesmiddelen". Emphasis on financial sustainability.	Influence of high-level meetings and personal interaction with patients on political decisions. Unchecked power of pharmaceutical companies highlighted. Urgent need for improved evaluation, communication, and management of orphan drugs recognized. Need for more control over orphan drug costs and a balanced approach in regulation agreed upon.

				Balancing expensive treatments with broader public health concerns required. Complexity of decision-making process in orphan drug policy highlighted.
2017 - 2023	Emphasis on real-world evidence in orphan drug evaluation. Introduction of Horizon Scan by VWS. Introduction of alternative drug production routes at AMC. Submission of the National Strategic Vision Document by patient umbrella rare diseases (VSOP). Launch of patient access pilot (ODAP), Evaluation report on conditional approval process. Progress report on conditional access programs.	Media concern over availability and affordability of orphan drugs. High-profile media coverage criticizing the high prices of orphan drugs and unethical practices by pharmaceutical companies. Media attention shifts to the new policy framework and the role of multiple involved actors. Focus on affordability and robust regulations. Coverage of Arphio launch, ODAP introduction.	Monitoring orphan drugs document series started. Strong emphasis on (cross-border) collaboration, affordability, real-word evidence, patient-centered approach, pricing transparency, and post-marketing surveillance.	High drug prices are recognized as morally reprehensible, and the importance of ongoing actor dialogue and innovative strategies is emphasized. Reimbursement mechanisms need to be more intelligent.

From 2000 to the end of 2018, the European Commission granted a total of 2,121 orphan designations under Regulation (EC) No 141/2000 (Rare2030, 2019). An orphan designation is a status granted by regulatory authorities to a drug or medical product intended to treat a rare disease or condition, providing incentives and exclusivity to encourage development in this area (EMA, 2023b). It aims to support the development of treatments for diseases that affect a small number of patients. This led to the authorization of 164 products specifically designated as orphan medicinal products (OMPs). Approximately 60% of these OMPs were for pediatric use, reflecting the effectiveness of the Regulation to address the specific health needs of children with rare diseases. The significant number of orphan designations and authorized OMPs demonstrates the positive impact on the number of orphan designations of the Regulation, as it has indeed increased the availability of treatment options for patients with rare diseases (see Figure 1).

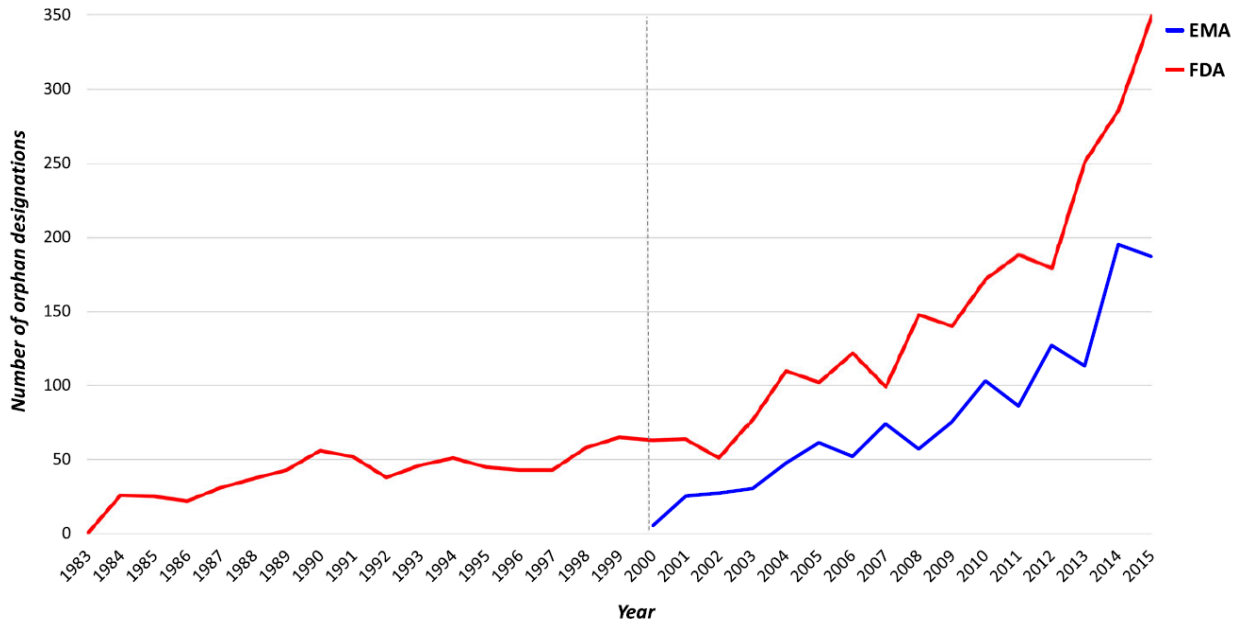

Figure 1: Orphan designations in the US (FDA) and EU (EMA) released per year (Giannuzzi et al., 2019).

4.1.3 Changes in EU Regulations

The European Commission has conducted a comprehensive review of the Orphan Regulation (EMA, 2023a). The evaluation identified both strengths and weaknesses of the regulatory framework. On the positive side, the Orphan Regulation has been successful in promoting the development of (as seen in Figure 1) and access to medicines for patients with rare diseases. It has done this by redirecting private and public investment to previously neglected areas through a variety of incentives, obligations, and rewards. As a result, the quality of life of rare disease patients has improved. However, the evaluation also highlighted some challenges. The Orphan Regulation has not adequately supported the development of medicines in areas of greatest need and has led to increased costs for healthcare systems (EMA, 2023a). As highlighted by M. Joachimsthal, pharmaceutical industry former CEO of GlaxoSmithKline Netherlands, there are two basic principles of healthcare systems in Europe, but the outcome of healthcare policies is dependent on the national level, since:

> "*In Europe, healthcare is paid for based on the principles of collectivity and solidarity. Those are two very important basic principles. (...) Negotiations take place at the country level because that is where the budget holders of those funds reside*" (Appendix B, Interview 7).

Orphan drug regulation therefore has different outcomes for each unique healthcare system, including the Netherlands, where the strong solidarity principle prevails.

4.2 Timespan 2001 - 2011: awareness of rare diseases

The Netherlands, known for their responsiveness to EU regulations and directives, often align their policies with those of Europe, as highlighted by a senior researcher of ZonMw, who stated:

> "New policies indeed have potential impact, and the Netherlands often follows Europe's lead" (Appendix B, Interview 4).

The resolution to start the 'Dutch Steering Committee Orphan Drugs' (Stuurgroep Weesgeneesmiddelen, from now on referred to as WGM) was established in the Netherlands in 2001 in response to the Orphan Regulation (Appendix F, VWS, 2004; BZK, 2002), as highlighted by a senior researcher of ZonMw, who stated:

> "*[The Orphan Regulation] has been a hugely important one for the Netherlands, because Minister Borst, then Minister of Public Health, felt that the orphan drugs should have more attention in the Netherlands and as a result she started setting up the WGM*" (Appendix B, Interview 4).

The aim of the independent WGM was to develop a national strategy for the development, evaluation, and reimbursement of orphan drugs in the Netherlands (Appendix F, IQ Healthcare, 2013). The group's mission was to identify and address the challenges in the development of and access to orphan drugs in the Netherlands. The mission was evaluated in 2004 (Appendix F, VWS, 2004), indicating that the WGM made significant strides in advancing the development and accessibility of orphan drugs within the Netherlands between 2001 and 2004.

Another key accomplishment was the enhancement of dialogue and cooperation among key actors, including regulatory bodies, insurers, and patient groups (Appendix F, IQ Healthcare, 2013). Additionally, the WGM effectively streamlined regulatory processes for orphan drugs and facilitated improved reimbursement procedures with insurance companies. This has led to an increased number of orphan drugs receiving market approval, as well as an improvement in their accessibility to patients. However, the evaluation also identified areas for further improvement. In particular, it highlighted the need for stronger efforts to address the high costs of orphan drugs, which continue to pose a barrier to patient access. Finally, the evaluation emphasized the importance of continual investment in scientific research and development to foster innovative treatments for rare diseases. The WGM received a total of two extensions from the ministry, and was discontinued in 2012 (Appendix F, IQ Healthcare, 2013), after which some of its tasks were taken over by ZonMw (in the National Plan for Rare Diseases, which was published in 2013) (Appendix F, ZonMw, 2013).

Between 2005 and 2011 orphan drug policy in the Netherlands underwent several significant changes, mainly due to the increasing number of high-cost biotechnological orphan drugs (Appendix B, Interview 4). The European Committee for Orphan Medicinal Products (COMP) and the Dutch WGM worked together to keep pace with these new products. The ZN became increasingly concerned about increasing reimbursement costs at an early stage (Appendix B, Interview 4).

During this time, there was a growing emphasis on a collaborative approach to addressing issues related to rare disease. The senior researcher of ZonMw noted that:

> *"Around 2009, the EU has paid quite a lot of attention to collective participation in rare diseases. (...) And there had to be a national plan for each country and it had to be in place by the end of 2013. So that was done in the Netherlands. With the help of the WGM" (Appendix B, Interview 4).*

The development of orphan drug policy in the Netherlands has also been partly influenced by both public and media discourse. Between 2005 and 2011, the country faced significant challenges in managing access to innovative drugs, with a prime example being the public furor over unequal access to the drug trastuzumab (Makady et al., 2019). This discrepancy led to the undesirable "ZIP code healthcare", where access to this life-saving treatment varied significantly across different regions. In response, the Netherlands Healthcare Authority (NZa) drafted two policy frameworks to support conditional financing of expensive and orphan drugs from the national healthcare insurance package.

