Examining proposed European Union Pharmaceutical legislation changes: A focus on pharmaceutical industry stakeholders' perspective of regulatory protection periods for innovation and access

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Abstract

There is a high prevalence of unmet medical needs and unequal access to medicines across EU Member States. To address this, there are proposed changes to the European Pharmaceutical legislation which includes changes to regulatory protection periods (data protection, market protection, and market exclusivity). At present, majority of extant literature focuses on the impact previous legislation has had on pharmaceutical research and development (R&D). The existing literature focusing on the impact of regulatory protection periods is limited, especially surrounding the pharmaceutical industry perspective on the proposed changes. This study aims to utilise key pharmaceutical industry stakeholders' perspective surrounding proposed changes to regulatory protection periods in EU pharmaceutical legislation to develop an understanding of how incentives in legislation impact organisational behaviour in the pharmaceutical industry.

This research adopted a qualitative research strategy to understand Swedish pharmaceutical industry stakeholders' perspective on the proposed changes. Nine participants were recruited using purposive and snowball sampling, and data was collected through semi-structured in-depth interviews. The research methodology met the University of Auckland ethics criteria.

The results of this research identified four key themes: role and value of regulatory protection periods, regulatory protection and investment in innovation, regulatory protection as an incentive for equal access, regulatory protection and orphan drug development. Regulatory protection is a highly valuable intellectual property asset, however proposed changes are a worsening of protection periods and weaken the intellectual property system. The proposed changes will not lead to equal access or an innovative friendly environment in the EU.

The results from this research are useful for both private and public stakeholders as it provides an understanding of the potential future direction of the industry in the EU. The results provide opportunity for constructive dialogue between stakeholders to refine the proposal to better address the legislative objectives.

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EU: European Union

EMA: European Medicines Agency

FDA: US Food and Drug Administration

HTA: Health Technology Assessment

ODA: Orphan Drug Act

OMP: Orphan Medicinal Product

R&D: Research and Development

SPC: Supplementary Protection Certificates

US: United States

1. Introduction

This chapter outlines the empirical context of this research. It includes the research purpose and question that were developed to direct the methodology and ensure the findings address the research aim and question. A summary of the research contribution, structure of the thesis, and scope is also provided at the end of the chapter.

1.1 Empirical Context

There is a high prevalence of unmet medical needs and unequal access to medicines across EU Member States (European Commission [EC] 2023d). This has been identified through evaluations of EU legislations including the general pharmaceutical legislation, orphan regulations, and paediatric regulations (EC 2023a; EC 2023b).

Science and technology are evolving, however, there are still diseases with no or sub-optimal treatment leading to unmet medical needs. Unmet medical needs are driven by high commercial risk involved in R&D to introduce new medicines (EC 2023a). The orphan regulation has successfully encouraged R&D of medicines for orphan diseases however, 95% of the over 6000 orphan diseases have either no or limited treatment options (EC 2023b). An orphan disease, sometimes termed rare disease, is defined in the EU as a disease with a prevalence below 5 in 10,000 people (Regulation 141/2000). Majority of treatments for orphan diseases are symptomatic and not curative.

Additionally, innovative medicines may be unaffordable or not launched in all EU Member States contributing to unequal access for patients across the EU (EC 2023a). Despite a central marketing authorisation allowing the product to enter all Member States, the decision to launch the pharmaceutical product depends on various commercial factors including market size/size of patient population, national pricing and reimbursement policies, and health system organisation (EC 2023e). Many Member States complete HTA to assess the products added therapeutic value compared to current standard of care, as well as health economic assessments (OECD, 2017). Unequal access to medicines across the EU is driven by the fact medicines are not launched or are withdrawn from EU Member States, and a lack of data on pricing and reimbursement decisions (EC 2023a). Access to orphan medicines across EU Member States

varies and is worse than access to standard medicines. The presence of unmet medical needs and unequal access across the EU demonstrates a disconnect between corporate pharmaceutical industry R&D strategy and public health needs. Current investments do not always prioritise greatest unmet medical needs (EC 2023e).

The reviews of the general pharmaceutical legislation (Directive 2001/83/EC and Regulation (EC) No 726/2004), orphan regulations (Regulation (EC) No 141/2000), and paediatric regulations (Regulation (EC) No 1901/2006) demonstrate similar issues across all legislations. To address these disparities there is a proposed revision of the of the pharmaceutical legislation. The revision sees the orphan and paediatric regulations merge with legislation applicable to all medicinal products to allow for simplification and increased coherence (EC 2023d).

The two legislative proposals are:

1. New directive repealing and replacing directives 2001/83/EC and 2009/35/EC, and incorporating relevant parts of the paediatric regulation.
2. New regulation repealing and replacing regulation (EC) No 726/2004, repealing and replacing orphan regulation, and incorporating relevant parts of the paediatric regulation.

Specific objectives from the proposed EU pharmaceutical legislation includes:

1. *"Make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines" – EC 2023e*
2. *"Offer an attractive, innovation- and competitiveness friendly environment for research, development, and production of medicines in Europe" – EC 2023e*

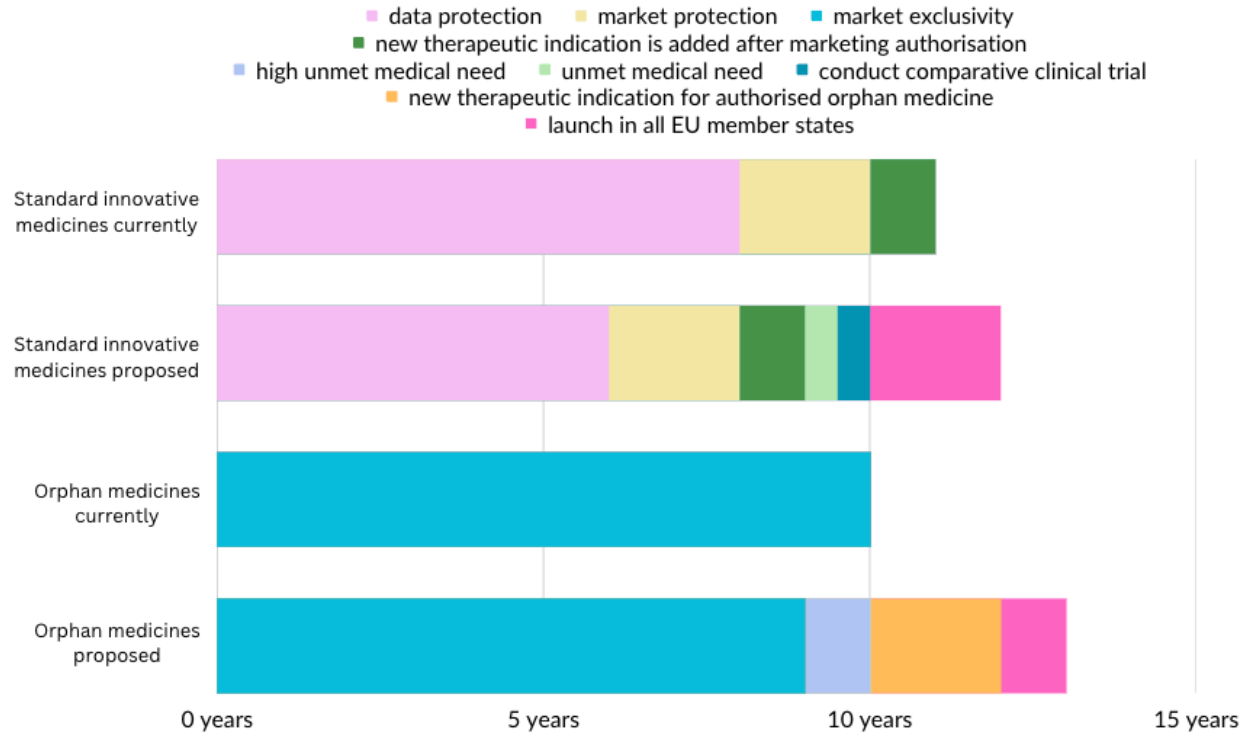
To achieve these objectives there are various proposed changes to the pharmaceutical legislation, including proposed changes to regulatory protection periods. Regulatory protection includes data protection, market protection, and market exclusivity (EC 2023e). In the EU, regulatory protection periods complement intellectual property rights (patents and SPC) to incentivise innovation. These changes incentivise and reward innovation that meets public health needs as the protection periods shift from a 'one size fits all' approach towards targeting patient access and address unmet medical needs.

Currently, from the time of marketing authorisation standard innovative medicines are provided 10 years of regulatory protection (8 years data protection and 2 years of market protection), which can be extended by 1 year (data protection) if a new therapeutic indication is added after marketing authorisation (EC 2023e). Orphan medicines are granted 10 years of market exclusivity (EC 2023e).

Under the proposed reform, the period of regulatory protection for standard innovative medicines is reduced from 10 years to 8 years, however the maximum is extended from 11 years to 12 years to incentivise improved patient access and drive development towards areas of unmet medical need (EC 2023e). For orphan medicines the standard duration of market exclusivity will be 9 years, a reduction from the current 10 year period (EC 2023e). However, this period can be extended under certain conditions to a maximum of 13 years (EC 2023e). These proposed changes for regulatory periods including conditions for extension are further demonstrated in figure 1, and definitions of key terms in table 1.

The differing regulatory protection periods between standard innovative medicines and orphan medicines provides specialised incentives and rewards. It recognises market forces alone are not enough to encourage R&D for certain conditions and populations. Innovators will continue to benefit from patents and SPC as the regulatory protection periods do not impact these intellectual property rights.

Figure 1: Current and proposed periods of Regulatory Protection



Developed by the researcher. Demonstrates the current and proposed regulatory protection periods for standard innovative medicines and orphan medicines.

Table 1: Key definitions

Term	Definition
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings (EC 2023e)
Market protection	Period of protection during which generics cannot be placed on the market (EC 2023e)
Market exclusivity	The period after the marketing authorisation of a medicine for an orphan disease when similar medicines for the same indication cannot be placed on the market and applications for those medicines cannot be validated (EC 2023e)
Orphan (rare) Disease (EU)	Disease with prevalence below 5 in 10,000 people. (Regulation 141/2000)
Orphan medicine (EU)	Intended for diagnosis, treatment, or prevention of a disease with a prevalence below 5 in 10,000 people, or if for a seriously debilitating or chronic condition where in the absence of incentives it is unlikely to generate sufficient returns to justify investment (Regulation 141/2000)
Unmet medical need	As defined in article 83(1) of proposed directive, there is no medicinal product authorised in the EU, or despite an authorised medicinal product morbidity and mortality associated with the disease remains high and the use of the medicinal product results in a meaningful reduction in disease morbidity and mortality for the relevant patient population (EC 2023c)
High unmet medical need	As defined in Article 70(1) of proposed regulation, there is no medicinal product authorised in the EU for the condition, or where a product is authorised the applicant demonstrated the orphan medicinal product will have significant benefit and bring exceptional therapeutic advancement. The use of the orphan medicinal product results in meaningful reduction in disease morbidity and mortality for the relevant patient population (EC 2023d)

1.2 Research Purpose

The body of literature focusing on the impact of regulatory protection periods is limited, especially surrounding the pharmaceutical industry perspective on the proposed changes. Most extant literature concentrates on the impact of legalisation on pharmaceutical innovation through quantitative and retrospective methodologies. There is a large body of literature surrounding the evolution of the pharmaceutical industry and the impact previous legislations, such as Bayh-Dole Act and orphan drug legislations, have had on pharmaceutical R&D.

Although the impact of previous legislation and industry trends can be used to predict the impact of proposed EU legislation, it should not be surmised to have the same impact. Furthermore, there is a lack of understanding of pharmaceutical industry stakeholders' perspective regarding proposed changes to EU pharmaceutical legislation. This aim of this research is to utilise key pharmaceutical industry stakeholders' perspective surrounding proposed changes to regulatory protection periods in EU pharmaceutical legislation to develop an understanding of how incentives in legislation impact organisational behaviour in the pharmaceutical industry.

1.3 Research Question

The research question below captures key Swedish pharmaceutical industry stakeholders' perspective surrounding the impact proposed changes to EU pharmaceutical legislation can have to achieve the aims of the research.

> What is the impact the proposed changes to regulatory protection periods could have on the direction of the pharmaceutical industry within the EU?

1.4 Methodology

Given the exploratory nature of the research, a qualitative research approach was used to address the research aim and answer the research question. The researcher came from an interpretative paradigm and used in-depth semi-structured interviews for data collection. Purposive sampling and snowball sampling were used to recruit participants based on an inclusion and exclusion criteria. Participants were key Swedish pharmaceutical industry stakeholders for two key reasons. Firstly, the researcher is situated in Sweden therefore it is practical to recruit Swedish stakeholders, and secondly Sweden is an innovative country in the realm of pharmaceutical R&D. The interviews were transcribed and analysed using thematic analysis where codes were established and assigned to key themes. Inductive reasoning was used to allow the themes to emerge from data naturally, and then build on institutional theory.

1.5 Research Contribution

Previous research examines the impact of legislation within the pharmaceutical industry US and EU legislation, and outlines existing trends in pharmaceutical R&D. Existing literature uses retrospective and quantitative methodologies to discuss the impact legislation has had on the pharmaceutical industry. This research contributes to literature by using qualitative research methodology to gain insights to pharmaceutical industry stakeholders' perspective on proposed changes to regulatory protection periods in EU pharmaceutical legislation. Additionally, it formally applies institutional theory in a different industry. In doing so this research addresses a gap in literature as there is lack of research surrounding proposed changes to EU pharmaceutical legislation utilising industry perspective to understand the impact it has on the direction of the industry. This information is useful for both private and public stakeholders as it provides an understanding of the potential future direction of the industry in the EU. The results provide opportunity for constructive dialogue between stakeholders to refine the proposal to better address the legislative objectives.

1.6 Thesis Outline

The following describes the structure of this thesis. Chapter 2 provides a detailed review of existing literature related to the thesis topic including the impact of previous legislation on pharmaceutical R&D, current pharmaceutical R&D trends, and an introduction to the theory this research takes place in the context of. Chapter 3 outlines the research methodology. Chapter 4 presents the research results, and Chapter 5 discusses the results to answer the research question and address the research aim. Lastly, Chapter 6 provides an overall conclusion including research implications, limitations, and areas for further research.

1.7 Thesis Scope

There are various proposed changes to the EU pharmaceutical legislation to achieve the aim of an attractive, innovation friendly environment and improve equal access to medicines across Member States. This research focuses solely on proposed changes to regulatory protection periods and the impact the changes will have on the direction of the pharmaceutical industry. There are many pharmaceutical industry stakeholders who are impacted by the proposed

changes, both within the EU and globally. The scope of this research is limited to Swedish pharmaceutical industry stakeholders as outlined in the methodology.

2. Literature Review

This chapter will provide a detailed review of existing literature. It begins by examining US federal funding and intra-industry relationships that influence drug development, as well as current trends in pharmaceutical R&D. It then focuses on the impact of legislations providing patent protection and regulatory protection periods, and their role in R&D efforts. The literature review further examines the impact of orphan drug legislations in the US and EU. It then introduces Institutional Theory and the theory in the context of this research. Finally, a summary which ties together key themes from the literature review to introduce the research aim and question.

Although this research takes place within the context of EU legislation, including relevant US legislation is important for understanding how legislation impacts drug R&D. This is for two key reasons. Firstly, the US pharmaceutical market is the largest, and secondly the US legislations are older compared to EU. Given the lengthy nature of drug development the impact of legislation is not seen immediately. Therefore, the US legislation is more extensively studied resulting in a larger library of literature.

2.1 US federal funding and intra-industry relationships

Federal funding in the US has played a crucial role in research, enabling a high scientific output of biomedical research. Following World War II there was an increase in federal funding to support biomedical research (Mowery et al., 2001; Mowery and Sampat, 2001). From the early 1970s the benefits of federal funded health research began to appear with progress in medical sciences leading to improved understanding of disease and the mechanism of action of drugs (Malerba & Orsengio, 2015). The high academic output in life sciences post-World War II resulted in advances in understanding of physiology and molecular basis of disease which expanded research areas (Cockburn, 2004).

The increased pace of biomedical science research and subsequent scientific breakthroughs due to the federal funding raised the importance of close relationships between universities and industry (Cockburn, 2004). Until the mid-1970s industry firms were large fully integrated companies active in every stage of drug discovery, development, and marketing (Cockburn, 2004). In the 1980s the structure of the industry started to become more complex with the entry

of biotech companies who positioned themselves as a link between academia and industry (Cockburn, 2004). The rapid rate of science and technological progress meant fully integrated companies could no longer rely on all internal capabilities and knowledge to discover and develop new drugs (Malerba & Orsengio, 2015). Large pharmaceutical shifted towards a vertical business model. Mergers and acquisitions along with licensing and collaborations began with both small biotech companies and academic institutes (Malerba & Orsengio, 2015). The tighter relationships between universities and biotech firms enabled the absorption and use of new scientific knowledge by larger pharmaceutical companies (Malerba & Orsengio, 2015).

However, according to Malerba and Orsengio (2015) in the early 2000s pharmaceutical R&D was becoming more expensive and less productive. R&D expenditure in the US was 30 times higher than the 1980s while the same number of drugs were being approved annually. Regulation is often blamed for rising costs and decreasing productivity. Furthermore, there were concerns surrounding pharmaceutical companies' innovative efforts due to the development of 'me-too-drugs' and minor improvements on existing products. This demonstrated incremental innovation rather than breakthrough innovation as had previously occurred. However, it is important to acknowledge the decrease in productivity and increased expenditure could be attributed to the increased difficulty in drug discovery for complex diseases as the 'low hanging fruits' were already picked (Cockburn, 2004; Malerba & Orsengio, 2015).

Innovative pharmaceuticals crucial for addressing unmet medical needs typically originate from the collaborative efforts of universities and biotech companies. Over half of FDA priority review drugs, which significantly enhance the safety and efficacy of treatments, diagnostics, or prevention of diseases, stem from these sectors rather than pharmaceutical companies (Kneller, 2010; US Food & Drug Administration, 2018). Additionally, large pharmaceutical companies require drug pipelines with ability to generate enough revenue to replace blockbuster drugs where patents are expiring (Cockburn, 2004 and Kneller, 2010). Many biotech firms specialised in orphan drugs and a large fraction of profit started to come from orphan drug designation (Malerba & Orsengio, 2015). Large pharmaceutical companies relied on research tools and product leads from the biotech firms, with 25-40% of sales coming from products and drugs that originated in biotech (Cockburn, 2004; Malerba & Orsengio, 2015). The absence of biotech companies would significantly reduce the number of drugs addressing

unmet medical needs, particularly orphan drugs, university discoveries, and biologics (Kneller, 2010).

2.2 Current trends in R&D and investment

Current trends in pharmaceutical R&D brings both optimism and concerns for industry stakeholders. Recent breakthrough innovations provide immense benefit to patients, and strong pharmaceutical pipelines globally show promise for further benefits especially in oncology. Oncology is the most targeted therapeutic area accounting for approximately one-third of recent approvals (OECD, 2017). 55% of these oncology medicines had an orphan designation and 65% had an indication linked to a biomarker (OECD, 2017). This indicates trends towards small populations and personalised medicine. Additionally, cell therapies, such as CAR-T cell therapies, are being developed in oncology and this holds some of the greatest potential for personalised medicine.

Intra-industry relationships remain important today, especially as small emerging pharmaceutical companies continue to be leaders in pharmaceutical innovation. Majority of biomedical innovation originates in these small companies that likely have never launched a product (IQVIA, 2022). Overtime, these companies either bring the product to market themselves or their asset is acquired by other larger companies. According to IQVIA (2022), small emerging pharmaceutical companies are responsible for 65% of molecules in the R&D pipeline, growing from 34% in 2001. Products filed with the FDA that originate in these small companies has quadrupled since in 2012. Small emerging pharmaceutical companies are strong in oncology as 39% of their pharmaceutical pipeline is oncology products. Additionally, these small companies are consistently the source of new products with the highest sales. However, these high sales occur most often when the product is launched by a larger company. When small emerging companies launch the product themselves the sales are lower, indicating the importance of intra-industry relationships not only in early stage R&D but continued to market launch ensuring the product reaches patients.

Europe continues to fall behind the US in the amount of investment made by pharmaceutical companies in R&D. In 2020 there was a difference between of approximately €25 billion, a large increase from the €2 billion difference in early 2000s (Wilsdon et al., 2022; EC 2023e).

Additionally, China displays strong growth as both the US and China represent a growing share of pharmaceutical R&D investment while Europe declines. As a result, R&D expenditure in China and the US are growing at a faster rate compared to Europe and China is leading the number of clinical trials for advanced therapies. Investment in early-stage companies in Europe is trailing behind the US and China which is concerning because innovative medicines originate in these early-stage emerging companies. The majority of innovation originates from US based small emerging pharmaceutical companies, and the share of European-headquartered emerging companies has declined in the recent decade while the US continues to dominate in both the number of emerging companies and contribution to global pipeline with strong growth in China (IQVIA, 2022; Wilsdon et al., 2022).

Different industry stakeholders possess different levels of expertise. Collaboration between them is imperative for successful drug development. This is evident through recent R&D efforts surrounding COVID-19. According to Agarwal and Gaule (2022), public institutions were a key driver in COVID-19 related R&D efforts. Public organisations, such as universities and hospitals, conducted 70% of clinical trials globally. However, private firms were more efficient at key stages in development and commercialisation. Private firms moved faster into pre-clinical COVID-19 vaccine stages compared to public organisations. Therefore, public and private R&D efforts complement each other enabling successful drug development.

Operation Warp Speed is a federal initiative in the US which aimed to accelerate the development of a COVID-19 vaccine through federal funding (U.S. Government Accountability Office, 2021). This early stage incentive impacted the speed of R&D efforts as US vaccine candidates entered pre-clinical and clinical trials faster compared to European (Agarwal & Gaule, 2022). This could be attributed to the fact that market size was largely uniform across different countries and market entry is a late stage incentive. The variation in speed of the COVID-19 vaccine R&D may be due to differing national incentives and illustrates the imperative role of funding in conjunction with industry collaboration.

2.3 Academic Patents

A patent is a legal document that is granted to innovations and the owner of the patent receives exclusive rights to the innovation for a period of 20 years from the filing date (WIPO, n.d). A

patent acts an incentive as it rewards innovation with a 20 year market monopoly giving the inventor exclusive rights to commercially exploit the innovation. A patent protects the innovation by legally preventing others from using it without permission of the owner. Typically, the inventor is the owner of the patent and they can give permission to others to use the innovation through licensing agreements.

The Bayh-Dole Act of 1980 in the US gave universities the ability to retain control of patent rights arising from federally funded research (Kesselheim, 2011). The goal of this legislation was to enhance commercial development of innovation by transferring IP ownership from government to the recipients of the federal funding. Universities and businesses argued that transferring the IP from government to innovators encourages investment and will bring more products of research to the market (Kesselheim, 2011). This argument was supported by the poor record of licensing government patents for commercial development with 30,000 patents rising from federally funded research and only 5% licensed. However, actual licensing rates for government-held patents in the biological sciences at 23% (Kesselheim, 2011). This demonstrates the commercial potential and interest in academic biomedical research. The Bayh-Dole Act was considered needed as it was viewed that industry needed exclusive patent rights to develop and commercialise university research (Mowery et al., 2001).

The surge in academic patents following the passage of the Bayh-Dole Act is commonly attributed to this legislation (Mowery et al., 2001; Mowery and Sampat, 2001). However, universities were already engaging in patenting before the Act, and its passage merely accelerated existing trends in academic patenting activity from 1970s (Henderson et al., 1998; Mowery et al., 2001; Mowery and Sampat, 2001). Instead of establishing the initial phase of academic patenting and licensing, the Act ushers a more recent stage in these activities (Mowery and Sampat, 2001). Analysing the impact of the Bayh-Dole Act, Mowery et al., (2001) demonstrates that US universities would have increased their patenting and licensing activities regardless of the implementation of Bayh-Dole in 1980. Patenting and licensing activities became less concentrated by a small group of elite academic researchers, and a more widespread activity amongst universities (Mowery et al 2001; Mowery and Sampat, 2001).

There was concern that the Bayh-Dole Act would shift university research away from basic research and towards applied research of commercial interest. However, this was not the case. Universities expanded patenting activity during a time of increase performance of basic

research resulting from increased federal funding for biomedical research (Mowery and Sampat, 2001). Academic research was already shifting towards biomedical research and the Act did not alter this trend. Research efforts did not begin to shift towards commercially valuable innovation following Bayh-Dole (Henderson et al., 1998).

Additionally, Shane (2004) notes that universities participate in a 'market for knowledge' and the Bayh-Dole Act led to a shift in university patenting in fields where licensing was a common and effective mechanism for acquiring new technical knowledge. The aggregate trend of increases in academic patents is not uniform across all fields as licensing is not equally effective across all technologies. The increase in patents was dominated by a sharp increase in biomedical patents compared to non-biomedical patents (Mowery at al., 2001; Mowery and Sampat., 2001). Hence, the increase in patents occurred in an area where licensing is common, such as biomedical research (Shane, 2004). Patenting growth and activities were influenced by the increase and dispersion of federal funding for biomedical research (Mowery and Sampat, 2001). Subsequently, the increase in patents may be due to advances in biotechnology and the birth of biotechnology during the same period (Cockburn, 2004; Mowery et al., 2001). The legislation enabled universities to transfer breakthrough science arising from federal funding to private firms for further development.

The combination of federal funding for biomedical research and the Bayh-Dole Act has been instrumental in pharmaceutical R&D. As previously described the bulk of societal benefits from university research comes from the private sector licensing and further developing it. Patenting is a strategy to improve knowledge transfer from academia to industry (Geuna & Rossi 2011). Commercial inventions are a secondary product of academic research as industry builds on existing knowledge as it pursues R&D (Henderson et al., 1998). Patenting promotes a university's ability to contribute to social and commercial development with 'contribution to society' now widely regarded as the third mission of universities (Compagnucci & Spigarelli, 2020). Before the Act, the research may not have been patented or licensed so the invention would not generate social or commercial benefit. A significant part of knowledge for discovering and developing new drugs is generated from federally funded research, therefore regulation should encourage licensing and transfer from academic institutes to industry (Henderson et al., 1998; Malerba & Orsengio, 2015; Sampat and Lichtenberg, 2011). Academic inventors exhibit above average scientific productivity, and highly productive scientists are more likely to become inventors (Lissoni, 2012). Academic patents are a useful indicator of

entrepreneurial activity as they commonly provide the basis for start-ups (Lissoni, 2012). Many biotech companies would not have been funded without key patents. Biological sciences fell within the scope of the patent system due to a pivotal US supreme court decision in Diamond v. Chakrabaty setting precedent for allowing the patenting of living organisms (Cockburn, 2004; Malerba & Orsengio, 2015).

The role of university research and innovation is reflected through patents not only in the US but also across Europe. Academics significantly contribute to patent activity in Europe, especially in science based areas of pharmaceuticals and biotech (Lissoni, 2012). Ownership of patents in the EU is different to the US. In the EU, most academic patents tend to be owned by companies rather than universities. However, Sweden has professor privilege allowing for the individual to own the patent. Most EU countries shifted away from professor privilege and towards company ownership however, there is no homogeneity amongst different EU Member States intellectual property rights (Geuna & Rossi, 2011).

2.4 Patents and Regulatory Protection Periods in the EU

Although patents are meant to be a vital incentive and reward for innovation, Budish et al (2015) demonstrates that the patent system provides little incentive for firms to engage in long-term research. Inventions that commercialise at the time of patent filing receive the full effective patent term. This is not the case for pharmaceuticals due to lengthy R&D time which reduces effective period of patent protection. Consequently, a lengthy R&D time reduces the inventors patent-based market monopoly and ability to generate return on risky investment.

Budish et al., (2015) demonstrates the phenomenon that companies underinvest in long-term research by comparing the number of clinical trials for localised vs. metastatic cancer. On average, metastatic cancer patients have a 5 year survival rate of 10% and double the number of clinical trials compared to localised cancer where patients have a much higher 5 year survival rate of 70%. This difference can be attributed to clinical trial lengths. Surrogate end points are utilised with metastatic cancer resulting in 3 year trial length, substantially shorter than the 18 year clinical trials for localised cancer. Evidently, the shorter clinical trials reduce R&D time resulting in increased investment. Budish et al., (2015) conclude that companies disproportionately invest in projects with longer effective patent protection and underinvest in

research that has a longer R&D time. Therefore, there is rationale for additional or different protection of innovation with lengthy R&D periods. Societal benefit can be maximised by awarding more post-commercial patent life to inventions with longer R&D time (Budish et al., 2015). This contrasts the patent system which gives shorter effective patent protection to inventions with longer R&D periods.

In the EU, innovative medicines receive concurrent legal protection through patents and SPC, and regulatory protection periods provided in EU pharmaceutical legislation (EC, 2023e). Patents are typically granted during the discovery phase and provide 20 years protection (WIPO, n.d). An SPC enables patents for medicinal products to be extended by up to 5 years (Swedish Intellectual Property Office, 2023). The SPC compensates for the time lost between patent filing date and the date the inventor is able to commercialise the innovation. It recognises the typically long drug development process by providing an additional 5 years protection. Regulatory protection of standard innovative medicines occurs through 8 years data protection and 2 years market protection (EC, 2023e). Only once patent, SPC, and the regulatory protection period expire can generics enter the market. In most cases regulatory protection expires before the patent and SPC expiry (Gaessler & Wagner, 2022). Regulatory protection only extends beyond patent and SPC when the drug market entry is 15 years after patent filing, usually due to very long drug development. This is demonstrated in Figure 2.