These policy rules for orphan drugs in academic hospitals (CI-952 & CI-1061) outline the guidelines and procedures for the reimbursement and administration of these specialized drugs developed to treat rare diseases (Appendix F, NZa, 2006, 2008). The policy aims to ensure that academic hospitals can provide access to orphan drugs while maintaining efficient and cost-effective healthcare practices. However, it was not until 2012 when the orphan drug policy started gaining substantial media attention.

4.3 Timespan 2012 - 2016: transdisciplinary collaborations

The year 2012 marked a turning point in the Dutch orphan drug policy landscape, with media coverage focusing on the escalating cost of orphan drugs and the contentious discussions on ceasing reimbursement for such high-cost drugs, particularly for rare lysosomal storage disorders like Pompe and Fabry (Appendix B, Interview 2-13; Appendix E, Article 33, 36). In fact, over the summer, an advisory document was leaked advising the VWS not to reimburse treatments for these rare diseases because the prices were too high. This was then highlighted in the media with personal stories from patients. For example, former CEO GlaxoSmithKline Netherlands and a senior researcher of ZonMw underlined that:

> *"(...) developed treatments for Pompe and Fabry [that were produced by big pharma], once they were registered, [ZN] advised against not reimbursing them. It was at that time that the patients were mobilized in the Binnenhof"* (Appendix B, Interview 6).

> "*We have also seen on occasion that it helped if someone in a wheelchair sat down at a gathering, so to speak. And that was high level, then the minister almost felt obliged to say hello to a person in a wheelchair*" (Appendix B, Interview 4).

This attention was further fueled by the personal stories of patients' struggles, suggesting a move toward a more personal- and patient-oriented orientation, as highlighted by senior researcher of ZonMw:

> *"You also have to realize that the whole media, and I did see that change in 20 years, (...) has obviously become enormously, at all, enormously more personal. You see that in newspapers. You see that on TV"* (Appendix B, Interview 4).

The Pompe and Fabry event shed light on the quandary of drug pricing and the importance of quality-adjusted life years (QALYs) in evaluating treatment value (Appendix E, Article 11, 12). More specifically, the increased media spotlight on Pompe and Fabry diseases in the Netherlands amplified concerns over the exorbitant cost of orphan drugs, igniting a public and political debate on pharmaceutical pricing strategies. Consequently, this led to policy shifts, such as the decision of VWS to include the therapies for Pompe and Fabry diseases in the basic health insurance package, and the implementation of trial inclusion of promising orphan drugs in the basic health insurance package for efficacy analysis, as well as enhancing discussions on affordability, accessibility, and transparency of pharmaceutical manufacturers within the Dutch orphan drug policy framework. This was highlighted by the a senior advisor of ZN, who stated that:

> *"It came after Pompe and Fabry in 2012. Then the minister started negotiating the price, so that did affect accessibility. It takes longer because of that price negotiation, but then again, [ZN states] that if the manufacturer asks a fair price, then the price negotiation is not necessary and then it can go very quickly"* (Appendix B, Interview 2).

In addition, interviews with involved actors that were involved in the Pompe and Fabry events, highlighted the complexity of the decision-making process and the need for improvement. (Appendix B, Interview 8-13). There was a recognized need to implement decision standardization and improved communication strategies, especially given the influence of patient narratives and public pressure. Balancing the collective and individual interests of patients, particularly in the context of cost-effectiveness, was a recurring theme. The role of the media was important in shaping public opinion and perceptions, with calls for more inclusive processes that consider real patient experiences. There was criticism of a perceived soft approach to presenting evidence, downplaying conclusions, and a lack of clear context for decisions, suggesting the need for stronger, moral and evidence-based approaches. The year also saw a push for broader societal discussions about the value of life, healthcare spending, and the controversial removal of some drugs from reimbursement (Appendix B, Interview 8-13).

Nevertheless, in 2013, pharma company Genzyme took full advantage of the Orphan Regulation to secure unprecedented margins. According to H. Termeer & H. Schikan, the orphan drug policy was being exploited, as they argue that:

> "*Now you often have a company that has the monopoly thanks to a patent with people who need the drug against it. That is a classic basis for exploitation*" (Appendix E, Article 7).

There was growing opposition to the financial interests of these companies, as evidenced by media coverage of Big Pharma's exploitation of the orphan drug regulation. Simultaneously, a major document was published by ZN in 2013 that focused on the concept of cost-effectiveness within the healthcare sector (VWS, 2013). Notably, the report discusses the increased scrutiny regarding the cost-effectiveness of various therapeutic interventions, including orphan drugs. This signifies a shift from focusing solely on clinical effectiveness to incorporating economic evaluations. The report reflects a nuanced approach towards orphan drug policy, balancing cost-effectiveness with equity considerations. Health equity was of particular relevance to orphan drugs, given their role in addressing the needs of patients with rare diseases who have limited treatment options (VWS, 2013). This may suggest an evolution towards a more comprehensive, economic orientated, and tailored approach in orphan drug regulation in the Netherlands.

Furthermore, The Nationaal Plan Zeldzame Ziekten (National Plan for Rare Diseases, or NPZZ) was developed by ZonMw to improve care and treatment for patients with rare diseases in the Netherlands (Appendix F, ZonMw, 2013). The plan highlights the challenges of rare diseases and proposes a multi-actor approach to address them. It serves as a roadmap for a more patient-centered approach and suggests potential shifts in orphan drug policy, including promoting research and development of orphan drugs, advocating for integrated care models, encouraging collaboration among involved actors, and emphasizing the role of patient advocacy groups in shaping policy and decision-making processes. These changes could lead to greater inclusivity, collaboration, and patient focus in orphan drug policy (Appendix F, ZonMw, 2013).

By 2015, renewed criticism in the media was directed at pharmaceutical companies, such as Alexion, which used these regulations to maintain exorbitant prices for essential medicines such as Soliris (Appendix E, Article 9). However, the impact of expensive drug policies, including some orphan drugs, was being reassessed since 2013. Since then, ZN started drafting the Pakketbeheer Weesgeneesmiddelen document, which was eventually published in 2015, in response to growing concerns about the regulation of orphan drugs. This was largely in response to the public outcry and media attention surrounding certain cases in 2012, particularly those involving treatments for Pompe and Fabry diseases (Appendix B, Interview 2). ZN recognized the need for stricter guidelines in the evaluation of orphan drugs to ensure cost-effectiveness and fairness compared to treatments for more common diseases (Appendix F, Zorginstituut Nederland, 2013). This led to a more systematic evaluation of these drugs, including aspects such as cost-effectiveness, rather than relying solely on assumptions. As a result, insurers also began to play a more active role in evaluating where and how these drugs should be used, and even began to negotiate prices. The document is therefore not only a response to government mandates, but was also driven by an internal desire to improve the evaluation and management of orphan drugs through novel collaborations (Appendix F, Zorginstituut Nederland, 2013).

The package management orphan drugs document provides an in-depth examination of the healthcare package management of orphan drugs, highlighting the complexities and difficulties related to the cost, accessibility, and evaluation of these drugs (Appendix F, Zorginstituut Nederland, 2015). It identifies substantial revisions in orphan drug policy aimed at increasing transparency, accountability, and patient participation, while monitoring the financial implications of orphan drug distribution. It emphasizes a rigorous evaluation of the costs of orphan drugs, signaling a policy shift towards more open and rigorous cost evaluations that could potentially impact pricing and reimbursement. The introduction of conditional reimbursement, where approval is dependent on certain conditions being met, represents a significant shift in policy. The document also emphasizes the need for initial and ongoing interaction with drug developers throughout the development and approval phases, potentially promoting more predictable and efficient approval processes. A proposal for increased post-marketing surveillance to continuously monitor efficacy and cost-effectiveness suggests a move towards continuous evaluation and potential reassessment of approval and reimbursement decisions based on post-marketing data. It also emphasizes the need for increased collaboration among actors, including patients, healthcare providers, drug developers and regulators, in the decision-making process (Appendix F, Zorginstituut Nederland, 2015).

The report of the 8th council of the CBG provided a comprehensive overview of a meeting of the Advisory Board of the CBG (Appendix F, CBG, 2015). It outlined the main points of discussion, decisions, and future recommendations on various facets of drug regulation, with a focus on orphan drugs. The report suggested a continued evolution of the Dutch orphan drug policy towards a more patient-centered, evidence-based and collaborative approach, characterized by efforts to broaden access, involve actors and improve the thorough evaluation and surveillance of orphan drugs. Moreover, the document emphasized the need for careful evaluation of orphan drugs and their unique challenges, illustrating a growing focus on specialized evaluation criteria (Appendix F, CBG, 2015). A strong call for improved patient access to orphan drugs reflects a policy shift aimed at increasing availability and reducing barriers to access for patients. The CBG considered the promotion of research and development in the field of orphan drugs, indicating an increased interest in promoting innovation and drug discovery for rare diseases (Appendix F, CBG, 2015). Furthermore, the importance of early actor engagement was highlighted, including with pharmaceutical manufacturers and patient advocacy groups, in the drug development and regulatory process, indicating a renewed emphasis on collaboration. In line with previous policy shifts, there was also an emphasis on rigorous post-marketing surveillance for orphan drugs reaffirms an ongoing commitment to monitor the real-world performance of these drugs (Appendix F, CBG, 2015).

Finally, a major step in terms of national collaboration was taken by the Dutch Minister of Health, Welfare and Sport, that recognized centers of expertise for rare diseases for the first time, making it more visible where patients and their healthcare providers can find knowledge and expertise about their conditions (Appendix B, Interview 4). A senior researcher of ZonMw stated that:

> "*Now there are roughly 350 Dutch centers of expertise around rare disease in the Netherlands, and the reason that that was done was, on the one hand, the request of a working group of the WGM, but on the other hand, Europe also wanted it, as a kind of pilot of the European Union*" (Appendix B, Interview 4).