Figure 2: Patent protection runs parallel to regulatory protection

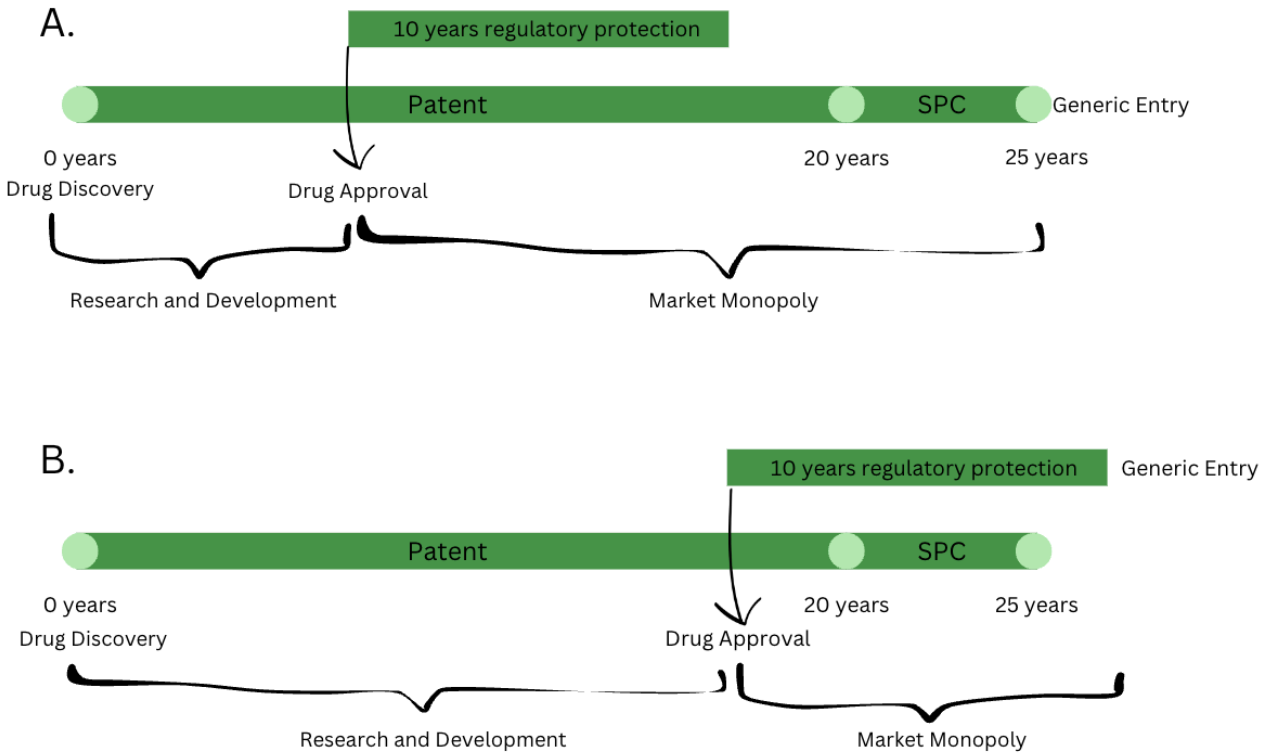


Figure Two. Adapted by the researcher from Gaessler & Wagner (2022). Demonstrates the concurrent Patent and SPC, and regulatory protection periods. Fig 2 A. Illustrates when there is a short drug development time and earlier drug approval leading to regulatory protection expiring before patent and SPC period. Fig 2 B. Illustrates when there is a long drug development time and later drug approval leading to regulatory protection expiring after patent and SPC period.

A key difference between patent protection and regulatory protection is patents can be challenged and invalidated whereas regulatory protection cannot. When a patent is invalidated sole legal protection occurs in the form of regulatory protection (Gaessler & Wagner, 2022). Regulatory protection period is an effective policy instrument to provide market monopoly when long pharmaceutical R&D results in shorter effective patent protection, or patent validity is uncertain (Gaessler & Wagner, 2022). In these cases regulatory protection may be an effective tool to restore incentives.

Data protection is a form of regulatory protection in the EU. Data protection protects a company's pre-clinical and clinical data from being referenced by another company in their regulatory filing for drug approval (EC 2023e; Gaessler & Wagner, 2022). Rewarding companies with data protection incentivises companies to pursue costly clinical trials as it creates barriers to entry for generics. Market protection then extends beyond data protection period as it is a period where generics cannot enter the market (EC, 2023e). Data protection is

controversial and debate often centres around the period of protection allowing for market monopoly and higher prices, and social gains from incentives to innovate. Strengthening legal protection increases incentives to invest in risky R&D projects, however, extending data protection periods results in prolonged higher drug prices due to limitations for generics entering the market (Gaessler & Wagner, 2022).

Gaessler and Wagner (2022) examine how the duration of market monopoly determines a company's innovation effort by observing R&D projects at risk of patent invalidation. Gaessler and Wagner (2022) model that when market monopoly is reduced by one year the likelihood of drug approval is reduced by 4.9%. This effect is driven by timing. When patent invalidation occurs early in drug development it has a greater impact compared to a loss later on during drug development (Gaessler & Wagner, 2022). This is likely due to greater sunk costs and reduced uncertainty further along the drug development timeline. Additionally, this is driven by larger firms with a bigger pipeline as abandoning a project with a reduced market monopoly frees up resources for other projects (Gaessler & Wagner, 2022). Smaller firms with fewer alternate projects to pursue are less responsive to the reduction in market monopoly.

Companies incentive to invest in risky and lengthy R&D projects depends on the return on investment. Overall, pharmaceutical companies tend to target R&D efforts towards drugs with a shorter development time to enjoy relatively longer market monopoly periods (Budish et al., 2015; Gaessler & Wagner, 2022). Longer market monopoly is associated with higher return on investment. This provides rationale for new, improved, and targeted protection periods for innovation.

2.5 Orphan drug development

In the US and the EU there is specific legislation to incentivise the development of drugs to treat orphan disease. Drugs can receive orphan designation when they meet criteria defined in legislation; the Orphan Drug Act in the US, and Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products in the EU. The criteria for orphan designation and their incentives for development of orphan medicinal products differs between legislation. However, the purpose of the legislations is the same. The presence of incentives recognises the low prevalence of orphan disease causes a limited market size compared to more

prevalent diseases. There are unmet medical needs for patients with orphan diseases, however industry is unwilling to invest in R&D for orphan diseases due to the small market size and limited prospect of return on investment (Tambuyzer, 2010). Regardless of disease prevalence or market size, R&D costs remain high and companies pursuing R&D for treatment of orphan diseases do not expect to recoup costs associated with the drug development (Braber et al., 2011). Incentives are used to encourage R&D for orphan drugs, recognising within standard market conditions the projected sales of these drugs are unlikely to cover costs incurred.

In the US, the ODA states a drug can receive orphan designation if it is intended for the treatment of a disease with a prevalence below 200,000 Americans (Rare disease at FDA, 2022). There are nearly 30 million Americans suffering from an orphan disease and most do not have an approved treatment option (Patel and Needleman, 2019). This Act provides a powerful economic incentive of a 50% tax credit for clinical trial expenses, 7 years market exclusivity from the date of the FDA's approval, exemptions of FDA fees, and regulatory advice (Tambuyzer, 2010; Yin, 2008).

In the EU, orphan disease is generally defined as a condition affecting below 5 in 10,000 people and designation is allowed based on medical plausibility and clinical benefit (Joppi et al., 2006; Maresova et al., 2016, Neez et al., 2020; Regulation 141/2000). More specifically, the Orphan Medicinal Product (OMP) regulations state medicinal product can gain orphan designation if:

a) it is intended for diagnosis, treatment, or prevention of a disease with a prevalence below 5 in 10,000 people, or if for a seriously debilitating or chronic condition where in the absence of incentives it is unlikely to generate sufficient returns to justify investment (Regulation 141/2000)
   AND
b) there is no authorised satisfactory method of diagnosis, prevention, or treatment, and if any do exist the OMP would be of significant benefit to those affected by the condition (Regulation 141/2000)

The approximately 7000 orphan diseases affecting 30-40 million individuals in the EU presents a public health issue and demonstrates need for treatment options (Joppi et al., 2009). The EU regulation incentivises investment for R&D of orphan drugs by providing research grants and protocol assistance to support development, and 10 year market exclusivity to increase return on investment (Neez et al., 2020; Regulation 141/2000).

2.5.1 Increase in orphan drugs development

The impact of these legislations in promoting orphan drug development is well-documented. Historically, the development of treatment for orphan diseases has been extremely limited. There is extensive discussion in literature surrounding how access to treatment for orphan disease has improved. In the decade before the ODA only 10 products had been approved by the FDA and bought to the market for the treatment of orphan diseases (Haffner, 2006). 24 years after the ODA this increased to 282 drugs and biologic products coming to market providing treatment to more than 14 million patients across the US (Haffner, 2006). From 1984 to 2008 the number of orphan drug approvals each year has remained constant but non-orphan drug approval peaked in the period 1994 to 1998 (Coté et al., 2010). Consequently, the proportion of drug approvals that are orphan drugs has increased and orphan drugs represent a large proportion of all newly approved FDA drugs and biologics (Attwood et al., 2018; Coté et al., 2010). In 2014, 55% of FDA approved drugs were orphan drugs and this dropped slightly to approximately 44% in the immediate years following (Attwood et al., 2018). The increase in orphan drug approvals follows the trend of increasing orphan drug designations per year (Attwood et al., 2018). Orphan drug designations have increased from roughly 60 in 2002, to over 200 in 2010, and 427 designations in 2017 (Attwood et al., 2018). Since the passage of the Act orphan drugs constitute an increasing proportion of new approved drugs. As published by Patel and Needleman (2019) there has been more than 700 orphan drug products enter the market. This provides evidence that since the passage of the ODA there has been a change in the trend of drugs entering the market. Since 1983 there has been more than 6,000 orphan-drug designation requests to the Office or Orphan Products Development (OOPD) with more 4,500 requests granted resulting in orphan drug designation. Approximately 50% of all drug-designations have been for oncology products, with 33% of orphan drugs being oncology drugs, which is followed by neurology, hematology, and gastroenterology (Maresova et al., 2016; Patel and Needleman, 2019).

The introduction of OMP regulation in the EU follows the same trends as seen in the US. Orphan drug development was slow to progress following the implementation of the OMP regulation. In the 4 years following the OMP regulations there were 255 orphan designations resulting in only 18 approved products, and average time between designation and approval

was approximately 2 years (Joppi et al., 2006; Macmillan, 2011). Orphan designation may occur at any time during the development process so time between designation to approval is not a great indicator of success. The shorter designation to approval time may reflect that some products received designation at advanced stages of the development process (Macmillan, 2011). Protocol assistance is a strong incentive designed to help during drug development as companies can ask questions regarding regulatory requirements (Macmillan, 2011). The earlier the company engages with the regulatory bodies the higher the chance of approval (Abedi et al., 2021). Orphan drug market authorisation between 2000-2007 was lower compared to non-orphan products (Joppi et al., 2009). The poor quality of dossiers accompanying orphan drug market authorisation applications slows the approvals (Joppi et al., 2006). This poor quality could be explained by insufficient funds for companies willing to pursue R&D for orphan drugs (Joppi et al., 2006).

While it was slow to progress in the initial years there has since been incremental growth in the number of orphan designations and approvals (Heemstra et al., 2008a). In 2000-2008 there were 58 marketing approvals in the EU for OMPs, a substantial improvement from the 18 approved by the end of 2004 (Brabers et al., 2011). In 2014, 17 products with orphan designation gained market authorisation (Maresova et al., 2016). The rate of orphan drugs approved is increasing with more and more products entering the market to address unmet health needs (Heemstra et al., 2008b). Orphan drug designation occurs during the development process before an application for market authorisation (Tambuyzer, 2010). As a result, the number of orphan designations will always be higher than approved OMP therefore a ratio of designations to approved products is not an appropriate measure of success of OMP regulation. (Tambuyzer, 2010). Development of drugs is a lengthy process and orphan drugs are no exception to this, therefore it is expected that orphan drug designation will always exceed the number of approved orphan drugs (Tambuyzer, 2010).

2.5.2 Innovative efforts for Orphan Drugs

Indicators of pharmaceutical innovation includes scientific output, number of patent applications, R&D expenditure, and pharmaceutical industry output of new chemical entities or top selling drugs (Heemstra et al., 2008a). In the EU, OMPs receive a central market authorisation granting approval in all EU Member States. The number of orphan designations

provides a good indication of OMP development in each EU member state (Heemstra et al., 2008a). Larger European countries have larger R&D expenditure and produce more orphan designations. However, when adjusting for size difference most orphan drug development occurs in North-Western Europe with Switzerland and Denmark as leaders (Heemstra et al., 2008a). These countries are leaders in biomedical scientific output, innovation in pharmaceutical development, and orphan drug output. While Sweden performs well in biomedical scientific output and innovation in pharmaceutical development it lags in orphan drug designations. This suggests Sweden struggles with the translation of science and innovation into pharmaceutical output (Heemstra et al., 2008a). This same trend is seen in other European countries such as the UK and the Netherlands. Orphan drug development is related to the performance of pharmaceutical innovation individual countries. Countries with more pharmaceutical SMEs, higher R&D expenditure, and more patents develop more orphan drugs. A pharmaceutical company's previous experience in developing orphan drugs increases the likelihood of product approval (Abedi et al 2021). Scientific output also plays a role in the development of orphan drugs however, the relationship between scientific output and orphan drug development is weaker than pharmaceutical innovation and orphan drug development relationship (Heemstra et al., 2008a). This identifies pharmaceutical innovation as the bottleneck in orphan drug development in the EU.

The increase in the number of orphan drugs entering the market following the introduction of orphan drug legislation does not accurately represent innovative efforts for orphan drugs, or where the innovative efforts are focused. Studying the number of new clinical trials better demonstrates innovation trends compared to focusing solely on products entering the market. Yin (2008) studied the impact of the ODA on R&D by using data on new clinical trials of long-established orphan diseases. Yin (2008) used a difference-in-difference strategy using orphan diseases and uncommon diseases with prevalence slightly over 200,000 as a control to assess the impact of tax incentives. There was an increase in the flow of new clinical trials for drugs treating orphan diseases immediately after the passage of the ODA compared to the clinical trials for the set of control diseases. An estimated 69% increase in clinical trials for drugs for orphan diseases is observed, and there is differing effect on innovation (Yin, 2008). Increase in innovative efforts occur amongst orphan drugs with a higher disease prevalence therefore a greater market potential (Yin, 2008). Orphan diseases with a lower prevalence saw an initial doubling of the flow of new clinical trials but this impact was not sustained. By lowering the fixed cost of drug development with the tax credit the ODA had a greater impact for innovation

surrounding orphan diseases with a higher prevalence (Yin, 2008). Therefore, stimulating R&D in smaller markets may require larger tax credits or multiple incentives (Yin, 2008). Nearly half of orphan drugs in clinical trials are for a rare cancer (Attwood et al., 2018). This is out of proportion with regards to orphan disease as there are approximately 500 rare cancer subtypes but there are around 7000 orphan diseases (Attwood et al., 2018). This suggests that market forces, such as disease prevalence and hence market size, still play a role in influencing R&D efforts for orphan diseases.

Market size is an important determinant of the level of R&D investment. Acemoglu & Linn (2004) show a 1% increase in potential market size leads to a 4% increase in innovative drug entry. This illustrates the relationship of market size and innovation, however there is a need for payers . In the US, when Medicare part D expanded drug coverage to include outpatient prescriptions there was expected increase in R&D efforts for diseases effecting Medicare beneficiaries (Blume-Kahoot & Sood 2012). According to Blume-Kahoot & Sood (2012), there was an increase in pre-clinical and clinical trials for drugs classes most likely to be impacted by expanded Medicare coverage. The Medicare market share for Alzheimer's disease is relatively large. Before the expanded coverage R&D for Alzheimer's disease was declining, however, the expanded coverage resulted in an increase in the number of clinical trials for treatment for Alzheimer's disease (Blume-Kahoot & Sood, 2012). However, Alzheimer's disease is not an orphan disease therefore these findings are not specific to R&D for orphan drugs. Blume-Kahoot & Sood (2012) establish that R&D effort is not only influenced by market size but also the ability for those within the market to pay. In the US, the funding of drug is determined by private insurance. This differs to the EU where each member state has their own pricing and reimbursement policy.

2.5.3 The impact of market exclusivity periods

The market exclusivity period is traditionally praised and credited for the increase in orphan drugs since the passage of the ODA in 1983. However, it is pertinent to note that most new drugs are also protected by a patent which provides 20 years market monopoly from the date of application. Patent offers the broadest level of protection as it may cover indications and uses, manufacturing, pharmaceutical composition, and dosage form (Seoane-Vazquez et al 2008). Patent protection and ODA market exclusivity period is concurrent. Therefore the 7 year

market exclusivity period is only utilised and provides benefit to the pharmaceutical company if the market exclusivity period outlasts the patent. Sarpatwari et al., (2018) illustrate the growth in orphan drugs likely has little to do with the 7 year market exclusivity as over time it has become increasingly redundant. Sarpatwari et al., (2018) evaluated small-molecule drugs that had an orphan disease indication at the time of FDA approval between 1985-2014. The result was 33% of new small-molecule drugs with an indication for an orphan disease outlasted expiring patents, and the 7 year market exclusivity protection accounted for 17% of their total market exclusivity (Sarpatwari et al., 2018). When further broken into 10 year periods (1985-1994, 1995-2004, 2005-2014), the proportion of small molecule orphan drugs where market exclusivity extends beyond the patent expiry date is decreasing. Consequently, majority of small molecule drugs with indication for orphan disease do not benefit from the 7 year market exclusivity period. This echoes previous research by Seoane-Vazquez et al., (2008) where market exclusivity extends orphan drug market monopoly by 0.8 years. It also mirrors the previously described trend in the EU where standard innovative protection is generally superfluous due to patent + SPC outlasting it (Gaessler & Wagner, 2022). Therefore, there is a diminishing role of legislative protection periods in addition to patents to incentivise and reward investment in R&D for orphan disease treatments.

Nevertheless, in event of successful patent challenge the market exclusivity period provided by the ODA is not withdrawn and is advantageous as it prevents generics entering the market. However, orphan drugs face less generic competition compared to non-orphan drugs (Seoane-Vazquez et al., 2008). 40% of biologic products have an orphan drug designation which can contribute to the lack of generics available for orphan drugs (Attwood et al., 2018). Approving generics for biologics is a complex process as they are biosimilar because they do not come from the same living organism as the innovator biologic. This results in *de facto* market exclusivity for the innovator pharmaceutical company, although there is no regulatory protection for this (Sarpatwari et al., 2018). Following orphan drug market exclusivity expiry it is rare that generics enter the market, indicating that other market factors such as small patient populations and low expected profits are barriers to generic entry (Seoane-Vazquez et al., 2008). The lack of generic competition can increase the price of orphan drugs.

In the EU, the 10 year market exclusivity period for orphan drugs is a key incentive for R&D for treatment of orphan diseases. However, there is concern and criticism that the 10 year market exclusivity period creates a market monopoly and allows for high prices (Roos et al.,

2010). High prices are costly to patients and health systems which can hinder access to treatment contradicting the aim of OMP regulation (Roos et al., 2010). The market exclusivity can be reduced to 6 years if the orphan product is substantially profitable, but this has never been enforced and is unlikely to be as it reduces investment incentives (Roos et al., 2010). Contrastingly, Brabers et al., (2011) negates this as the presence of follow-on OMPs demonstrates no prolonged market monopoly. A follow-on OMP in the EU is another pharmaceutical that has been approved or has received orphan designation for the same orphan disease (Braber et al., 2011). By 2008 there were 58 approved OMP for the treatment of 44 different orphan diseases indicating some diseases had more than one treatment option (Brabers et al., 2011). R&D of a follow-on orphan drug is unlikely to be discontinued after marketing approval of the first (Brabers et al., 2011). If there were high levels of discontinuation it would support Roos et al. (2010) hypothesis that there is a prolonged market monopoly. If there is only one OMP it is due to a company being first to develop it and competition is yet to enter the market, or the market is too small to attract further competition (Brabers et al., 2011; Tambuyzer, 2010).

There are several factors beyond the 10 year market exclusivity period influencing the likelihood of a follow-on orphan drug. Increased scientific output leads to a greater understanding of disease which increases the chance of a follow-on OMP (Brabers et al., 2011). Orphan diseases with a higher prevalence, and diseases where the first OMP generated high annual sales were also associated with follow-ons (Brabers et al., 2011). Oncologic orphan diseases were likely to have follow-on, and orphan drugs for rare cancer represent 30-40% of orphan drugs developed in the US and Europe (Brabers et al., 2011; Tambuyzer, 2010). Oncology is the most common therapeutic area for authorised orphan drugs (Macmillan, 2011).

Overall, trends influencing orphan drug development are the same between the EU and US, and suggest that the incentive of market exclusivity is not the sole cause of orphan drug development. Disease prevalence and market size are important factors as no company would be motivated by market exclusivity if no market exists (Tambuyzer, 2010). Basic biomedical research is carried out in publicly funded academic institutions and drug development for orphan disease is more likely when there is high scientific output. This research provides scientific knowledge which is transferred to industry to build on it and pursue pharmaceutical R&D.

2.5.4 Other factors driving orphan drug development in the US

The ODA in the US was a landmark legislative piece, however there are many challenges in orphan drug development. These include a poor understanding of the natural history and biological nature of disease, difficulties with clinical trials and appropriate end points, and challenges to gain needed R&D investment (Macmillian 2011; Tambuyzer, 2010). In the US, to address these challenges the Office of Orphan Products Development has introduced grant programs which assist the development of orphan drugs (Imoisili et al., 2014; Patel and Needleman, 2019). These initiatives address challenges associated with developing drugs for orphan disease. They complement incentives in the ODA, recognising that more support is needed to address orphan diseases.

In 2016 the FDA launched a $2 million Natural History Grants Program with the purpose of supporting studies to gain a better understanding of orphan disease (Patel and Needleman, 2019). The grant aims to address a challenge in drug development for orphan diseases which is the limited knowledge surrounding the natural history and biological basis of disease compared to common more prevalent diseases (Patel and Needleman, 2019). Improved understanding would allow for better clinical research and development for treatment including improved clinical trial design.

2.6 Institutional Theory

Institutional theory explains how organisations interact with the world around them (Furusten, 2013). As proposed by Meyer and Rowan (1977), it explains how organisations adopt and conform to institutional rules to gain legitimacy, even though these rules commonly conflict efficiency. Formal organisation structures arise in highly institutionalised contexts. The formal structure refers to the rules, policies, and procedures within organisations and these structures are shaped by both internal and external factors. The formal structure is influenced by public opinion, laws and regulations, views of important stakeholders, and the education system. Therefore, organisations do not develop these structures in isolation instead they are influenced and reflective of societal norms, beliefs, and expectations. These structures are rationalised and serve as institutional rules which organisations must follow in order to be viewed as legitimate within their social context. Meyer and Rowan (1977) argue that these institutional rules

function as myths as organisations adopt them ceremonially due to social expectation and to gain legitimacy. In this context myths are not a falsehood but rather shared beliefs and behaviours.

A central concept to the theory developed by Meyer and Rowan (1977) is isomorphism. Meyer and Rowan (1977) argue that the rise of the state and expansion of jurisdiction results in organisations that lose their autonomy as they adapt to external pressures is a misleading view. Instead, they contrast this suggesting that organisations do often adapt to their institutional environment but also commonly have a key role in shaping it. Powerful organisations attempt to build their goals and procedures into society as institutional rules. Organisations in a competitive environment establish themselves and seek protection in the form of institutional rules. Competitors must compete within these rules predefined by existing organisations. Organisations that do not follow these rules lack legitimacy and are more vulnerable to claims they are negligent.

DiMaggio and Powell (1983) further build on Meyer and Rowan (1977) as they explore institutional isomorphism and its impact on organisations. Organisational change can be attempted by three fundamental isomorphic mechanisms: coercive, mimetic, and normative (DiMaggio & Powell, 1983).

Coercive isomorphism results from formal and informal pressures exerted on organisations by other actors they are dependent on (DiMaggio & Powell, 1983). In some cases, organisational change is a response to legislation. Legal and technical requirements of the state shapes organisations behaviour. The existence of a common legal environment affects many aspects of an organisation's behaviour and structure. The effects of coercive isomorphism can be subtle, and organisations are increasingly homogenous within certain environments (DiMaggio & Powell, 1983).

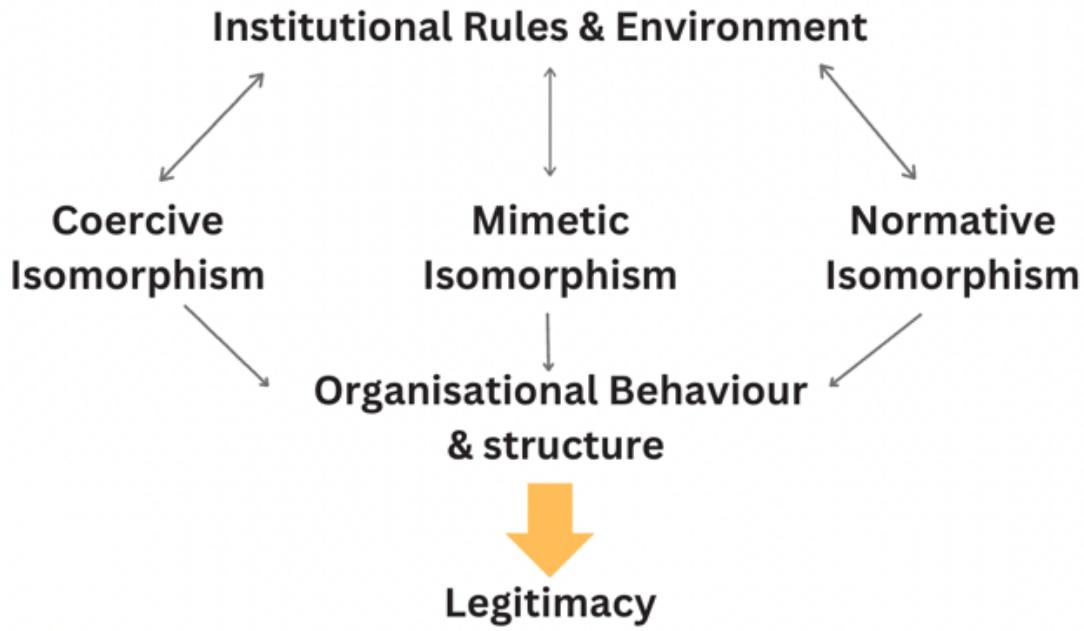
Mimetic isomorphism is a response to uncertainty (DiMaggio & Powell, 1983). Uncertainty is a powerful force that encourages imitation. Organisation's mimic structure and strategies of extant successful organisations resulting in organisations becoming more similar. This can occur when there is competition, when technology is poorly understood, goals are vague, or the environment creates uncertainty (DiMaggio & Powell, 1983). Organisations will model

themselves off existing and successful organisations to be seen as legitimate and enhance survival prospect.

Normative isomorphism is associated with professionalism and shared beliefs within an institutional environment (DiMaggio & Powell, 1983). Formal education plays an important role in this as universities and professional training institutes are centres where professional and organisational norms are developed (DiMaggio & Powell, 1983; Jaja et al., 2019). An obvious example of normative isomorphism is doctor bedside manners (Jaja et al., 2019). Doctors in different healthcare environments behave in similar ways when interacting with patients due to formal education and established professional standards. Therefore, while various professionals within an organisation may differ from each other they exhibit similar norms to professional counterparts in different organisations (DiMaggio & Powell, 1983). The growth of professional networks across organisations allows for new norms and values to spread.

Organisations do not experience all external pressures at the same time or to the same level, but intermingle and co-exist (Frumkin & Galaskiewicz, 2004; Furusten, 2013). Isomorphic processes of institutional change can be used to explain the homogeneity of organisational behaviour and structure within their environment (Beckert, 1999). The interaction between institutional rules, isomorphism, and organisational behaviour is demonstrated in figure 3.

Figure 3: Institutional Theory



Developed by the researcher to demonstrate how institutional rules and environment exert pressures on organisations. These different pressures result in isomorphic behaviour of organisations as they seek legitimacy to enhance survival prospects. The double headed arrows between institutional rules & environment and isomorphism demonstrates how powerful organisations can embed their beliefs, norms, and values into institutional rules and environment

2.6.1 Institutional theory in the context of this research

The pharmaceutical industry is highly institutionalised therefore it can be expected isomorphism occurs due to external pressures. These external pressures drive organisational behaviour, particularly the adoption and implementation of regulations. Government agencies are some of the most influential environmental actors to encounter organisations, commonly through legislation (Frumkin & Galaskiewicz, 2004). This holds true for the highly regulated pharmaceutical industry. Regulatory compliance within the pharmaceutical industry is a clear form of coercive isomorphism. Government agencies set regulations and industry standards that must be followed (EC 2023a). Adhering to these guidelines allows for organisations to operate legally, gain approval for their products, and provides legitimacy.

Although the theory does not explicitly include legislative incentives such as regulatory protection periods, this does fit within the context of institutional theory. As previously described legislation and regulations have impacted pharmaceutical industry activities. While it is not a legal mandate for stakeholders within the industry to patent research and innovations,

or pursue R&D for orphan diseases, the regulatory incentives coerce industry to behave a certain way. Incentives protected by legislation are a powerful tool for driving institutional change through coercive isomorphism.

Although Institutional Theory has not been applied to the pharmaceutical industry in previous literature the evolution of business models in the pharmaceutical industry displays key characteristics that align with institutional theory. As large pharmaceutical companies shifted away from their fully integrated business models and relied on external capabilities, particularly the specialist knowledge emerging in biotechnology, a prominent vertical business model emerged (Malerba & Orsengio, 2015). The change in business model was largely a response to uncertainty as large pharma companies needed to rapidly absorb breakthrough science which was beyond current expertise and capabilities. Additionally, as this proved successful in the US other countries and regions attempted to replicate (Malerba & Orsengio, 2015). Mimetic isomorphism can explain the shift in organisational structure and behaviour. Globally, organisations attempted to mimic successful models in the US to continue to be seen as legitimate and enhance survival prospect.

Additionally, during this time the Bayh-Dole Act and orphan drug legislations were introduced. These legislations impacted organisational behaviour in the pharmaceutical industry. As previously described, there was increase in academic patents which was important for commercialising basic early stage research. Subsequently, Orphan Drug legislations in both the US and EU resulted in increase in orphan drug development (Coté et al., 2010; Haffner, 2006). The legislation was an external factor influencing organisational behaviour through the mechanism of coercive isomorphism.

While there are no empirical examples of institutional theory in the pharmaceutical industry, it has been used within the healthcare industry. Sherer et al., (2016) utilises institutional theory to explain Electronic Health Records (EHR) adoption in a healthcare environment in the US. Healthcare is a highly institutionalised environment with a high degree of professionalism and regulation. The study by Sherer et al., (2016) demonstrates that institutional forces can have a major impact on adoption of new technology in healthcare. Mimetic isomorphism occurred at first due to uncertainty surrounding the technology and its use. Mimetic isomorphism was almost as strong as normative isomorphism in the absence of coercive isomorphism. However, when new legislation (the HITECH Act) was implemented, all providers needed to adopt the

EHR technology to participate in regional health information exchange. This reduced the uncertainty as there was less concern that a healthcare provider would bear the cost of the technology without reaping the benefits due to other practitioners not adopting it. In this situation regulation acted as an external force resulting in coercive isomorphism which was as strong as normative isomorphism for influencing organisational behaviour to achieve legitimacy.

While it does not appear to be used in previous studies of pharmaceutical industry this theory can apply when examining how the pharmaceutical industry responds to institutional pressures such as legislation changes. The proposed changes to the EU pharmaceutical legislation, especially the changes to regulatory protection periods, attempt to push the industry's R&D efforts towards public health needs. The regulation protection periods are not mandated therefore industry still has choice in R&D pursuits. The regulatory protection periods act as an incentive and reward for R&D efforts that address public health needs. Using the theory in this context seeks to understand how regulatory protection periods impact the direction and delivery of healthcare. In this research context this theory will be used to develop an understanding of the impact proposed changes to regulatory protection periods have on the direction of pharmaceutical R&D.