In 2016, the media showed that the Dutch Minister Schippers took center stage in the fight against the rising cost of orphan drugs (Appendix E, Article 6) Accordingly, the financial evaluation document was published, which provided an analysis of the financial impact of orphan drug provisions and reinforces the need for a balanced approach in the area of orphan drug regulation (Appendix F, Zorginstituut Nederland, 2016). The document acknowledged the financial challenges posed by orphan drugs and advocates for policy changes that balance accessibility, cost-effectiveness, and financial sustainability. It presented an in-depth exploration of the fiscal implications of orphan drug regulation, demonstrating an increased focus on financial sustainability within orphan drug policy. It also proposed a periodic reassessment of reimbursement conditions, highlighting the need for regular review and adjustment of reimbursement conditions, considering new evidence and fiscal assessments (Appendix F, Zorginstituut Nederland, 2016).

A key part of the document highlighted the importance of price negotiations with pharmaceutical companies (Appendix F, Zorginstituut Nederland, 2016). This marks a shift in orphan drug policy towards a more proactive engagement with manufacturers to control the increased costs associated with orphan drugs. In addition, the document advocated for increased transparency in orphan drug pricing, which could have potentially influenced the way pricing is formulated and communicated in the orphan drug sector. Finally, the document reiterated the importance of cost-effectiveness assessments in the approval and reimbursement processes for orphan drugs (Appendix F, Zorginstituut Nederland, 2016). This reaffirmation reinforces the trend towards incorporating economic evaluations into orphan drug regulation to ensure that the most effective treatments are financially viable and accessible to patients.

4.4 Timespan 2017 - 2023: cross-border collaborations

The following year, 2017, saw increased media concern about the availability and affordability of orphan drugs (Appendix E, Articles 21, 17). Patients with rare diseases such as pulmonary hypertension also called for more research and awareness. Furthermore, an alternative opportunity has been described to expedite access for patients through the "less-medicine-method". In this method, a specialist physician administers less medication to the patient, contrary to pharmaceutical guidelines, but in a safe manner. The principles of this method were explained by a professor at RadboudUMC, who argued that:

> "*While the drug was very expensive, the pharmacist also said: if you have to start the drug, you have to give it for life. (...) [In our research we showed that it was possible to give it for] 3 months instead of for life* (Appendix B, Interview 3).

In light of these developments, it was once again clear that there was an urgent need for continued dialogue and innovative strategies in orphan drug policy to address the growing

concerns about the availability, affordability and appropriate use of these vital treatments, thereby ensuring that the needs of rare disease patients were met in an economically sustainable manner. Therefore, starting this year, ZN has issued annual publications to monitor orphan drugs in practice (Appendix F, Zorginstituut Nederland, 2017-2021). The first review document of 2017 highlighted the increasing importance of real-world evidence (RWE) in the evaluation of orphan drugs, suggesting a shift towards more evidence-based regulation. It also highlighted the challenges of high prices and the need for improved patient access, indicating a policy direction aimed at improving the affordability and accessibility of these drugs (Appendix F, Zorginstituut Nederland, 2017). Moreover, the document called for increased collaboration between different key actors, including regulators, healthcare providers, pharmaceutical companies, and patient advocacy groups. It reaffirmed the importance of ongoing monitoring of the safety, efficacy, and cost-effectiveness of orphan drugs in real-world settings. It also emphasized the need to stimulate innovation in the development of orphan drugs, in line with a consistent policy focus on facilitating new treatments for rare diseases (Appendix F, Zorginstituut Nederland, 2017).

In addition to the annual monitoring documents, an assessment tool called Horizon Scan was introduced by VWS at the end of 2016 (Zorginstituut Nederland, 2017). This strategic tool was created to forecast and manage the uptake and pricing of innovative and, in particular, high-cost medicines. The initiative was driven by the need for a comprehensive, objective and publicly accessible overview of the likely trends of high-cost medicines in the Dutch market. The Horizon Scan was developed in recognition of its value to healthcare providers, pharmacists, insurers, and the government - all actors who need to prepare for the procurement of these medicines. It provides regular updates on the expected market entry of new high-cost medicines, the expected expansion of indications for such medicines, and the imminent generic entry of patent-protected, high-cost medicines. This proactive measure helps identify potential financial risks and determine which medicines may require financial arrangements. As of January 1, 2017, ZN took over the management and further development of the Horizon Scan (Zorginstituut Nederland, 2017). The Horizon Scan was a crucial step towards policy making based on prevention, enabling actors to effectively plan and manage the introduction and pricing of high-cost orphan drugs.

Finally, a major step in European collaboration was the establishment of the ERNs. ERNs are virtual networks of reference centers across Europe that aim to address complex or rare diseases and conditions that require highly specialized treatment and concentrated knowledge and resources (European Commission, 2017). ERN coordinators organized virtual meetings using a specialized computer system and telemedicine tools. These meetings brought together medical specialists from different disciplines to discuss a patient's diagnosis and treatment. This allows medical expertise to be shared among specialists without requiring patients to travel. Instead, patients can stay in the comfort of their own homes while receiving support. The first 24 ERNs were launched in March 2017, involving more than 900 highly specialized healthcare units from over 300 hospitals in 26 member states (European Commission, 2017). In addition, a senior researcher of ZonMW indicated a strong commitment of Dutch experts in the field of rare diseases:

> "Out of the 24 European Reference Networks, seven ended up being coordinated by the Dutch" (Appendix B, Interview 4).

The year 2018 saw significant progress regarding the battle against high orphan drug prices. According to Prof. Dr. C. Hollak, the course of action by pharmaceutical companies who designate existing drugs as orphan drugs to obtain higher profits were:

> "*(...) legal, but in my view morally reprehensible*" (Appendix E, Article 5).

Responding to the increasing trend by pharmaceutical companies, alternative routes were developed by the Amsterdam UMC, location AMC.

> "*AMC [that] makes the drug according to a 'magistral preparation': it is made separately for each patient. In the Netherlands, there are around sixty*" (Appendix E, Article 5).

Hollak, professor and academy medal award winner for her research and commitment to benefit society, is employed at Amsterdam UMC. Together with hospital pharmacist Marleen Kemper and other colleagues, she started producing affordable versions of expensive drugs, such as CDCA for CTX, using alternative methods to control prices. These initiatives have been prominent in the media this year, even though they actually launched the initiative in 2017 (Het Parool, 2018; Medicijn voor de Maatschappij, 2023).

In addition, there has been a critical examination of how orphan drugs contribute to maintaining high prices through practices such as evergreening (Appendix E, Article 10). In this news article, comments are made about strategies employed by pharmaceutical companies.

> "*a standard patent [that] runs for 20 years, but pharma companies always come up with a gimmick to extend the patent on the drug*" (Appendix E, Article 10).

Evergreening, as defined by Hemphill & Sampat (2012), refers to the strategic practice employed by pharmaceutical companies to extend the exclusivity and profitability of their existing patented drugs. It involves making incremental changes or improvements to an existing drug and obtaining additional patents for these changes. By doing so, pharmaceutical companies can effectively extend their monopoly rights and delay the entry of generic competitors into the market (Hemphill & Sampat, 2012).

Furthermore, another document to monitor orphan drugs in practice was published (Appendix F, Zorginstituut Nederland, 2018). Compared to the previous year, this document placed a stronger emphasis on several key areas. It continued to prioritize the use of RWE for evaluating orphan drugs, reinforcing the importance of monitoring real-world outcomes alongside clinical trial data. It also underscored the need for affordable access to orphan drugs, expressing concerns about high prices and advocating for policies to ensure affordability. Furthermore, this year's document promoted cross-border collaboration for research and evaluation of orphan drugs, indicating a renewed EU regulation similarity to last year's ERNs document. It also highlighted the need for greater transparency in pricing, and reiterates the call for robust post-marketing surveillance

(Appendix F, Zorginstituut Nederland, 2018). These changes indicate an evolving policy landscape with a focus on RWE, accessibility, international collaboration, pricing transparency, and ongoing monitoring.

In 2019, the political focus shifted to accessibility and affordability of medicines. Prof. Dr. Hollak and her colleagues at Amsterdam UMC received a grant for their exceptional work on alternative routes for orphan drugs to patients (Appendix E, Article 2). The purpose of the grant from VriendenLoterij was to stimulate research into making orphan drugs accessible.

> "*[Our efforts] led to us getting a grant through the lottery. Actually a grant to create a platform 'Medicine for Society' [with] an important goal, and that is to improve accessibility to medicines for rare diseases"* (Appendix B, Interview 7).

'Medicine for Society' (Medicijn voor de Maatschappij) is an online platform focused on providing affordable medicines for rare diseases and ensuring their continued availability (Medicijn voor de Maatschappij, 2023). The platform facilitates knowledge sharing and collaboration, while also carrying out projects to ensure long-term access to specific medicines for patients. In addition, they are engaged in research related to the laws and regulations governing orphan drugs (Medicijn voor de Maatschappij, 2023).

Meanwhile, a policy brief was published, where Minister Bruins of the VWS, describes how he is implementing the conditional approval of medicines in the basic package (Appendix F, VWS, 2019). This policy brief discusses a new policy framework, highlighting a move towards a more flexible, evidence-based regulatory approach. This framework could potentially facilitate earlier patient access to these drugs while ongoing data on their efficacy and safety are collected. The document emphasizes the importance of affordability and proposes linking conditional approvals to pricing agreements with drug manufacturers, indicating a shift towards more proactive pricing regulation. It also emphasizes the need for continued data collection, particularly RWE. Increased actor engagement is encouraged, indicating a trend towards a more inclusive decision-making process. Finally, the policy framework emphasizes the critical role of robust post-marketing surveillance in the conditional approval process (Appendix F, VWS, 2019).

While there has been repeated criticism in the media of high orphan drug prices and evergreening strategies by pharma companies (Appendix E, Articles 8, 14, 19, 24), attention has also been paid to the new framework implemented by the ministry (Appendix E, Articles 12, 26). The 12th news article stated that:

> "*[some promising drugs for rare diseases temporarily enter the basic package and] during this period, effectiveness and efficiency are tested. If the test turns out positive, they stay. The manufacturer must apply for and fund the study. The cost of the drug comes out of the basic health insurance package. The government requires the manufacturer to contact researchers before the test. Patient associations must also be involved*" (Appendix E, Article 12).

Both the new framework and the news article about it address a new multi-actor approach that requires collaboration between pharmaceutical companies, researchers, patient groups,

government, and health insurers to ensure that medicines are not only effective but also meet the needs of patients.

The orphan drug monitor report continued to emphasize the integration of RWE into the regulatory and reimbursement decision-making process, highlighting the importance of RWE in the evaluation of orphan drugs (Appendix F, Zorginstituut Nederland, 2019). It also re-emphasized the need for affordability, maintaining the push for affordable orphan drugs to ensure patient access. With regard to international collaboration, the report proposed greater recognition of the benefits of combining resources, knowledge, and efforts across borders to advance orphan drug research and regulation. The report also continued to advocate for greater transparency in the pricing of orphan drugs, reaffirming the commitment to more transparent and accountable pricing mechanisms. Similarly, it reaffirmed the role of robust post-marketing surveillance in monitoring the real-world performance of orphan drugs, reinforcing the policy commitment to ongoing safety, efficacy, and cost-effectiveness assessments. Finally, the report introduced a renewed emphasis on a patient-centered approach to orphan drug policy, potentially signaling a policy shift towards more active inclusion of patient perspectives in decision-making processes (Appendix F, Zorginstituut Nederland, 2019).

The media focus on affordable alternatives and robust regulations continued in 2020, where the effectiveness of orphan drug policies came under scrutiny. The limitations of EU regulations became apparent by statements such as:

> *"It now appears that the rules are only partially successful in getting drugs to rare disease patients. Of the 131 orphan drugs approved under the scheme, an evaluation estimates that the regulation is crucial in 20 percent of cases"* (Appendix E, Article 20).

This news article reflected the EU evaluation of Regulations (EC) No 1901/2006 and No 141/2000, which revealed that the orphan drug policy has successfully stimulated the development of treatments for rare diseases, benefiting patients with limited options (European Commission, 2020). The evaluation highlighted the importance of a harmonized regulatory framework in Europe for the efficient development of pediatric and orphan drugs, while acknowledging challenges such as high costs and the need for continuous safety monitoring.

The annual document on the monitoring of orphan drugs highlighted a number of aspects (Appendix F, Zorginstituut Nederland, 2020). First, there was continued emphasis on the importance of RWE in the evaluation of orphan drugs, reflecting the ongoing policy trend to incorporate RWE into decision-making processes. Affordability and patient access remained key concerns, with the report highlighting the need for affordable orphan drugs to ensure patient access. There was also a focus on increased international collaboration in orphan drug research and regulation, emphasizing the importance of multinational collaboration. The report also called for greater transparency in the pricing of orphan drugs, potentially influencing future policy directions. Robust post-marketing surveillance was reaffirmed as a priority, demonstrating the commitment to continuous evaluation of the safety, efficacy, and cost-effectiveness of orphan drugs. Finally, the report reaffirmed the shift towards a patient-centered approach, promoting the

integration of patient perspectives in the decision-making process (Appendix F, Zorginstituut Nederland, 2020).

In 2021, pharmaceutical companies' high prices and monopolistic tendencies came under renewed scrutiny (Appendix E, Articles 16, 22). Furthermore, the annual update on the monitoring of orphan drugs remains the same as in the previous year, as the same points are discussed, but new orphan drugs are discussed and updates on existing orphan drugs are provided (Appendix F, Zorginstituut Nederland, 2021). While more orphan drugs are becoming available, the costs of orphan drugs have risen significantly without clear evidence of their benefits in the Dutch healthcare system. The report highlights the need for data collection, evaluation, and structural funding, as well as transparency in pricing, while also identifying future areas of focus such as evaluating pilot programs and understanding the role of expertise centers (Appendix F, Zorginstituut Nederland, 2021).

Finally, as a sequel to the NPZZ 2013, a National Strategic Vision Document was submitted by the national patient alliance for rare and genetic diseases (VSOP), the national patient alliance for rare and genetic diseases in The Netherlands, to the VWS (VSOP, 2021). The vision document provides an overview of the current state of orphan drug policy and identifies key limitations, such as issues related to funding, pricing, accessibility of treatments and the predominant focus on individual diseases rather than a holistic approach. It calls for new financing mechanisms and pricing strategies to alleviate the burden of high costs, improved access to specialized care and treatment through improved care networks and information provision, and strengthened research and development initiatives, including greater coordination at national and international levels. The vision document also recommends active patient involvement in policy development to ensure a patient-centered approach, and the development of innovative strategies such as group purchasing and transparent pricing to improve the accessibility and affordability of orphan drugs. The vision document reiterates the need for collaboration by advocating for a more coordinated approach at national and international levels to accelerate the development of new and effective treatments for rare diseases. It also emphasizes the importance of inclusive collaboration, involving patients and their families, healthcare providers, researchers, and policy makers, to ensure effective and patient-centered solutions for the treatment and care of rare diseases (VSOP, 2021).

In 2022, the media highlighted the launch of Arphio, a global company solely dedicated to improving access to essential orphan drugs (Appendix E, Article 3). Furthermore, the Dutch pilot Orphan Drug Access Protocol (ODAP) was introduced as a novel approach to accelerate patient access to these drugs (Amsterdam UMC, 2022; Appendix E, Article 29). ODAP was a new, controlled access pathway being explored by healthcare providers, patient organizations, health insurers and the ZN to accelerate access to promising but expensive orphan drugs for rare non-oncological diseases in the Netherlands (Medicijn voor de Maatschappij, 2022). The goal of the pilot phase is to make a few selected non-oncology orphan drugs available to patients more quickly and at a socially acceptable price, while evaluating their efficacy in real-world practice (Medicijn voor de Maatschappij, 2022). This approach was novel because it involves a collaboration between manufacturers, healthcare providers, patient organizations,

health insurers and the ZN to explore a new access pathway for orphan drugs to ensure earlier availability, reasonable pricing and appropriate use while collecting additional data on efficacy and outcomes. In other words, the pilot was a step toward appropriate care, as argued by Prof. Dr. C. Hollak, who points out that:

> "[she] *really believe[s] that we can improve the quality of care, we can realize the cost savings, and we can lower the cost of healthcare if we apply a much more appropriate use of care. But then it has to be enabled, and an ODAP pathway is a tiny example of that, and it is just beginning, it is still a pilot*" (Appendix B, Interview 7).

Furthermore, the first evaluation report on the conditional approval process for orphan drugs in the Netherlands, published by the ZN, highlighted the commitment to principles such as affordability, accessibility, RWE, equitable pricing, post-marketing surveillance and actor engagement (Appendix F, Zorginstituut Nederland, 2022). The report emphasized the importance of continuous evaluation and improvement of regulatory processes and the importance of affordability, accessibility, and RWE in the policy framework. It also recognized the need for price negotiations that promote fairness and efficiency. In addition, the report underscored the commitment to post-marketing surveillance to monitor safety, efficacy, and cost-effectiveness, while emphasizing the involvement of various actors, including patients, in the decision-making process. In the report, ZN advised the Minister of VWS to evaluate the conditional admission procedure every 2 years (Appendix F, Zorginstituut Nederland, 2022).

While the latter evaluation report regarding conditional approval was more strategically oriented by setting out broader principles (Appendix F, Zorginstituut Nederland, 2022), the progress report that was published 2023 was more practical and provided a specific update on the implementation and progress of conditional access programs (Appendix F, Zorginstituut Nederland, 2023). This year's report included details on the first programs that were initiated and the specific drugs involved (Appendix F, Zorginstituut Nederland, 2023). Furthermore, 2023 saw a significant legal challenge against the big pharma company Abbvie by Stichting Farma ter Verantwoording, accusing them of profiting from the high price of Humira, reinforcing the narrative of ethical and legal battles against pharmaceutical companies (Appendix E, Article 1).

Finally, a letter from the Minister to the House of Representatives showed that the Netherlands has over many years implemented robust measures to ensure access to innovative orphan drugs by establishing a rigorous evaluation and reimbursement framework focused on efficacy, cost-effectiveness, and appropriate use (VWS, 2023). Despite different processes for extramural and intramural drugs to improve efficiency and transparency, the average review time for extramural drugs was reduced in the past years. Intramural drugs underwent a two-part process: a sluis (lock) for high-cost drugs, and an open instroom (open flow) for others. Efforts were underway to improve the efficiency and transparency of these processes, including an information dashboard for the lock process and increased transparency in the add-on process for high-cost drugs that do not go through the lock process (VWS, 2023).

In short, there was a renewed focus on improving existing models, with an emphasis on efficacy,

cost-effectiveness, and appropriate use of care. These recent developments were shared by former CEO of GlaxoSmithKline Netherlands, who argued that:

> *"[he] believe[s] that innovation will continue and that reimbursement mechanisms need to be thought through more intelligently, with a fair sharing of risk. Not just on the shoulders of the government, but not too much on the shoulders of pharma. We have to think about it intelligently. And that's going to require some customized thinking, because it's going to be very different for one file than it is for another file in terms of where the risk is. But the big cloud that will continue to hang over this is, by definition, you're talking about expensive drugs that just cost a lot of money per patient. How can we and do we want to continue to reimburse that in solidarity and collectively in a system that is under less and less cost pressure and humanity pressure?"* (Appendix B, Interview 6).