2.7 Summary

The pharmaceutical industry needed to respond to increased federally funded biomedical science from universities to maintain strong innovative pipelines. This resulted in large pharmaceutical companies shifting away from a fully integrated business model and participating in licensing deals to pursue innovative R&D efforts. Relationships between academic, biotech, and pharmaceutical companies was strengthened. Concurrently, barriers to academic patenting in the US were broken with the implementation of Bayh-Dole Act. There was no shift from basic research to applied research, but the Act accelerated existing trend in academic patenting. Basic biomedical research from academic institutions and patents are vital assets in drug development.

In the EU regulatory protection periods occur alongside patent and SPC protection. However, they are largely superfluous due to expiry before the patent and SPC. This trend is observed

with orphan drugs, however, the passage of orphan drug legislation in both the US and EU resulted in an increase in orphan drugs. Regulatory protection periods are commonly credited for the increase in orphan drugs, however there are several other factors which have influenced this. These include disease prevalence and market size, basic science output, and biological understanding of disease.

Given the challenging and lengthy nature of pharmaceutical R&D, the trends in drug development and their outcomes cannot be attributed to one key change but rather a cumulation of funding, intra-industry collaboration, legislation, and market demands. It is evident that the pharmaceutical industry has been subject to regulation as an external force, resulting in coercive isomorphism influencing organisational behaviour to remain legitimate.

Most existing literature assesses the impact of legislation by utilising retrospective methodologies. There is a focus on the outcome of regulations through trends in patenting, number of orphan drug designations, and orphan drugs with regulatory approval. There is a lack of understanding of industry perspective surrounding regulatory protection period as incentives for R&D, especially regarding the proposed changes in EU pharmaceutical legislation. Institutional theory will be used in the context of this research to address aims and research question. This research aims to address a gap in literature surrounding industry perspective of regulatory protection periods as incentives. The aim of this research is to utilise key pharmaceutical industry stakeholders' perspective surrounding proposed changes to regulatory protection periods in EU pharmaceutical legislation to develop an understanding of how incentives in legislation impact organisational behaviour in the pharmaceutical industry. The research question to be answered is "What is the impact the proposed changes to regulatory protection periods could have on the direction of the pharmaceutical industry within the EU?"

3. Methodology

This chapter describes the methodology used by the researcher in this thesis and outlines rationale for decisions. It includes the qualitative research strategy, study design, trustworthiness, and ethics.

3.1 Qualitative research strategy

Qualitative research is able to provide complex textual descriptions of a person's experience and perspective with a given research topic (Mack et al., 2005). The researcher comes from the interpretative paradigm and the research objective is to gain insights into the perspective of key pharmaceutical industry stakeholders on proposed EU pharmaceutical regulatory incentive changes. The key research question is "what makes industry go in a certain direction and what is the basis for the decision?"

Extant literature on the impact of regulatory incentives shows heavy bias towards retrospective methodologies using quantitative methods such as counting. This focuses primarily on outcome and excludes the perspective of key industry stakeholders leading to a lack of understanding of what drives decisions for organisations to pursue certain R&D activities. Although qualitative strategies are uncommon in this field utilizing them is important in broadening understanding of the topic. Qualitative research aids the interpretation and deepens understanding of the complex nature of a particular situation, which gives more context to quantitative data (Mack et al., 2005).

Qualitative methods are less dependent on sample size for generating meaningful results. Employing a qualitative research strategy emphasises the detail, quality, and depth of data collection rather than volume of data (Mack et al., 2005). Focusing on key industry stakeholders best suited to answer the research question allows for a focused in-depth exploration of the topic. This generates comprehensive and valuable data to answer the research question.

3.2 Study Design

Semi structured one-on-one in-depth interviews formed the data collection method for this qualitative research. This type of data collection method is optimal for gaining participants perspective (Mack et al., 2005). The researcher was the interviewer and the interviews aimed to gain a deeper understanding of the participants perspective on the EU pharmaceutical regulatory changes. Allowing the natural flow of conversation and being able to follow up and explore participants responses more deeply was a key benefit of the in-depth interviews (Belk et al., 2012). The researcher directed the conversation using a protocol with open-ended questions to explore the participants perspective on proposed changes to EU regulatory incentives. Open-ended questions were beneficial for this research as there is no limit on the length or range of response the participant can offer (Mack et al., 2005). Qualitative research strategy allows for flexibility where the study design is iterative, therefore data collection and research questions are adjusted based insights gathered (Mack et al., 2005). How participants respond affected how the researcher responded and what questions were asked next.

The interviews were organised in four key sections to guide the interview. These sections are understanding the history and background of the participant, opportunities the regulatory incentive changes provide, challenges the regulatory incentive changes propose, and how these proposed changes impact the industry direction. The interview was structured this way as it enabled a greater understanding of the participants experience within the industry, it then established the participants perspective surrounding the proposed changes, and finally bought all the information together to gain insight into industry perspective of how regulatory changes impact industry activity. Full interview protocol is provided in Appendix One

Structured interviews were avoided by the researcher due to their rigid nature. Questionnaires are standardised on a pre-determined set of identical questions and therefore not appropriate for the exploratory nature of this research (Mack et al., 2005; Saunders et al., 2019). As structured interviews do not allow for flexibility there is no chance to ask follow-up questions to gain a deeper understanding of what has been said. There is a higher possibility of missing essential data leading to weakened insights. Focus groups were not appropriate for this research topic as they lack the depth one-on-one interviews have and are often complicated by group dynamics (Belk et al., 2012). Focus groups are not the best method when aiming to gain

attitudes of participants regarding a specific topic. Furthermore, the ethical approval from the University of Auckland for this research does not include focus groups.

Before the interview, the researcher provided the participant with some background on the topic. The purpose of this was to establish a mutual understanding of the topic, especially as there are various proposed changes to the EU pharmaceutical legislation, and this research focuses on regulatory protection periods. The researcher also provided the participant key questions for the interview. This allowed the participant to prepare for key sections in the interview with the aim of generating deeper insights. The information provided to the participant before the interview is provided in Appendix Two.

3.3 Participant selection

There is a wide variety of pharmaceutical industry stakeholders. This includes academics and researchers, pharmaceutical companies, state legislation and policy makers, regulators, investors, health care professionals, patient advocacy groups, and patients. To select appropriate participants for semi-structured in-depth interviews purposive sampling was used by the researcher. Purposive sampling is non-probability sampling technique where participants are selected relevant to the research question (Bell et al., 2022; Saunders et al., 2019). It relied on the judgement of the researcher as to what individuals are best equipped to answer the research question. Purposive sampling allowed the researcher to select participants based on an inclusion and exclusion criteria.

Inclusion and exclusion criteria: Individuals from organisations within the pharmaceutical industry with expert knowledge regarding pharmaceutical public policy and the impact EU pharmaceutical regulatory protection periods have within the industry. The organisations must be in Sweden. Individuals must speak fluent English as this is the researcher's native language, no translation will occur.

The inclusion and exclusion criteria was limited to organisations in Sweden for two key reasons. Firstly, the researcher is based in Sweden therefore it is feasible to recruit participants from Swedish companies. Secondly, Sweden is a highly innovative country in respect to

pharmaceutical R&D (Heemstra et al., 2008a). Therefore, it can be expected that stakeholders in Sweden can provide in-depth insights to answer the research question.

Snowball sampling was another non-probability sampling technique used by the researcher. Snowball sampling is advantageous when the potential interview participants are hard to identify or contact (Saunders et al., 2019). It was used when recruiting participants as contacts were asked if they knew someone who would be interested and suitable to interview about the topic. This generates a referral chain. Snowball sampling usually generates a homogenous sample as contacts are likely to refer someone with characteristics similar to themselves (Saunders et al., 2019).

Participants were invited to participate in the research by the academic supervisor. When a positive response was received the participant's information was passed on to the researcher. This is in line with the ethical approval for this research. Both parties agreed on a time for the interview and for the interview to take place online using Microsoft Teams where the record function is used to obtain an audio recording. During the interviews, the researcher utilised a pre-developed semi-structured interview protocol to guide the conversation.

A total of nine participants were recruited for the study and interviews averaged 50 minutes. Although research participants were associated with different areas of the pharmaceutical industry the study sample was homogenous; participants all meet the one inclusion and exclusion criteria, were all provided the same pre-interview information, the same interview protocol was used for all participants, and one analysis was conducted.

3.4 Data analysis

Semi structured in-depth interviews were audio recorded and then transcribed by the researcher. The transcriptions were sent to participants via email within 14 days of the interview. The participant then had 14 days to respond with any corrections to the transcription. This is in line with University of Auckland ethics approval for this research.

The researcher used an inductive approach to data analysis. This aligns with the interpretative paradigm the researcher identifies with as an inductive approach has strong emphasis on

subjective interpretation. The inductive approach moves data to theory allowing to generalise from specific to more general as theory is generated or built upon (Saunders et al., 2019). It is appropriate for the researcher to use an inductive approach as institutional theory has not been explored in this research context. In the context of this research the perspective of pharmaceutical industry stakeholders regarding regulatory incentives will allow the researcher to build on the branch of coercive isomorphism from institutional theory.

Once interviews were transcribed the researcher analysed the data using a thematic analysis. Data was imported to a NVivo 20 software for thematic analysis. Thematic analysis allows themes and patterns to emerge from the data (Saunders et al., 2019). The researcher used codes to identify themes or patterns in relation to the research question. Thematic analysis allows for different interview data to be integrated to identify key themes for further exploration. This aligns with the researcher's inductive approach as it allows themes to organically emerge and unknowns be explored, and then contribute to theory.

3.5 Ensuring quality of research design

The quality of qualitative research is assessed through dependability, credibility, and transferability (Saunders et al., 2019). The researcher ensures the quality of research by taking steps to achieve these different criteria and by acknowledging bias.

The researcher sought to achieve dependability through a rigorous methodology. The researcher sent the same pre-interview information to all participants. This established a base and mutual understanding of the topic to minimise any researcher or participant error related to misunderstanding. The researcher allowed each participant to suggest a time and meet online for their convenience. This enabled the participant to find a suitable time and space to minimise participant bias.

The researcher acknowledges their bias. The researcher comes from a healthcare and pharmaceutical background therefore has prior knowledge surrounding drug development and delivery of healthcare. Although not employed, the researcher is supported in this research by a global pharmaceutical company. Therefore, the researcher naturally developed preconceived opinions and ideas surrounding the topic. To reduce this bias effort was made to ask interview

questions in the same manner and avoid leading questions. The one researcher conducted all interviews and then analysed the data. A semi-structure interview protocol was used and any changes to key questions asked will be recorded in the researcher's diary notes. The same researcher throughout achieves consistency.

The researcher aimed to achieve credibility through checking their semi-structured interview guide with their supervisor. Adjustments to questions were made based on feedback. After the interview, the transcripts are sent to the participants to allow for any correction to ensure accuracy.

The researcher provides a full description of research design, interview protocol, context, results and interpretations aiming to provide the reader the ability to judge if the research results can be transferred to other settings.

3.6 Ethical considerations

The study's ethical approval was approved by University of Auckland Human Participants Ethics Committee (UAHPEC) for "Masters in Bioscience Enterprise Coursework Ethics" with ethics approval expiring 16 April 2025 (Reference number UAHPEC20382). Research was conducted in accordance with the ethical standards set by UAHPEC. The researcher completed and passed the quiz of the four required ethics modules before conducting interviews. These modules were *introduction to ethics, anonymity and confidentiality, informed consent, and conflict of interest.*

All participants were provided with a Participant Information Sheet (PIS) and a Consent Form (CF) before interviews were conducted. Participants are informed their participation is voluntary and have the right to withdraw themselves or data from the research without giving a reason within 14 days from the interview. The PIS outlines there is no conflict of interest, and the CF obtains written informed consent.

Due to the nature of semi-structured in-depth interviews anonymity could not be achieved, however confidentiality regarding participants identity was upheld. Research participants confidentiality was protected as each participant was allocated a code, i.e. participant A,

allowing their identity to not be recorded in final report. The code is only familiar to the researcher and reduced the risk the identity of the participant will be recognised. Confidentiality was maintained throughout the transcription process as interviews are transcribed by the researcher themself.

4. Results

This chapter will discuss the results to address the research aim and question presented in chapter 1. First an overview of the participants characteristics, then key themes that emerged from thematic data analysis using inductive reasoning. There are four main themes; role and value of regulatory protection periods, regulatory protection and investment in innovation, regulatory protection as an incentive for equal access, regulatory protection and orphan drug development. The third theme, regulatory protection as an incentive for equal access, is divided into two subthemes; barriers to launching in 27 Member States, and companies will not launch in the EU. These four main themes present participants perspective on the impact the proposed changes to regulatory protection periods will have on the pharmaceutical industry in Europe. The research results will be discussed in Chapter 5: Discussion.

4.1 Participant characteristics

Nine research participants were recruited for this research. The research participants represent a cross-section of the industry, however it is a homogenous sample as all participants had similar professional experience and knowledge surrounding the research topic. Table 2 displays the participants' characteristics illustrating they meet the inclusion and exclusion criteria, are a homogenous sample, and are appropriate participants for addressing this research question and aim. The first column lists the research participants and following this the participants will be referred to as P1-P9 when connected quotes to the participants. The second column specifies the area of the pharmaceutical industry the participant was from, and all organisations were based in Sweden. The final column describes the participants professional background and experience.

Table 2: Participant Characteristics

Participant	Area of Pharmaceutical Industry	Participant Experience
P1	Large Pharmaceutical Company	Experience in public affairs and market access for both Sweden and Europe.
P2	Trade Organisation for life science companies	Experience with small and big pharmaceutical companies and drug discovery.
P3	Organisation at the intersection of academia, industry, and society	Experience in research, marketing, sales and pharmaceutical policy surrounding growth and innovation in Sweden.
P4	Trade Organisation for researched based innovative pharmaceutical companies	Experienced with intellectual property strategy in life science.
P5	Small BioPharmaceutical Company	Experience in all stages of pharmaceutical product life cycles, including sales, marketing, and management.
P6	Patient Advocacy Organisation	Experience in patient advocacy representing patient perspective on medical and pharmaceutical issues.
P7	Venture Capital investing globally in drug development	Academic and professional experience in medical science before transitioning into Venture Capital.
P8	Consulting company providing strategic advice within public affairs	Experienced providing advice to life science companies surrounding government and international affairs.
P9	Medium sized Pharmaceutical company	Experience in the pharmaceutical industry focusing on market access and EU policy.

4.2 Theme One: The role and value of regulatory protection periods

Analysis of interview transcripts identified that the proposed changes to regulatory protection periods would be unlikely to impact basic research, as research in this early stage is not focused towards reaching the market. Early stage research decisions are not influenced by regulatory protection because there is poor predictably that a product from this research will enter the market. Therefore, regulatory protection periods are not seen to incentivise certain research, or push research towards commercial opportunity, because in the early stage there is no predictability of research reaching the market. The period of regulatory protection that will be awarded does not influence research decisions because the regulatory protection period is an end stage reward which is received when entering the market.

"If you're doing research today, it's so hard to predict what will happen to that research in 20 years or 10 years. So I don't think that it will stop anyone or it definitely won't stop any sort of scientists or researchers from saying no I won't develop this drug because I may not be able to protect it for that extra year" – P6

"…If you look back to when you make those decisions because those decisions are probably made 10 years ago, it's very difficult to know what will happen in 10 years because that's prior to phase two trials, prior to phase three trials and so on, so you don't care much. I would also say that it doesn't really matter too much because if you have a 10 years or 12 years and you have no predictability if you even going to reach the market…" – P3

Regulatory protection periods contribute to a more comprehensive intellectual property framework. The protection periods play a pivotal role in incentivising pharmaceutical companies to engage in drug development. Participants attributed high value to regulatory protection periods as an intangible asset compared to a patent. It is a fundamental incentive for both big and small pharmaceutical companies to invest in R&D as it is stronger than a patent. The value and strength of regulatory protection surpasses a patent. Regulatory protection and patent may occur concurrently, but a patent may be successfully challenged unlike regulatory protection. However, these proposed changes weaken the intellectual property framework. Commonly regulatory protection expires before a patent and upon it's expiry it is common for there to be patent challenge, often successful patent challenge. The shorter the regulatory protection, the earlier the expiry, the sooner patent challenges begin. The proposed changes essentially weaken the intellectual property system because the period of because intellectual property protection will be shorter as successful patent challenges will occur earlier.