4.5 Institutional Entrepreneurship in the field of Rare Diseases

4.5.1 Norms and values of solidarity

Faced with an urgent public health need due to the lack of economic incentives for the development of orphan drugs, Minister Borst, an actor of high social status, catalyzed the creation of the WGM in 2001. This new group acted as an institutional entrepreneur because it stimulated dialogue among actors in the field, raising awareness and stimulating public discourse on the unmet medical needs of rare disease patients.

Between 2005 and 2011, institutional entrepreneurs such as the WGM, COMP, and ZN, navigated the evolving field of orphan drug policy. Recognizing the disruption caused by pharmaceutical companies inflating the prices of formerly pharmacy-made drugs after EMA approval, they responded by establishing new policy rules for academic hospitals (Appendix F, NZa, 2006, 2008). This provoked regional disparities in access to care and stimulated public and media discourse that put pressure on the system. The institutional change, which gained momentum in 2012, reflected a shift towards equal cost-effective access to treatment in academic hospitals.

4.5.2 Collective efforts for institutional change

The years 2012 and 2016 were marked by disruptions within existing institutions, catalyzed by public debates about the high cost and accessibility of orphan drugs, triggered by high-profile cases such as Pompe and Fabry diseases. These ‘jolts and crises’ (Battilana et al., 2009, p. 74) acted as catalysts for institutional entrepreneurs such as patient organizations who began to challenge established norms and seek change. Key actors such as patients and the media, often with lower formal but considerable informal social status, were instrumental in stimulating change. Their narratives and pressure, presented in public forums and through policy debates, drew attention to the need for equitable drug pricing, instead of exorbitantly high prices demanded by patent holders (Appendix B, Interview 1, 3), and forced authorities to re-evaluate

existing policy frameworks. This initial disruption led to an important institutional change: the inclusion of promising orphan drugs in the basic health insurance package for efficacy testing.

Institutional entrepreneurs, including pharmaceutical companies, took advantage of the existing orphan regulation and the resulting focus on cost-effectiveness, which introduced a new, economic dimension to the drug evaluation process. Meanwhile, ZN and ZonMw took the lead in initiating change within the existing institution of healthcare financing. They published important documents advocating comprehensive, patient-centered and cost-effective approaches to orphan drug policy, which represented the creation of new institutional norms. The Pakketbeheer Weesgeneesmiddelen document and the National Plan for Rare Diseases (NPZZ) were also instrumental in modifying the existing institutional framework, in particular the traditional evaluation and pricing mechanisms for orphan drugs.

Institutional entrepreneurship continued as pharmaceutical companies maintained high prices for orphan drugs, prompting renewed media criticism and a rethinking of drug policies by the authorities. Consequently, the institutional landscape evolved toward a more patient-centered, evidence-based, and collaborative approach to orphan drug management. By 2016, the Minister of Health had emerged as a prominent institutional entrepreneur, engaging in price negotiations with pharmaceutical companies and incorporating monetary implications into orphan drug policy. This marked a significant shift towards a more economically sustainable and patient-focused orphan drug policy.

Driven by institutional entrepreneurs such as Carla Hollak in 2017, together with a collective of involved actors, it challenged existing norms by disrupting dominant pharmaceutical practices (such as high prices and evergreening). This disruption, embedded in increased media attention and moral questioning, led to the creation of new institutions such as the Amsterdam UMC's alternative production method for orphan drugs. Furthermore, on a European scale, initiatives emerged such as the Horizon Scan, which indicates a shift to a more proactive policy engagement. The conditions that enabled these mechanisms were characterized by complex interdependencies, high costs, and the rarity of disease. Respected for her contributions to society, Hollak used her social status to effect change within existing institutional structures. Her efforts resulted in policies focused on RWE, affordable access, and robust post-marketing surveillance.

In addition, the introduction of ERNs and tools such as the Orphan Drug Access Protocol (ODAP) highlighted the Dutch propensity for international collaboration and innovative policy development. This, coupled with an emphasis on patient involvement and transparency in pricing, indicated further attempts to initiate change within existing structures. However, the institutional field remained contested. Despite steps towards more equitable access, criticism of ineffective EU regulations, high prices and monopolistic practices persisted. While the National Strategic Vision Document and the conditional approval process signaled strategic responses to these critiques, ongoing legal battles against pharmaceutical companies underscored ongoing tensions, or ‘jolts and crisis’, within the field. While significant progress has been made, these tensions underscore the need for collaborative and continued institutional innovation and

vigilance to ensure affordability and accessibility of orphan drugs in a manner consistent with societal expectations and values.

5. Conclusion and Discussion

This thesis investigated the role of institutional entrepreneurs in the field of rare diseases in the Netherlands since the introduction of the first EU orphan drug policy. I examined the main actors involved, their strategies and the impact of these changes on the Dutch orphan drug policy in detail. My findings highlight the influential role of organizations such as WGM, COMP, ZN, pharmaceutical companies, and individuals such as Carla Hollak and colleagues, and Minister Borst. These institutional entrepreneurs initiated strategic changes that challenged established norms, created new institutions, or modified existing ones. The thesis also highlights the significant influence of enabling field characteristics including public discourse, media pressure, and high-profile cases (‘jolts and crises’) that created a supportive environment for institutional change. Concretely, this involves the move toward a more patient-centered approach and the introduction of an economic dimension to the drug evaluation process, which reflects the process of institutionalization of cost-effectiveness as criterion.

This study makes a unique contribution to the understanding of institutional change in orphan drug policy in the Netherlands. The findings extend the theory of institutional entrepreneurship, especially in the health sector. In particular, it both complements and challenges the work of Lockett et al. (2012) and Breton et al. (2014) respectively, by demonstrating the significant role that institutional entrepreneurs can play in initiating and driving institutional change.

While the social position of the institutional entrepreneur is recognized by Lockett et al. (2012) as a condition for institutional change, enabling field characteristics were not considered. This study shows, however, that field characteristics were indeed identified in the form of jolts and crises. The main event identified as a jolt and crisis was the increased media attention surrounding orphan drug reimbursement for Pompe and Fabry diseases, which influenced major policy shifts such as reimbursement decisions and incremental changes in the orphan drug policy framework.

Berton et al. (2014) emphasize the critical need to initiate collective action with influential actors in the field to gain sufficient legitimacy and resources to effect institutional change. However, this study has shown that individual institutional entrepreneurs, such as Prof. Dr. C.E.M. Hollak and her colleagues, can have a significant impact in initiating change within existing institutions by modifying their core features to better meet the needs of rare disease patients. By introducing alternative routes through magistral preparation, patient access was significantly improved and drug prices were reduced. Moreover, this example shows that institutional entrepreneurs with high social status can indeed be willing to engage in institutional change, contrary to the findings of Lockett et al. (2012), but in line with the findings of Battilana et al. (2009) and Hoogstraaten et al. (2020).

In terms of policy implications, the findings illustrate the importance of international cooperation as seen in the establishment of WGN, VSOP, and ERNs. Huttin (1999) projected shifts towards increased European integration, efforts towards price transparency, and an increasing emphasis on evidence, which were indeed observed in this study. However, a shift toward uniform pricing mechanisms at the European level was not observed, given the unique pricing mechanisms in the Netherlands and in each respective national health care system.

The research process was not without limitations. The reliability of the research was challenged by potential biases in the selection of interviewees, which could affect the representativeness of the data. The validity of the research could be questioned due to the complexity of accurately capturing the dynamic nature of institutional change. Furthermore, while this study focused primarily on media analysis from the past decade due to time constraints, it should be recognized that the broader scope of this thesis extends to the exploration of orphan drug policy in the Netherlands over the past two decades. In addition, although the selection of documents for analysis was based on the combined judgment of the researcher, the thesis supervisor, and the insights gained from the expert interviews, it is important to note that not all available documents were included in this research. Therefore, while the findings are drawn from the most relevant resources, there remains a potential range of unexplored information that could provide additional insights into the evolution and shaping of orphan drug policy in the Netherlands. Finally, the institutional entrepreneurs highlighted in this study were derived from information gathered through interviews, literature, document analysis, and media analysis. In particular, these entities were explicitly coded and identified as significant. However, it is recognized that there may be other institutional entrepreneurs with significant influence on the Dutch healthcare system that have been overlooked. In order to reveal these additional actors, future studies might consider employing extensive network analysis, conducting additional interviews with key stakeholders, broadening the geographic scope, and utilizing additional data sources such as archival records and various online platforms. By adopting a more comprehensive and thorough research methodology, it is possible that subsequent research may reveal other important institutional entrepreneurs who have been central in shaping the rare disease landscape in the Netherlands.

In conclusion, this master's thesis contributes to the understanding of institutional change in the field of rare diseases in the Netherlands, especially with regard to the role of institutional entrepreneurs. It underlines the continuous need for innovation in policymaking to ensure the availability and accessibility of orphan drugs. It also highlights the importance of a patient-centered approach, international collaboration, and societal involvement. Although the path to policy change is complex and multifaceted, it is clear that strategic efforts by institutional entrepreneurs, combined with public discourse, societal pressure and patient-centeredness, can drive significant change. Future research should focus on exploring these dynamics in other healthcare sectors to understand whether similar strategies employed by institutional entrepreneurs can also drive meaningful change, thereby promoting more patient-centered, cost-effective, and internationally integrated healthcare policies. Ultimately, this research underscores the pivotal role of institutional entrepreneurs in orchestrating significant institutional

change in the field of rare diseases, thereby shaping a more patient-centered, economically responsible, and internationally collaborative healthcare landscape in the Netherlands.

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Appendix A: Media analysis script and Figures

Script: The following R script reads all .docx documents from a folder. The documents must be news articles downloaded from Nexis Uni in order for the script to work properly. It then extracts the relevant data, such as the text of the article and the year it was published. Finally, it creates a WordCloud, a frequency table, and a matrix to calculate the Jaccard distance (see explanation in the script). Each step in the script is annotated with explanatory comments.

R version 4.2.0 (2022-04-22 ucrt)
Copyright (C) 2022 The R Foundation for Statistical Computing

```
# Media Analysis for master thesis, by C.C.Steenen (6592554)
# Utrecht University, Version 1.6, date April 30th, 2023
pacman::p_load(tm, stopwords, dplyr, tidyverse, tidytext, officer, wordcloud,
               corpus, janitor)

# clean variables and ensuring reproducibility
rm(list = ls())
set.seed(999)

# set the working directory to personal preferences
setwd(
  "C:/Users/steen/OneDrive/Bureaublad/Master thesis/Media Analysis/R"
)

# 1. Prerequisites.
# This script only works with articles downloaded from Nexis Uni, since
# the start and stop criteria are tailored to these specific files.
# After searching and filtering, download full documents as separate files,
# without attachment, in .docx format. After downloading all documents, remove
# one .docx file that is not a news article, which ends with
# "(...)_doclist.docx".

# 2. Import all articles and extract relevant data.
my_foler = "Articles" # enter folder that is present in working directory
file_names <- list.files(my_folder, pattern="*.docx", full.names=TRUE)

# create vector with Dutch stopwords
stopwords_nl <- stopwords::stopwords("nl", source = "stopwords-iso")

# initialize an empty list to store the article texts
articles <- list()

# read all the articles into a single data frame
article_df <- data.frame(
  text = character(),
  file = character(),
  stringsAsFactors = FALSE
)

# loop over all files and extract the relevant text
for (file_name in file_names) {

  # read the document
  doc <- read_docx(file_name)
  # extract the text
  doc_summary <- docx_summary(doc)
  # get the start of the text (all Nexis Uni documents start after "Body")
  start_index <- grep("Body", doc_summary$text)[1]
  # get the end of the text (all Nexis Uni documents start after either
```

```
  # "Load-Date" or "End of Document")
  end_index <- grep("Load-Date|End of Document", doc_summary$text)[1]
  # store the selected relevant article text in a variable
  article_text <- doc_summary$text[(start_index+1):(end_index-1)]

  # Extract the published year
  # get the entire line where the Copyright symbol is located, followed by year
  start_year <- grep("©|Copyright", doc_summary$text)[1]
  # get the complete line as a character
  article_year <- doc_summary$text[(start_year)]
  # remove all symbols except for the numbers, and transform to numeric
  article_year <- as.numeric(gsub(".*?([0-9]+).*", "\\1", article_year))

  # store both the text variable and year variable in the article list
  articles[[file_name]]$text <- article_text
  articles[[file_name]]$year <- article_year

  article_df <-
    rbind(
      article_df,
      data.frame(
        text = paste(article_text, collapse = "."),
        file = file_name,
        stringsAsFactors = FALSE
        )
      )
}

# remove exact duplicates
articles_unique <- article_df %>%
  distinct(text, .keep_all = TRUE)

# print which values are present in the one file but not in the other
setdiff(article_df$file, articles_unique$file)

# make matrix for distance check
dist_matrix <- matrix(nrow=length(articles_unique$text),
                      ncol=length(articles_unique$text))

# check distances (the Jaccard distance measures how dissimilar two multisets
# are. The lower the distance, the more similar the two multisets)
for(i in 1:length(articles_unique$text)){
  for(j in 1:length(articles_unique$text)){
    dist_matrix[i,j] <- stringdist(articles_unique$text[i],
                                   articles_unique$text[j],
                                   method = "jaccard")
  }
}

# 3. Analysis of all the words used in all documents
# initialize an empty list to store all text
df_text <- list()

# loop through all items in the articles list and store text in variable df_text
for (i in articles){
  df_text <- append(df_text, i$text)
}

# create a corpus file for convenient text cleaning
docs <- Corpus(
  VectorSource(
```

```
    df_text
  )
)

# clean text
toSpace <- content_transformer(function (x , pattern ) gsub(pattern, " ", x))
docs <- tm_map(docs, toSpace, "/")
docs <- tm_map(docs, toSpace, "@")
docs <- tm_map(docs, toSpace, "\\|")

# convert the text to lower case
docs <- tm_map(docs, content_transformer(tolower))
# remove numbers
docs <- tm_map(docs, removeNumbers)
# remove English and Dutch common stopwords
docs <- tm_map(docs, removeWords, stopwords("english"))
docs <- tm_map(docs, removeWords, stopwords("dutch"))
# alternative: specify stopwords as a character vector
docs <- tm_map(docs, removeWords, stopwords_nl)
# specify your own stopwords as a character vector
docs <-
  tm_map(
    docs,
    removeWords,
    c("zegt", "gaat", "gaan", "komen", "bart" # personal input for exclusion
    )
  )
# remove punctuations
docs <- tm_map(docs, removePunctuation)
# eliminate extra white spaces
docs <- tm_map(docs, stripWhitespace)

# construct a term-document matrix, and sort by frequency
dtm <- TermDocumentMatrix(docs)
m <- as.matrix(dtm)
v <- sort(rowSums(m),decreasing=TRUE)
d <- data.frame(word = names(v),freq=v)
# you could delete words smaller than 2 characters
# d <- subset(d, nchar(as.character(word)) > 2)

# 3 show top 20 used words
head(d, 20)

# make WordCloud with the most popular words used
wordcloud(words = d$word, freq = d$freq, min.freq = 20,
          max.words=200, random.order=FALSE, rot.per=0.35,
          colors=brewer.pal(8, "Dark2"))

# 4. Exploring the data:
# search for the meaning between (unknown) words by analyzing their correlation

# In the context of orphan drugs, the word "pompe" was a common word
# identify which words are associated with “pompe” in all texts:
findAssocs(dtm, terms = "pompe", corlimit = 0.3)
# the term "pompe" is correlated the most with "fabry"
# identify which words are associated with “fabry” in all text
findAssocs(dtm, terms = "fabry", corlimit = 0.3)

# to find words that occur at least 100 times:
findFreqTerms(dtm, lowfreq = 100)
```

```
# to plot the frequency of the 10 most frequent words:
barplot(d[1:10,]$freq, las = 2, names.arg = d[1:10,]$word,
        col ="darkred", main ="10 most frequent words",
        ylab = "Word frequencies")
```

Figure A.1: WordCloud of Dutch words in news articles

```
> findAssocs(dtm, terms = "pompe", corlimit = 0.3)
$pompe
                fabry                  cori glycogeenstapelingsziekte glycogeenstapelingsziekten
                 0.41                  0.38                       0.38                        0.38
                  gsd             patholoog                   putschar                   vertoonde
                 0.38                  0.38                       0.38                        0.38
           glycogeen
                 0.31
```

Figure A.2: Screenshot 1 of word correlation. Pompe is correlated with Fabry, and other words that describe the disease.

```
> findAssocs(dtm, terms = "fabry", corlimit = 0.3)
$fabry
  adjusted    quality      pompe onhaalbaar therapieën      years
      0.42       0.42       0.41       0.40       0.40       0.40
```

Figure A.3: Screenshot 2 of word correlation. Fabry is correlated with Pompe, but also with QALY.

Appendix B: Interviewees

Interview number	Date	Name interviewee	Profession	Organization
1	March 29, 2023	Dr. Eddy Adang	associate professor Health Evidence	RadboudUMC
2	April 11, 2023	*anonymous*	senior advisor	Zorginstituut Nederland
3	June 2, 2023	*anonymous*	professor	RadboudUMC
4	June 7, 2023	*anonymous*	senior researcher	ZonMw
5	June 9, 2023	Dr. Mariëtte Driessens	policy officer	VSOP
6	June 9, 2023	Marcel Joachimsthal	pharmaceutical industry former CEO	GlaxoSmithKline Netherlands
7	June 14, 2023	Prof. Dr. C.E.M. Hollak	professor	Amsterdam UMC

Appendix C: Interview Guide

Informed Consent

a. Your participation today is solely for the purpose of this interview.
b. I would like to record this interview.
c. The information you provide me during this interview will be used for academic purposes. There are no right or wrong answers, it is about your personal thoughts, ideas, and experiences. Please take as much time as you need to answer the questions. You can decline to answer any question and end this interview at any time.
d. In our reporting, I will anonymize your responses, but will mention the initiative itself.
e. Do you have any questions at this time?
f. Do you confirm that:
    i. You are satisfied with the information about the research that you have received,
    ii. You have been given the opportunity to ask questions and that your questions have been answered to your satisfaction,
    iii. Have you had the opportunity to consider your participation carefully?
g. Do you agree that:
    i. The interview will be recorded, and the collected data will be stored for scientific purposes,
    ii. The collected, anonymized data can be shared and reused by scientists to answer other research questions?
h. Do you understand that:
    i. You have the right to withdraw your consent for the use of the data at any time,
    ii. You have the right to review the report afterward?