"… I contribute a lot of value to the regulatory data protection because that is the say basic or most essential type of intellectual property protection you can have for your new pharmaceutical compound, and I think that is what really incentivizes both big and small pharma to develop new drugs" – P7

"when I speak with my lawyer colleagues, they always explain me that although both are legally binding the regulatory data protection is stronger … once RDPs (regulatory data protection) are over but patents are still on, there's a lot of attempt and actually quite a significant amount of success… so that's why the RDP (regulatory data protection) and market protection is of course very important." – P9

"the main challenge is that you are worsening the incentive system and the intellectual property framework, because regulatory data protection is an ex ante right, meaning that if you collect the data that you have to in order to get market approval then you will get these number of years for protection and that cannot be protected by a patent." – P4

Participants highlighted the patent system is not fit to protect the most modern and advanced therapies which emphasises the importance of strong regulatory protection when an innovation falls outside the scope of patents. Regulatory protection captures the most innovative treatments that are beyond the scope of patent protection, and provides strong protection for them.

"I think that's one of the beautiful things with this entire track of regulatory data protection that it actually adds the possibility to get your research protected even if you have built on something, I mean academic research that you didn't really see the business opportunity in, it went public then that patenting opportunity is lost… so this is a modern way of grasping the value of innovative ideas that isn't really suitable for the patent system" – P2

Furthermore, the value of regulatory protection is expected to continue to increase as science advances and treatments become more complex, and therefore do not fall within the scope of patent protection. Pharmaceutical R&D pipelines are trending towards these complex personalised treatments but strong regulatory protection is needed for this to continue. Participants emphasised the importance of strong regulatory protection for personalised medicines. This illustrates the vital role regulatory protection periods plays in R&D for personalised medicines.

"...if you have product in the pipeline that may not be patent protected or where the patent may lapse before you have a market approval and that you will only be relying on regulatory data protection that those products will maybe not be as developed or invested in Europe as they could have if the system will stay as it is now or even improved... products are becoming more complex and then the data protection is becoming even more important. So in the future, we will see that the data protections value, according to me, is more important than we have seen it is today..." – P4

"...for a lot of the more upcoming types of treatments, advanced therapies which is based on cell therapy for instance...that's the process that's quite difficult to catch in a patent application, then it's the regulatory data protection that will be a very important part" – P2

"If you're doing a CAR T cell therapy, you're doing this patient by patient. It's not the same molecule for all the patients, you are extracting cells from the patient yourself and sending them to a centre...for those drugs where you actually don't have a molecule to protect with the patent, the regulatory data protection will be of even greater importance" – P8

Overall, theme one presents the participants discussion surrounding the role and value of regulatory protection periods for pharmaceutical innovation. Early stage research focus' are not expected to be impacted by regulatory protection periods. Basic research in the early stage is not focused towards market outcomes as there is limited predictability of the product reaching the market. Therefore, there is not a strong relationship between regulatory protection periods and early stage research decisions. The period of protection is not perceived to be an incentive for specific research directions, such as towards unmet medical need, during the early stage. However, participants recognise the crucial role of regulatory protection describing it as the strongest intellectual property protection for pharmaceuticals. The value of regulatory protection periods increase when innovation falls outside the scope of patents, such as personalised medicine.

4.3 Theme Two: Regulatory protection and investment in innovation

Participants discussed the relationship between regulatory protection periods and investment. Regardless of the presence of intellectual property protection there is a high cost associated with drug development. Investment in all stages of R&D is crucial for products reaching the market. As regulatory protection periods begin at market authorisation they provide protection for the earlier investment in R&D. They are especially beneficial for innovative drugs with a long development time due to the higher R&D costs and consequently larger investments. Therefore participants attributed value of regulatory protection periods with protection of investment.

> *"… it will cost you as much to develop a drug with this strong patent protection as one without patent protection, so what the data protection system is doing is that you are actually protecting the actual investment and the development of your pipeline, so it's very much connected to the actual value that you have put in…" – P2*

> *"for projects that are complex, that puts additional time to the development, this is where the regulatory data protection is of more importance, because that means that the actual patent period will be shorter" – P8*

Participants emphasised that in practise the proposed changes to regulatory protection periods are a decrease and will therefore harm the attractiveness and willingness to invest in the EU pharmaceutical industry. The proposed changes would introduce higher levels of uncertainty, consequently increasing risk and therefore decreasing the attractiveness of investing in the EU pharmaceutical market. Investors will look to more attractive industries or markets to invest which puts the EU pharmaceutical industry into a less competitive position, and investment is driven into other more attractive markets.

> *"… pharma business is extremely dependent on the stock market and that means that if insecurity increases even more, so patent and data protection go down, money moves to other businesses, we lose competitive power….this has been proved again and again that less data protection makes investments go away" – P1*

"...investors work under the premise of expected return, the higher the risk, the higher the expected return…. If today there is a good reason for investors to invest in healthcare and in drugs and all of that, but if tomorrow there is a better return elsewhere, investors would have no problem whatsoever to move from healthcare" - P9

Data analysis showed the increase in uncertainty is largely attributed to the criteria for extensions of protection periods. When seeking investment, especially in early R&D stages, companies do not know if they will meet the criteria for extensions. It is not known what the drug's specific indication is or if it can treat multiple indications. Therefore, the total period of regulatory protection that will be rewarded cannot be predicted. This poor predictability harms ability to gain crucial investment. This poor predictability of total protection period increases the risk for investors as they would now assess the ability to gain a return on investment in the shorter but predictable protection periods. The investor will not take into account the possibility for gaining extensions, they only calculate on what they know they will receive. If the investor cannot see that they will be able to generate a return on investment in the shorter time period, those potential drugs will suffer. This unpredictability is expected to have a greater impact on small companies.

"I would say when you take the decision to invest in the development, you cannot rely on the extensions because the circumstances that needs to be clear before you know if you have an extension or not … I assume that you go will go for the lower option and then you see this as a possible add-on, but you cannot factor it into your calculations" – P8

"...unmet medical need and new indication, these are two parameters that are uncertain. We don't know when we invest into a new drug if it will be able to address unmet medical need… that's a risk and it's something unpredictable as compared to the regulatory data protection basic period which is very predictable." – P7

> *"...the sort of extension that is very difficult to predict, and what is important for these projects and companies is to have reliable system when you are looking for funding because if the investor cannot make a very straight case to understand how many years of protection will I be given, it's impossible to make an assumption of how much time will you have to get back what you have invested...it's the unpredictability that makes this so dangerous for smaller companies." – P2*

There is a connection between incentives, investment, and innovation reaching society. Incentives, such as regulatory protection periods, play a role in influencing investment and investment is required to drive pharmaceutical innovation. Ultimately, society benefits from these innovations. Participants suggest the proposed changes to regulatory protection periods may have repercussions on the broader societal impact of pharmaceutical innovation. The changes make the incentive system worse as there is a shorter guaranteed protection which negatively impacts investment, therefore it negatively impacts pharmaceutical innovation and any benefit is not realised by society.

> *"If you are making the system worse that will have a negative effect on innovation because innovation is driven on incentive in some sense. You both have to have the idea, but if you have the idea but you do not have the money to develop it well the value will not be reached by the society" – P4*

This theme presents how participants talked about the critical link between regulatory protection periods and investment in the pharmaceutical industry. Regulatory protection periods start at market authorization and are viewed as safeguarding investments in R&D, particularly for innovative drugs with extended development timelines. There were concerns raised that the proposed changes would adversely affect the attractiveness of the EU pharmaceutical industry for investments. This was largely due to higher levels of uncertainty the proposed changes introduce. This uncertainty stemmed from the criteria for gaining extensions to protection as during early stage R&D there is poor predictability that the drug will meet the criteria. Investors will only calculate on the predictable and certain period of protection, which is shorter. The shorter guaranteed protection periods were perceived to be worsening of the intellectual property system which will likely lead to reduced investment, reduced innovation, and reduced societal benefit.

4.4 Theme Three: Regulatory protection as an incentive for equal access

Participants discussed that the proposed changes to regulatory protection periods will have an impact that contradicts the objectives of the EU pharmaceutical legislation reform. Participants understood what the European Commission was trying to achieve through these proposed changes but shared views that this proposal will not achieve the objective of increased innovation and equal access.

> *"The shorter exclusivity which we in practice are talking about, it's a bad thing and it's not conducive to better access or more innovation it's really counterproductive." – P5*

> *"That's what we need to make legislator understand, that the mechanism that they try to apply will not lead to what they anticipate in terms of a larger quantity of the European population getting access to new treatments and it will be detrimental for the potential to be innovative in Europe." – P2*

4.4.1 Barriers to launching in 27 Member States

The reform of the EU pharmaceutical legislation aims to achieve equal access to medicines across all EU Member States. In the proposed changes, companies are incentivised to launch the product in all EU 27 Member States by being rewarded with additional regulatory protection periods. Participants noted that to reach the same period of regulatory protection provided today (10 years) companies would need to launch their product in all 27 Member States.

> *"to get to essentially where we are today is to make sure that you launch in all 27 countries within two years after being granted market authorization, with the current plethora of processes in the countries for gaining reimbursement, that's not going to happen. It's virtually impossible." – P5*

However, participants shared it is impossible to achieve an EU wide market launch highlighting various barriers, notably 27 different Member States means 27 different healthcare systems.

To launch in 27 different countries requires high levels of expertise, and is resource intensive. This is unachievable, big pharma could perhaps make it work but smaller pharmaceutical companies will not be able to launch in all EU Member States. Companies, especially smaller pharmaceutical companies, will continue to look towards markets which are easier to launch as they do not have the human capital or financial capital to successfully launch in the 27 Member States. Companies have limited resources and market launch is resource intensive so companies will allocate resources towards launches in countries where it is easier to introduce. They will likely look to launch their pharmaceutical product in countries with lower barriers, better reimbursement mechanisms, and a higher likelihood of acceptance.

> *"Here you have 27 different markets with different authorities, different procedures and handling all of this takes time, and it also costs a lot of money and the proposal that you will receive another two years if you launch and then continuously supply in all different Member States within two years, that's almost impossible" – P4*

> *"most pharmaceutical companies are not like big pharma… they will never hire a health economist in all the 27 states to do this kind of assessment. So it sounds beautiful 'Oh we should force companies to launch in 27 markets' but it's not going to happen" – P1*

> *"to launch in all 27 Member States within two years, small companies cannot do this because they don't have the manpower … It's impossible, and it's absolutely possible for the bigger companies, but for the small ones to negotiate the same product in 27 markets at the same time with the setup as of today, that cannot be done" – P8*

> *"It is a huge problem that the different countries in the EU have such different mechanisms for approving and introducing drugs to the market…the companies will then sort of cherry pick which country is the easiest to introduce" – P6*

The current plethora of processes for launching in the different countries and gaining reimbursement essentially makes launching in 27 Member States impossible. The national HTA system is complex and time-consuming and reduces the effective regulatory protection periods. The national HTAs erode the regulatory protection period the company benefits from.

The combination of the HTAs reducing the effective regulatory protection periods and the shortening of regulatory protection periods results in very little time left for the companies to reap the benefits of regulatory protection. The current reimbursement systems pose a significant barrier to rapid market entry, and not all EU countries have the ability to reimburse expensive treatments.

> *"… the problem is that this takes two to three to four years in all these different countries to do a little extra assessment…we lose because every Member State wants to do their own assessment … the effective protection time is not 10 years, already today it's very short…" – P1*

> *"if you take the that you need to get the approval in all the European countries within two years, I think everybody agrees that they want to, the industry itself. Will the societies help? Probably not. Will the societies create delays? Ah well I would say definitely but maybe not doing it on purpose, which means that will it then be possible for industry to be able to reach the target? No, not with today's standards" – P3*

> *"there are certain countries in Europe where these new expensive type of treatments, they will not be reimbursed because they are too expensive. And that puts the companies in a in a totally impossible situation because how much they even try they're drug will not be accepted" – P2*

Modern medicines require modern healthcare systems and not all 27 Member States have the infrastructure to support these modern medicines. If countries are not able to support and enable the delivery of modern innovative medicines they cannot be launched there. Not all EU Member States will have the required infrastructure and healthcare system capacity to deliver these modern medicines, and therefore it is effectively impossible to launch them there regardless of companies efforts. Additionally, there are added challenges for launching in a country if the local healthcare professionals are not familiar with the treatments and innovative medicines.

"you know that CAR T can only be literally produced in hospitals, in very specific places, very specific conditions, they often do not exist in every country… So that's another limitation. Is the type of technology may not allow for that" – P9

"a lot of these product will probably only be prescribed within hospitals, meaning that you have to have healthcare professional with a good level of expertise within these treatment and disease areas, and if you do not have the innovation and presence of clinical trials or other testing, it can be a challenge as well to make sure that we have a healthcare professional that is up to date with the standards today." – P4

4.4.2 Companies will not launch pharmaceuticals in the EU

The proposed changes to regulatory protection periods will lead to slower and reduced access to innovative medicines, at the cost of it being accelerated in other parts of the world as the EU is not seen as an attractive place to launch. The regulatory periods cannot achieve both incentivising innovation and equal access to innovative medicines. Shorter regulatory protection periods enables faster generic entry, however innovative pharmaceutical companies will likely increase price of products in response to shorter regulatory protection periods to ensure return on investment. Eventually, pharmaceutical companies will not look to launch in the EU and launch in other large attractive markets such as the US instead. When innovative pharmaceuticals are not launched, patients do not have access to them until generics are available. Although generics are cheaper and therefore lower the cost to the healthcare system, the time that generics enter will be the time that patients first have access to the treatment. At this point the treatment is no longer innovative, and therefore patients have slower and reduced access to innovative medicines.

"… European patients will get access to these new treatments when they are no longer new, when they are off patent, when they are off their regulatory data protection systems and went into the generic space like 10 years after things have been launched in the US…. European population does not get access to the original compound or antibody, but actually just get it when it's in the generic phase." – P2

"So we know based on this framework that it will speed up the entry of new generics because now they simply have shorter regulatory data protection period, and of course I think that will force the big pharma to increase the prices.... over time I think pharma won't buy into this and it will simply lead to fewer launches of medicine in the European Union. So over time, what started out as being speed up of entry of generics and competition will slowly reduce itself, at the cost of more launches in the US and the European Union being left behind" – P7

"... you are making the incentive system worse when you should instead make it better if you would like to incentivize the pharmaceutical companies to make even more effort to secure that you have both new medicines but also that you have access to them... maybe some of the products will not be released or they will be released after quite a lot of time" –P4

The reduced and slower access to medicines as a result from proposed changes has a negative downstream impact on the ability to conduct clinical trials in the EU. Participants commented that when the most innovative products are not launched on the market there is not an appropriate standard of care to use as a comparator in clinical trials. The absence of an appropriate comparator impairs the ability for clinical trials to occur in the EU. This not only harms the EU ability to conduct clinical trials, but also reduces patients access to the most innovative treatments through clinical trials.