Interview questions and notes

(introduce myself, ask participant for introduction)

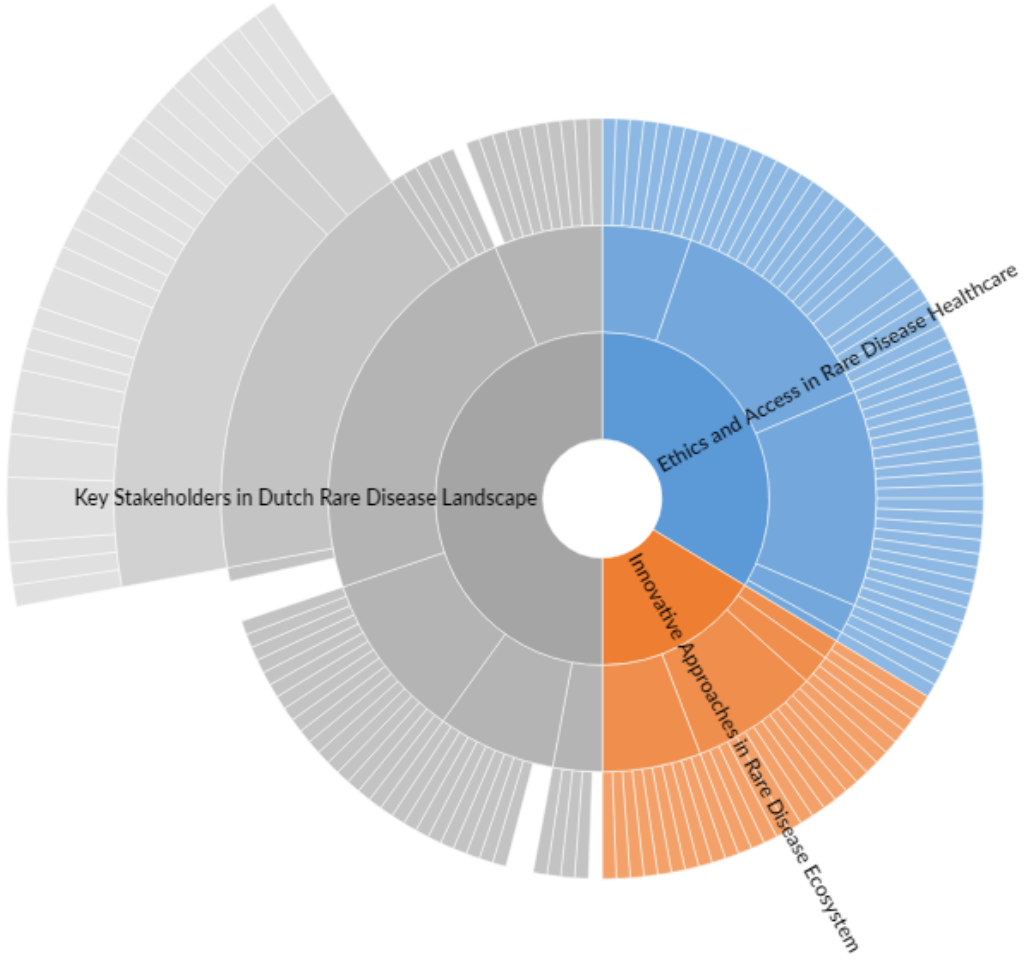
I would like to talk about the Dutch history regarding orphan drug policy.

- Thinking back over the past 20 years, what were the key moments?
    - What was the trigger?
    - What was the effect?

(Continue asking)
(Share excerpt from my timeline for validation)

- What are your ideas about the changing role of the CVZ/ZIN?
- What are your ideas about the role of industry?
- What are your ideas about the role of hospitals/doctors/expert centers?
- What are your ideas about the role of the media?

Appendix D: Hierarchical overview of themes and codes



.
Figure D.1: A hierarchical view generated by the NVIVO software that shows three overarching themes

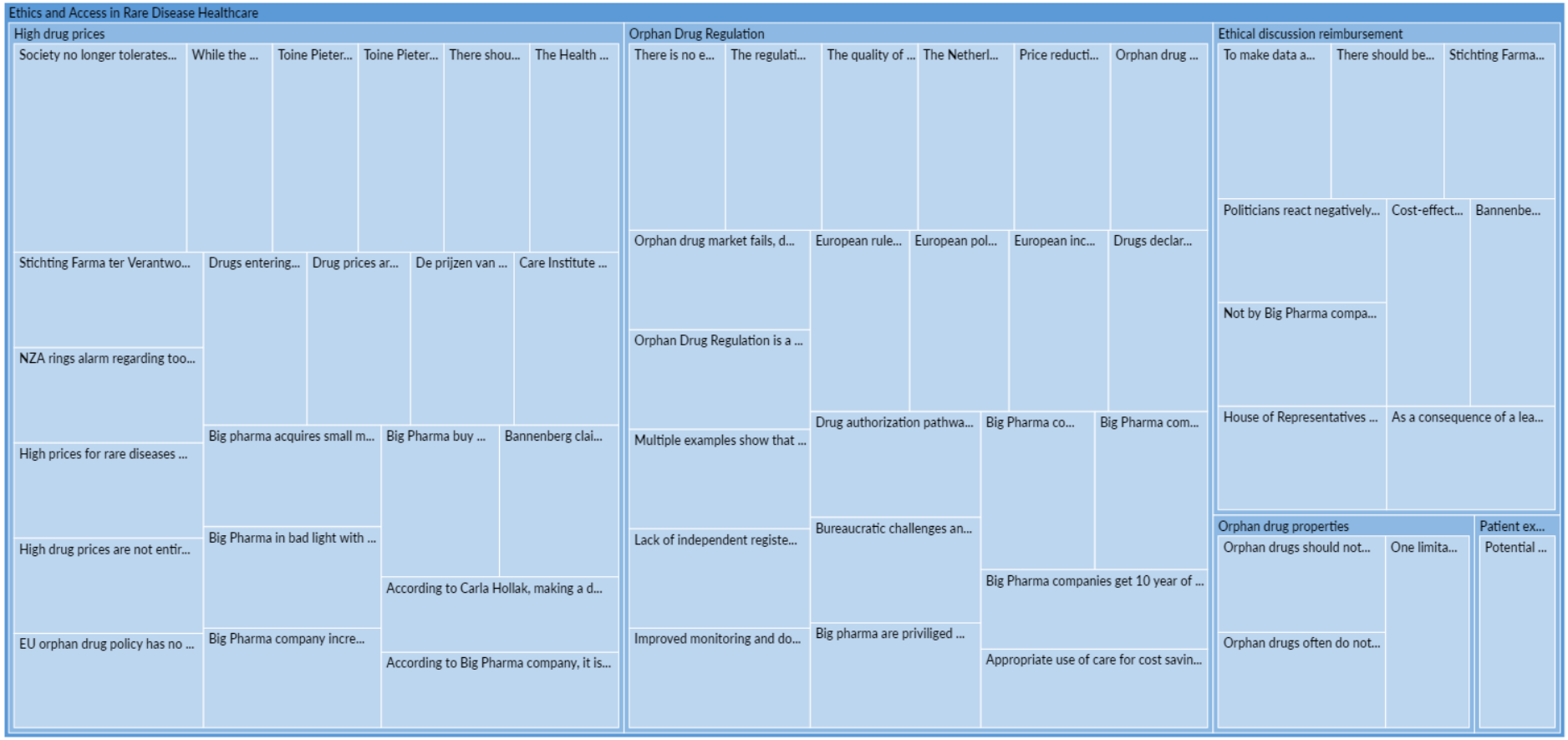


Figure D.2: A hierarchical view generated by the NVIVO software that shows one of the overarching themes: Ethics and Access in Rare Disease Healthcare.

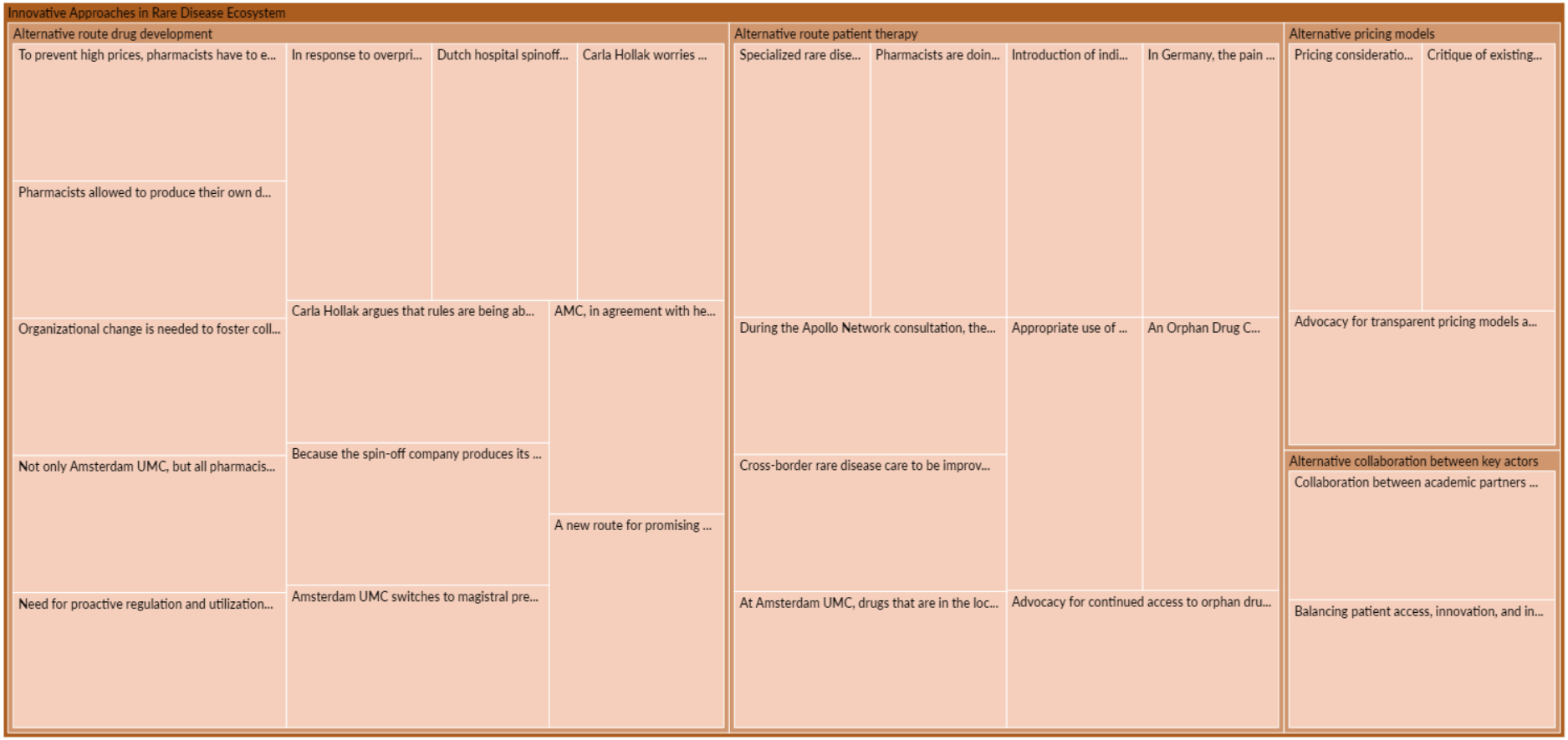


Figure D.3: A hierarchical view generated by the NVIVO software that shows one of the overarching themes: Innovative Approaches in Rare DIsease Ecosystem.

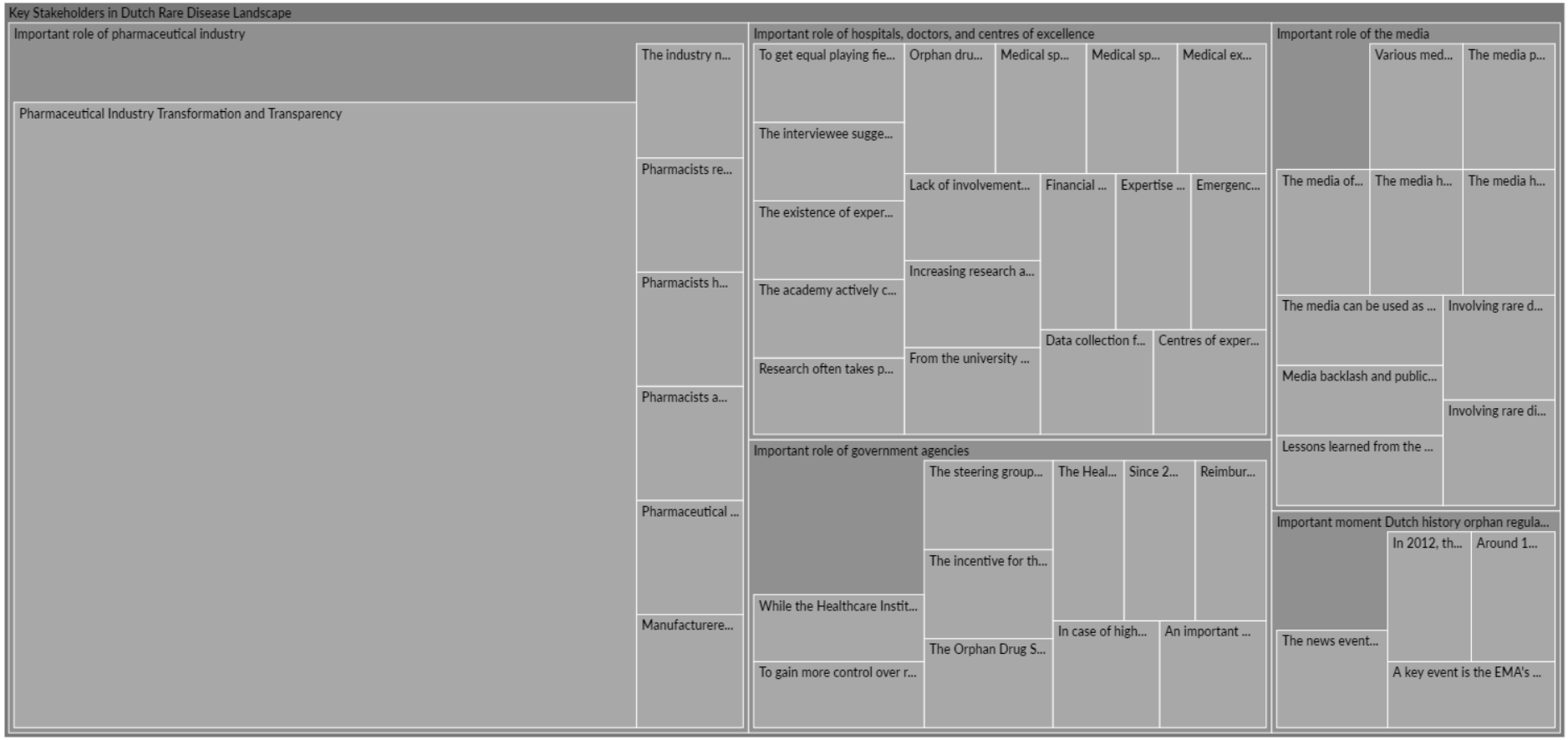


Figure D.4: A hierarchical view generated by the NVIVO software that shows one of the overarching themes: Key Actors in Dutch Rare Disease Landscape

Appendix E: Included news articles

Article #	Title	Year
1	Aanklacht tegen farmaceut van het lucratiefste medicijn_ _De hoge prijs schendt de mensenrechten_.docx	2023
2	Aanval op peperdure medicijnen.docx	2019
3	Adalvo is een samenwerkingsverband aangegaan met SK Pharma voor het opzetten van Arphio, een nieuwe.docx	2022
4	AMC breekt markt open met eigen medicijn.docx	2018
5	Amsterdam UMC gaat dure medicijnen vaker zelf maken.docx	2018
6	De 8 stappen naar veel te dure pillen.docx	2016
7	De markt van 7.000 zeldzame ziekten Interview Henri Termeer en Hans Schikan.docx	2013
8	De medicijnprijs maal zestien_ _Wat geeft de fabrikant het recht__.docx	2019
9	De onbestemde verontwaardiging over Alexion.docx	2015
10	De pil is hetzelfde, de prijs een veelvoud.docx	2018
11	Dure medicijnen Bladwijzers _ De beste online bronnen bij het nieuws.docx	2012
12	Duur medicijn eerder in pakket.docx	2019
13	EINDELIJK ERKENNING.docx	2015
14	Grote farmaceut handelt amoreel'.docx	2019
15	Herman leeft voort.docx	2020
16	Hoe duur wordt Diego_s medicijn_ De prijs van een oud middel gaat bij een nieuwe eigenaar hard omhoo.docx	2021
17	Hoe kinderen de dupe zijn op Zeldzame Ziektendag.docx	2017
18	Hoge medicijnprijs is schending van mensenrechten'.docx	2023
19	Kosten pillen rijzen steeds verder uit de pan.docx	2019

Article #	Title	Year
20	Kritiek op weesgeneesmiddelenbeleid.docx	2020
21	Luka krijgt medicijnen, zijn zieke zusje niet	2017
22	Maak nieuwe regels voor toelating dure geneesmiddelen	2021
23	Maurice en Vincent uit Ootmarsum hebben een zeldzame ziekte_ _Als ouder wil je strijden	2019
24	Medicijn werkt. En is ineens peperduur.docx	2019
25	Medicijnen voor zeldzame ziekten zijn extreem duur door kleine markt vier vragen over Weesgeneesmidd.docx	2012
26	Medicijnen zeldzame ziekten kunnen eerder in basispakket.docx	2019
27	Red het kapitalisme van de ceo's	2018
28	Slikken of stikken_ Het kan ook anders.docx	2017
29	Sneller een middel voor zeldzame ziekte.docx	2022
30	Succes van EMA.docx	2019
31	TiGenix en Takeda kondigen aan dat Alofisel_ (darvadstrocel) de goedkeuring krijgt voor de behandeli.docx	2018
32	Troetelkinderen van Big Pharma.docx	2015
33	Wat mag een leven kosten_.docx	2012
34	We kunnen maar kleine stapjes zetten bij de grote farmaceuten	2019
35	Zeldzame ziekte knevelt hele familie_ _De gemiddelde prognose is vijf jaar_.docx	2021
36	Zijn sommige ziekten te duur_.docx	2012
37	Zo kwamen twee artsen tot goedkoper kankermedicijn.docx	2018
38	Zorg Opnieuw verhoogt een farmaceut de prijs van een 'weesgeneesmiddel' fors.docx	2019
39	Zorg stopt niet aan de landsgrens.docx	2019

Appendix F: Orphan drug policy documents

Title	Year	Organization
Verordening (EG) Nr. 141 2000 van het Europees Parlement en de Raad	1999	European Parliament
Subsidie stuurgroep weesgeneesmiddelen	2004	VWS
Beleidsregel weesgeneesmiddelen in academische ziekenhuizen - CI-952	2006	Nederlandse Zorgautoriteit (NZa)
Beleidsregel weesgeneesmiddelen in academische ziekenhuizen - CI-1061	2008	Nederlandse Zorgautoriteit (NZa)
Kosteneffectiviteit in de zorg	2013	Zorginstituut Nederland
Masterplan Expertisecentrum	2013	IQ Healthcare
Nationaal Plan Zeldzame Ziekten (NPZZ)	2013	ZonMw
Pakketbeheer Weesgeneesmiddelen	2015	Zorginstituut Nederland
Verslag 8e vergadering Raad van Advies CBG	2015	College ter Beoordeling van Geneesmiddelen (CBG)
Overzicht Financiele Effect Rapporten Zorginstituut (weesgeneesmiddelen-arrangement)	2016	Zorginstituut Nederland
Monitor Weesgeneesmiddelen in de praktijk	2017	Zorginstituut Nederland
Monitor Weesgeneesmiddelen in de praktijk	2018	Zorginstituut Nederland
Monitor Weesgeneesmiddelen in de praktijk	2019	Zorginstituut Nederland
Kamerbrief over beleidskader voorwaardelijke toelating geneesmiddelen	2019	VWS
Monitor Weesgeneesmiddelen in de praktijk	2020	Zorginstituut Nederland
Monitor Weesgeneesmiddelen in de praktijk	2021	Zorginstituut Nederland
1e Evaluatierapport VT weesgeneesmiddelen, conditionals en exceptionals	2022	Zorginstituut Nederland
Voortgangsrapportage voorwaardelijke toelating weesgeneesmiddelen	2023	Zorginstituut Nederland