"If we don't get pricing for a drug or the most recent drug approved in Sweden the drug will not be used, something older will be used as standard, and when the next new drug comes we will not have the second newest drug available in Sweden, that will not be a comparator in clinical trials. Whereas everywhere else it will be a comparator. So that means that it will not be interesting to place the second trial in Sweden because the standard therapy in Sweden would be obsolete... if we don't do clinical trials our patients would not get access to the most innovative therapies available" – P5

"If you can't compare something to standard of care because you don't have that those types of medicines approved. So I mean, this becomes an evil circle, right? If you don't have access to standard of care, you can't do comparative trials. It just reinforces that where you have standard of care where you have the launches is where you want to do your clinical trials" – P7

Overall, theme three suggests the proposed changes to regulatory protection periods will likely have an impact that contradicts their objectives. Participants said it was impossible to launch in all 27 Member States because of the 27 different healthcare and reimbursement systems. Additionally, not all countries have the modern infrastructure to support the most complex treatments which adds to the challenge for an EU wide launch. Companies are likely to prioritise launching the pharmaceutical products in the countries with lower barriers and better reimbursement schemes, and even shift towards other more attractive markets. As a result, it is anticipated there will be slower and reduced access to innovative medicines. The reduced access to innovative medicines is expected to have a negative downstream impact on the ability to conduct clinical trials in the EU. Participants showed concern that the proposed changes compromise the fine balance of incentivising innovation and creating equal access to innovative medicines across the EU.

4.5 Theme Four: Regulatory protection and Orphan Drug development

Participants spoke about the changes to regulatory protection periods, notably market exclusivity, impacting orphan drug development. The proposed changes to regulatory protection periods provide targeted incentives with an additional protection period linked to public health needs such as the product addressing unmet and high unmet medical needs. Participants shared views that these extensions do not incentivise R&D towards these areas, especially for orphan drugs as the definition for 'orphan disease' becomes increasingly narrow therefore it becomes more challenging to meet the definition and increases R&D risk. Innovative efforts for orphan drugs are not expected to accelerate in response to the changes because the definition of 'orphan drug' becomes too hard to reach.

"If you see how high the bar now is, and for orphan drugs when it comes to incentives I think it's really very discouraging. Before a rare disease was a rare disease, there is a definition of rare disease which is no more than 5 in 10,000 right now. So the rarity is not discussed, but then the degree of unmet medical needs, high unmet medical needs, all these different subcategories touching upon morbidity, mortality. So the bar is a lot higher." – P9

"…also the definition of a unmet medical need and high unmet medical need, which is mainly relevant if you look on the OME (orphan market exclusivity) but also a bit on the RDP (regulatory data protection). They are quite high, especially high unmet medical need… having these high criteria could or will mainly hamper innovation instead of incentivize because you do not want to take the risk…" – P4

Participants spoke about the extension in market exclusivity for add-on indications being potentially detrimental for innovative efforts, and therefore negatively impacting patients with orphan disease. Science, rather than commercial opportunity, leads drug development especially in early stages as indication is not known. Following science allows researchers to continue to build on existing knowledge. This incremental innovation is beneficial for science as new knowledge is produced, but it is also beneficial for patients as small clinical benefits occur more frequently. The changes to orphan drug market exclusivity threatens incremental innovation. Under current regulation an orphan drug will receive 10 years of market exclusivity for every indication. Under the proposed changes an orphan drug with an add-on indication will receive an additional 1 year of market exclusivity, a 9 year decrease. Decreasing the market exclusivity does not incentivise companies to pursue R&D for add-on indications. As a result it slows the progression of science and will essentially decrease future treatment options for patients with orphan diseases.

"The drug is approved already in another indication but for this indication it's one per million people, hadn't it been that it's an add-on indication of course it wouldn't be viable to do it… but I don't think we can do that moving forward." – P5

"There's this illusion that industry has 20 indications in their pockets and then they just bring them one after the other in a way that maximizes profit. Again, this is not true. It is driven by science and I have the experience where sometimes the indication that we find out afterwards is actually really problematic from a commercial point of view… we have allowed science to progress so much just by continuing to do research on this incremental clinical benefit, which not only benefits patients, but at the end also science" – P9

This is interesting because the study results presented in theme one demonstrate that regulatory protection periods do not influence early stage R&D decisions because research at that stage is not market oriented. However, there is fear that the reduction to market exclusivity will be detrimental to innovative efforts and slow progression of science. Despite being driven by science, perhaps regulatory protection periods do play a greater role in early stage R&D decisions in orphan drug development.

Additionally, participants also mentioned there is a key difference between the proposed EU and US legislations for incentivising orphan drugs to be extended into new indications. The two different legislations oppose each other as the US discourages multiple indications while the EU encourages it.

"I think there is some discrepancy what's happening in the European Union right now compared to the United States in terms of the IRA (Inflation Reduction Act), where if you have orphan indications in the United States, then according to the IRA, if you extend it into new indications it will be subject to this maximum fair pricing.... but in the European Union you are being incentivized to take an orphan medicine and extend it in to more indications" – P7

Theme four focuses on the proposed changes to regulatory protection periods and the perceived impact on orphan drug development. The proposed changes greatly dissect the definition of orphan disease and meeting the increasingly narrow definitions will be detrimental to innovative efforts for orphan disease. Focusing on R&D for commercial opportunity rather than scientific progress could negatively impact patients. Incremental innovation driven by scientific exploration is viewed to be beneficial for both increasing scientific knowledge and for patients as small clinical benefits occur frequently. Although breakthrough innovation is

sought it is rare, incremental innovation is more common and enables smaller benefits at a higher frequency. Participants expressed concerns that these proposed changes would not effectively incentivise orphan drug R&D which suggested regulatory protection periods may play a role in early stage R&D decisions. Interestingly, there are key differences between the EU and US legislations regarding incentives for multiple indications which companies will have to navigate.

5. Discussion

This chapter will discuss the four themes presented in the results to further address the research question and aim, and discuss the results in the context of institutional theory. The research results display similarities to previous trends exhibited in literature as described in Chapter 2, the literature review.

The proposed changes to regulatory protection periods see a decrease in the minimum period of protection and the opportunity to gain additional periods of protection when the innovative product, or the company, meet certain public health objectives. Inductive thematic analysis of participant transcripts revealed these changes negatively impact the ability for the EU to be an innovative and competitive market. Despite extensions to regulatory protection providing opportunity for protection to extend beyond what is currently offered today the proposed changes to regulatory protection periods are viewed as a decrease in protection. Even if some criteria are met and extensions granted, companies will still be worse off compared to today. Multiple conditions need to be met for the protection periods to extend beyond what is offered currently.

5.1 Regulatory Protection is a valuable intellectual property asset

The results suggest these proposed changes to the period of regulatory protection will not have an impact on early stage science. When research is in its embryonic form decisions for R&D are not made based on its commercial potential. This displays a similar expected trend to post-Bayh Dole era in the US. Following the implementation of Bayh-Dole Act in the US early stage research did not shift towards applied research of commercial interest as feared (Mowery et al., 2001). During early stages of R&D the product is so far from the market, therefore decisions upon the direction of further R&D pursuits are not made based on the period of regulatory protection that will be awarded. Participants expressed that the regulatory protection periods do not incentivise pharmaceutical R&D to pursue a certain direction, e.g., unmet medical needs or multiple indications, because those decisions are based on the potential of the science rather than the commercial potential of the research.

The study demonstrates regulatory protection periods are recognised to hold significantly high value and be the strongest intellectual property right. Once awarded at market authorisation it

cannot be removed, even in event of successful patent challenge (Gaessler & Wagner, 2022). According to this study, regulatory protection is the strongest and most reliable intellectual property right especially when a patent is weak or the innovation does not fall within scope of a patent. The results show that in future the value of regulatory protection is expected to increase, but for this value to be realised, science needs to progress to deliver complex treatment beyond the scope of patents. Pharmaceutical innovation is trending towards more personalised medicine with cell therapies such as CAR T Cell providing the most promise for personalised medicines (OECD, 2017). For these treatments regulatory protection periods are the most important intellectual property right because these treatments are beyond the scope of the patent system. However, these proposed changes to regulatory protection periods risk the ability to bring these innovative treatments to the market in the EU because there is shorter protection enabling a market monopoly compared to today.

5.2 Decreased Regulatory Protection decreases Investment

Although the results show regulatory protection does not influence early stage research pursuits, the results also show regulatory protection does contribute to R&D decisions further along the drug development timeline. This is in line with Budish et al., (2015) who showed that pharmaceutical companies wish to benefit from relatively longer market monopoly periods therefore target R&D activities towards drugs with shorter development times. This provides rationale for different incentives that provide increased market monopoly for drugs with a longer R&D period. Regulatory protection periods attempt to achieve this with their protection beginning at market authorisation rather than during development. The proposed changes to regulatory protection periods further attempt to increase post-market reward by including extensions to the periods which could see a total of 12 years protection. However, multiple extensions are needed to be met for protection to extend beyond the current period. Additionally, meeting the plethora of conditions for extensions is largely regarded as impossible. Realistically, it is a decreasing of the regulatory protection period and therefore decreasing secured market monopoly which does not incentivise companies to pursue drugs with longer development time. A pertinent example of this is that current investments do not prioritise the greatest unmet medical needs, especially for diseases with longer development times due to higher scientific challenges such as lack of understanding of disease (EC, 2023e). As a result adequate treatment options are lacking. Under the proposal if a product addresses

unmet medical need, the regulatory protection extends by 6 months giving a total of 8.5 years, still short of the 10 years protection that would be rewarded today for the same product. Consequently, it does not incentivise companies to invest in products with longer development time and address unmet medical need.

The results from this research indicate decreasing the standard period of regulatory protection does not incentivise companies to pursue risky innovative R&D projects. This echoes the research by Gaessler and Wagner (2022) where the duration of market monopoly determines a company's innovative effort. They show that a patent invalidation in the early stage of drug development decreases the likelihood of drug approval. As this standard regulatory protection period decrease would be known in these early stages of development, companies will pursue less risky R&D projects and perhaps less innovative projects to utilise limited resources better. However, this finding by Gaessler and Wagner (2022) is driven by large pharmaceutical companies whereas smaller companies do not abandon projects due to having less alternatives to pursue and continue to do R&D in their area of expertise. Importantly, smaller emerging companies are largely the source of innovation therefore it is not expected they will stop pursuing certain projects due to decreased regulatory protection periods.

However, what will impact small emerging pharmaceutical companies ability to continue R&D is their ability to gain crucial investment. Currently, the EU is declining in its attractiveness for R&D investment (Wilsdon et al., 2022). This study's results suggest that these proposed changes to regulatory protection periods is expected to exaggerate this trend, and it will be increasingly difficult for smaller emerging companies to gain investment. This negatively impacts the EU ability to produce innovative medicines because innovation comes from these small emerging companies. Diminishing their ability to gain investment is harmful for their R&D pursuits. As a result small emerging companies will go offshore to more attractive and growing markets such as the US and China.

Although regulatory protection periods do not directly impact early stage science pursuits, it impacts the commercial progression of early stage science through investment decisions. This research demonstrates that the proposed changes to regulatory protection increases uncertainty. This increased uncertainty is attributed to the extensions as it results in poor predictability of the final period of regulatory protection that will be received. This poor predictability forces investors to add additional risk on their investment because there is too much uncertainty

surrounding the drug's ability to meet criteria to obtain extensions. The uncertainty associated with the regulatory protection periods further harms the EU ability to attract needed investment for pharmaceutical R&D.

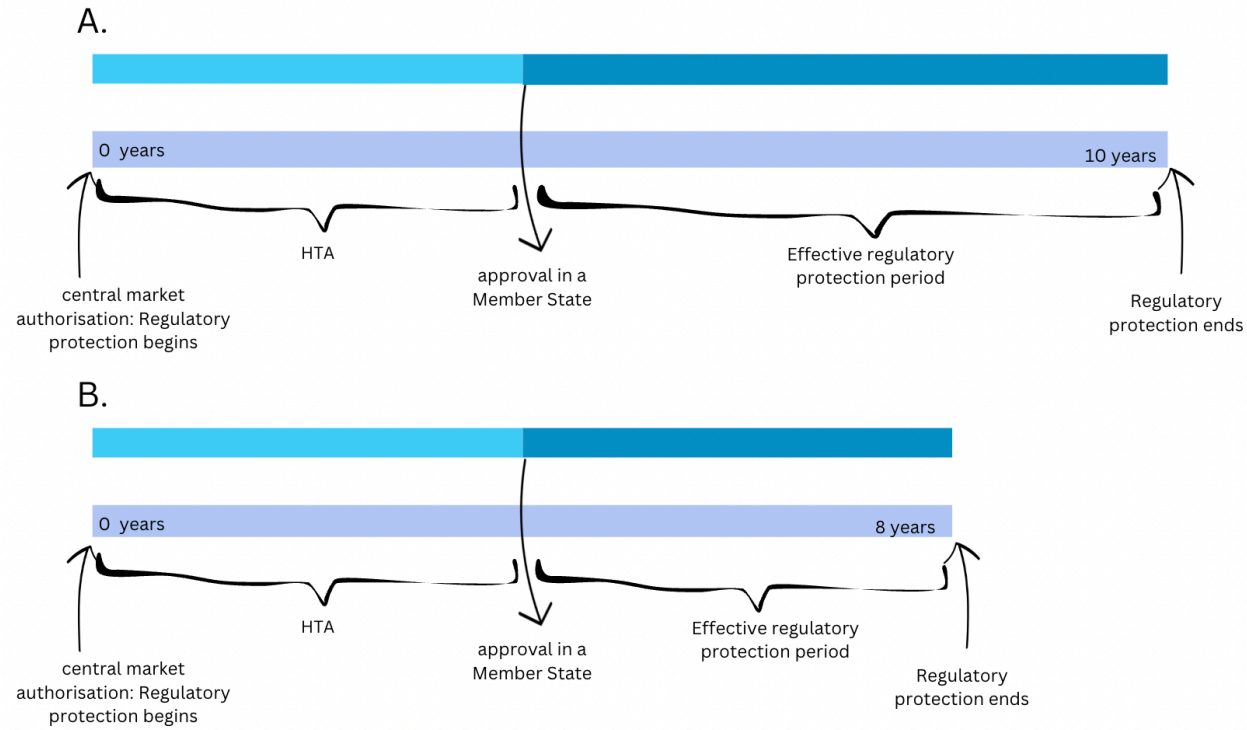
5.3 Worsening equal access to innovative medicines across the EU

Regulatory protection periods have traditionally been an incentive for innovation. The proposed changes see them become a tool to achieve equitable, affordable access to medicines across the EU. However, regulatory protection periods cannot incentivise both innovation and equal access. High levels of innovation introduce competition within a disease or drug class, rather than competition with generics. This has been previously demonstrated by Brabers et al., (2011) with the presence of follow-on drugs for orphan diseases. Orphan drugs face competition not from generics but from new medicines for the same orphan disease. High levels of innovation are beneficial for patients because it results in improved treatment options, but it is bad for the payer because treatment costs remain high. Conversely, when there are low levels of innovation, competition arises not between different treatment options but from generics. This is beneficial for the payer because it lowers costs, but it is bad for patients as new improved treatments are not being developed. Consequently, incentivising improved equal and affordable access through regulatory protection does not encourage innovation, and incentivising innovation does not result in more affordable medicines. Therefore, the gap is access across EU Member States is not expected to narrow. Additionally, this study implies these changes do not make the EU an attractive place to launch medicines because regulatory protection is reduced. According to the results from this research, these changes are expected to slow and reduce access to innovative medicines at the cost of it being accelerated in other parts of the world as pharmaceutical companies are likely to prioritise more attractive markets.

However, the European Commission consider the EU to have one of the most attractive markets due to regulatory protection being longer than other countries such as China and Japan (EC 2023e). The results from this research show while in legislation this may be the case, realistically the protection period companies benefit from is lower due to national HTA. Currently, the effective period of regulatory protection is not 10 years, it is less than this due to the national HTA carried out individually by Member States. As the HTA, pricing, and reimbursement decisions are a national competence it is beyond the scope of EU

pharmaceutical legislation. The proposed changes reduce standard regulatory protection periods and do not influence HTA periods. The results of this research highlight the poor alignment between the period in legislation and the effective protection period. This phenomenon is demonstrated in figure four. While the European Commission consider the periods to be competitive and longer than what is provided in other global markets this is not the case because the complex national HTA erode regulatory protection periods.

Figure 4: Effective regulatory protection period



Developed by researcher showing HTA and regulatory protection periods following Central Market Authorisation. Fig 4a: Illustrates current protection period where the actual regulatory protection period received is not 10 years due to HTA. Fig 4b: The proposed changes reduce regulatory protection periods but do not impact HTA time, effective period of regulatory protection is not 8 years.

This study suggests these proposed changes do not make the EU an attractive place to launch medicines. Based on the findings of this research, it is anticipated that these proposed changes will decelerate and limit the availability of innovative medicines, while simultaneously expediting access in other global markets.

The proposed changes to EU pharmaceutical legislation aim to reduce inequalities in access to medicines across EU Member States. One attempt to achieve this is an extension to regulatory protection which is provided to incentivise and reward launching in 27 Member States.

However, this study's results specify it is essentially impossible to launch in all 27 Member States within two years of market authorisation therefore the extension associated with EU wide launch will not be obtained. Based on this study's results there are a variety of reasons launching in 27 Member States is not realistic including market launches being resource intensive. Successful HTA require human capital and expertise which is not feasible especially for smaller companies. This research demonstrates the incentive for an EU-wide launch is not expected to achieve its aim of reducing inequalities in access to innovative medicines because barriers to launching have not been reduced and smaller companies are the origin of innovative medicines. This research indicates that Member States that are the easiest to launch in will continue to be prioritised, which does not address issues surrounding equal access. Additionally, many barriers to EU-wide launches are beyond the scope of EU legislation as they are national competencies. Healthcare systems require modern infrastructure to deliver modern medicines, such as CAR T Cell therapies which is where personalised medicines holds strong potential.

According to this study, the proposed changes to regulatory protection drive companies away from launching in the EU. It is expected patients will have access to medicines when they are no longer new. This impacts the EU ability to conduct clinical trials, a key component in pharmaceutical R&D. Currently, the EU is an attractive place for clinical trials to be conducted. However, when it comes to advanced therapy, China is leading clinical trials and the EU lagging far behind (Wilsdon et al., 2022). The study's results imply the EU will continue to fall behind other leading regions as these proposed changes are expected to slow and reduce access to innovative medicines impacting the EU ability to conduct robust clinical trials. When innovative medicines are not launched in the EU, clinical trials cannot be done because the desired comparator is not available. This not only reduces access to the newest innovation but also pharmaceutical R&D in Europe.

5.4 Decreased Orphan Drug development

When EU orphan drug legislation was first implemented it introduced 10 years of market exclusivity to incentivise orphan drug development. Following the passage of orphan drug legislation the number of orphan drugs increased, and market exclusivity is commonly credited for this (Coté et al., 2010; Haffner, 2006; Sarpatwari et al., 2018). However, according to this

research, the proposed changes to the orphan drug market exclusivity period will be detrimental for orphan drug innovative efforts, and therefore negatively impacts patients with orphan disease. Currently, an orphan drug receives 10 years market exclusivity per indication but the proposed changes reduce this to 9 years and one additional year for an add-on indication. The orphan drug market exclusivity becomes linked to the drug rather than indication, as it is today, which negatively impacts innovative efforts towards orphan drug development. Based on this study's results, the reduction in regulatory protection for additional indications does not incentivise further research for new indications for a drug. This has a negative consequence for patients as potential treatments for orphan diseases will not be discovered. As previously mentioned, early-stage research and science are not influenced by regulatory protection periods. However, the results from this research demonstrate there is concerns that orphan drug R&D will slow, especially for additional indications as incremental innovation is not rewarded with the same market exclusivity as today. This suggests that regulatory protection periods do play a role in orphan drug R&D, providing rational for differing rewards and incentives.

An orphan drug with an indication for a 'high unmet medical need' will gain an extension to the market exclusivity period. While the EU legislation uses regulatory protection periods to focus R&D efforts towards these high unmet medical needs, the regulatory protection is only one factor in orphan drug development. Market size has previously been shown to be one factor in encouraging orphan drug development as orphan diseases with larger market sizes are more likely to have a treatment option (Brabers et al., 2011; Tambuyzer, 2010**).** The definition of 'high unmet medical need' increases granularity of orphan disease making an already small market size smaller. The smaller market size does not establish a favourable market for orphan drug development. Also, it is acknowledged that high scientific output leads to improved biologic understanding of disease and contributes to orphan drug development (Brabers et al., 2011). Increased funding and investment led to higher scientific output (Cockburn, 2004; Malerba & Orsengio, 2015). This strategy is implemented in the US where there is government funding to improve biologic understanding of orphan disease (Patel and Needleman, 2019). However, government funding is beyond the scope of EU pharmaceutical legislation as these types of grants are a national competence.

5.5 Research in the context of Institutional Theory

Institutional theory as published by Meyer and Rowan (1977) demonstrates organisations exist in an institutional environment and behave in a similar way to achieve legitimacy and enhance survival prospects. Their behaviour is a response to different external pressures. Not all external pressures exert the same force or exist at the same time (Frumkin & Galaskiewicz, 2004; Furusten, 2013). These different external pressures impact organisational behaviour and can cause change through coercive, mimetic, and normative isomorphism (DiMaggio & Powell, 1983). The context of this research sees that proposed changes to regulatory protection periods, a component of legislation, act as an external pressure on the pharmaceutical industry. This pressure impacts organisational behaviour through both coercive isomorphism and mimetic isomorphism.

Interestingly, regulatory protection exists as an incentive and reward for innovation. While the period of protection is set in the legislation, unlike other aspects of legislation it is not a mandate for how industry must behave. It is not a set of rules that must be followed but rather an incentive and guaranteed downstream reward for new pharmaceuticals entering the market. This provides more space for how organisations may respond to the proposed changes. However, this research proves that intellectual property protection is an asset for pharmaceutical companies, and it will become increasingly valuable as science progresses. Based on this study's results it can be seen that legislation impacting regulatory protection periods will impact organisational behaviour.

Coercive isomorphism is a mechanism that influences organisational behaviour (DiMaggio & Powell, 1983). It causes change in response to external pressure from actors the organisation is dependent on. The pharmaceutical industry is dependent on EU legislation and therefore it is a formal pressure exerted on the industry and impacts organisational behaviour. According to this research, the pharmaceutical industry views the proposed changes to regulatory protection to be a decrease despite the opportunities for the periods to extend beyond what is currently given in legislation. The decreased periods make the EU a less attractive market in which to launch the pharmaceutical product. As a result, companies will look towards other markets with more favourable, or predictable periods, to launch the product. The EU will have slower and reduced access to innovative medicines at the cost of it being accelerated in other parts of the world.

More powerful organisations have a key role in shaping the organisational environment (Meyer and Rowan, 1977). The pharmaceutical industry is global and therefore there are a range of legislations acting on the industry influencing its behaviour. The US is the largest and most influential market as majority of innovative medicines originate in companies based in the US, as well as high levels of pharmaceutical R&D investment and expenditure (IQVIA, 2022; Wilsdon et al., 2022). As a result, legislation in the US influences the pharmaceutical industry globally.

Interestingly, as one participant highlighted, there are key differences between the proposed EU legislation and proposed IRA legislation in the US. These legislations oppose each other, and when legislations oppose each other, it is likely the more powerful organisation or market will imbed their rules into the institutional environment. In this case, it is likely the US legislation would imbed itself into the environment these global companies exist in and influence organisational behaviour through coercive isomorphism. Although industry could still apply to EMA for approval for additional indications for the orphan drug this is unlikely. Firstly, because the extension provides one additional year of market exclusivity and as previously described this is significantly reduced compared to additional indications today. Secondly, there are various challenges in conducting clinical trials and obtaining the level of evidence required for approval. Thirdly, market size is a factor in orphan drug development (Brabers et al., 2011; Tambuyzer, 2010). Losing the US market reduces market size and decreases likelihood of orphan drug development.

Mimetic isomorphism is a mechanism that influences organisational behaviour as a response to uncertainty (DiMaggio & Powell, 1983). The results suggest these proposed changes to regulatory protection periods increase uncertainty for investors. As a response to uncertainty, organisations will look to follow existing trends within the industry. These existing trends see the US and China as leaders in pharmaceutical R&D for investment, expenditure, contribution to global pipeline, and advanced therapy clinical trials (IQVIA, 2022; Wilsdon et al., 2022). The extensions to protection aim to incentivise pharmaceutical R&D towards public health needs and achieve equal access across EU Member States, however these extension are a source of uncertainty. Early-stage R&D follows science rather than commercial application. In this early stage when companies are seeking investment the final indication or ability for multiple indications are not known. Companies and investors cannot predict the total period of

regulatory protection as the ability to obtain extensions is uncertain. The study's results suggest a perceived uncertainty created by these changes increases difficulty for obtaining required investment. As a result, it is expected investors will look towards other more predictable markets decreasing investment in pharmaceutical R&D in the EU. In response, industry are likely to follow existing trends and move pharmaceutical R&D activities to where the investment can be obtained such as the US and China.

According to this research, as a response to regulatory protection periods the pharmaceutical industry in the EU will shift towards other more attractive and growing markets, through mechanisms of coercive and mimetic isomorphism. The industry and markets exist in an equilibrium. This research implies that when legislation changes make one market less attractive another market attractiveness increases, and resources are focused towards launching products there instead. This indicates slower and reduced access and investment in innovation in the EU, at the cost of it being accelerated in other markets.

6. Conclusion and Implications

This chapter provides an overall conclusion, as well as research implications, limitations, and areas for future research.

6.1 Overall conclusion

The proposed changes to EU pharmaceutical legislation aim to offer an attractive, innovation-friendly environment for pharmaceutical R&D, and improve equal access to medicines (EC 2023e). There are several proposed changes to the legislation aiming to achieve this, but this research has focused on regulatory protection periods. The results from this study demonstrate changing the regulatory protection periods as proposed will not achieve this aim.

Regulatory protection periods are a strong form of intellectual property protection that differ from a patent (Gaessler & Wagner, 2022). The regulatory protection periods hold immense value when innovation falls outside the scope of patent protection, or patent protection is weak. As pharmaceuticals continue to trend towards more complex and personalised medicines it is expected more innovation will fall outside the scope of patent protection. This raises the importance and value of regulatory protection periods as it becomes the sole source of intellectual property protection. The proposed changes weaken the regulatory protection as the guaranteed period of protection decreases which does not result in increased innovation.

The proposed changes to regulatory protection do not make for an attractive and innovative environment in the EU because it reduces attractiveness for investors. The criteria surrounding extensions to protection introduce more uncertainty to the industry and increases challenges to gain investment. Science drives innovation and in early stages it is not clear what the final indication is or if it has multiple indications. This means there is poor predictability for the total period of protection that companies will benefit. This decreases the attractiveness for investors. This is especially harmful for smaller companies to obtain crucial investment for pharmaceutical R&D. Consequently, this diminishes the EU ability to be innovative because innovative medicines originate in smaller and emerging pharmaceutical companies (IQVIA, 2022). If smaller emerging companies cannot gain needed investment, they will move offshore to other attractive and growing markets such as the US and China. These changes accelerate existing trends where pharmaceutical R&D investment and expenditure is growing faster in the

US and China compared to the EU (IQVIA, 2022; Wilsdon et al., 2022). Additionally, it exaggerates the trend where the majority of the drug development pipeline originates in US-based emerging pharmaceutical companies, with strong growth in China and declining in the EU (IQVIA, 2022).

Proposed changes to regulatory protection will not result in equal access to medicines across EU Member States. EU legislation is incentivising companies to launch in all Member States with additional periods of regulatory protection. However, it is impossible to achieve EU wide launches due to factors beyond the control of the European Commission. There are 27 different healthcare systems and many perform HTA which is time consuming for companies and requires high level of expertise. Modern medicines require modern healthcare systems and not all Member States possess the infrastructure for delivering these innovative complex treatments. These factors are national competencies and beyond the scope of EU legislation. Additionally, the reduced protection periods decreases attractiveness of the EU market to launch innovative pharmaceuticals. As a result EU citizens will have slower and reduced access to the most innovative treatments.

Previously, orphan drug legislation has seen the introduction of market exclusivity which has been successful in increasing orphan drug development (Kesselheim, 2011). However, the proposed changes see a decrease in the period of protection therefore it has the opposite impact. The changes do not incentivise companies to pursue orphan drug development. This is due not only to the decrease in market exclusivity but also the extensions further modulating the definition of orphan disease. ‘High unmet medical need’ is a small patient population and the smaller the market size the less likelihood of orphan drug development (Brabers et al., 2011; EC 2023e; Tambuyzer, 2010).

This research takes place in the context of Institutional Theory. Due to the proposed regulatory protection periods, the pharmaceutical industry in the EU is expected to transition toward more attractive and growing markets, displaying coercive and mimetic isomorphism mechanisms. When uncertainty increases organisations behave in a more similar way displaying mimetic isomorphism. As the changes bring uncertainty for the ability to gain investment organisations will look to more attractive markets and follow existing trends. Legislation is an external force acting on the industry and influencing organisations behaviour through coercive isomorphism. The proposed changes results in organisations changing their behaviour as they focus on

markets with a better environment for pharmaceutical R&D. More powerful markets, such as the US, are able to imbed their rules and norms into the institutional environment and influence organisational behaviour change through coercive isomorphism. Organisations within the pharmaceutical industry will respond to these changes in order to be seen as legitimate and enhance survival prospects.

6.2 Implications

This research contributes to existing literature in a unique way. Previous literature examines the impact of legislation affecting pharmaceutical R&D using retrospective and primarily quantitative methodologies. This research utilizes qualitative research methods to examine pharmaceutical industry stakeholders' perspective on the proposed changes to regulatory protection periods. This perspective provides an understanding of the impact these changes would have on the direction of the pharmaceutical industry in the EU. It suggests how these proposed changes will influence current trends in pharmaceutical R&D and offers insight to the global competitiveness of the EU pharmaceutical industry.

The insights from this research are useful for both private and public pharmaceutical industry stakeholders. The research provides an understanding of the future of the pharmaceutical industry in the EU both for innovation and for access to medicines. It demonstrates that intellectual property is a highly valuable intangible asset that requires strong and predictable protection for innovation to reach society. The research highlights the limitations of EU pharmaceutical legislation to improve equal access as these are national competencies. These findings can provide a constructive dialogue between public policymakers and private industry stakeholders to collaboratively refine the proposal to better address the overarching objectives. This can lead to more effective and widely accepted legislation.

6.3 Limitations and area for further research

The study has limitation despite adopting necessary measures to minimise the study's limitation. The study focuses on how the proposed changes to regulatory protection periods will impact the direction of the pharmaceutical industry in the EU. The researcher inclusion and exclusion criteria was limited to only pharmaceutical industry stakeholders in Sweden.

Sweden is not the only country to be affected by these changes but the study uses the perspective of stakeholders in Sweden to address the research question and aim. However, the methodology outlines key reasons why participants from organisations in Sweden were used. Although transferability of results is not an aim of qualitative research, caution should be exercised when transferring these results to other industry stakeholders inside or outside the EU. An area of further research is to explore the perspective of stakeholders in other Member States and globally. This would add to this study and better inform how these changes can impact the direction of the pharmaceutical industry.

Another limitation of this research is that no payers or representatives from public healthcare systems were recruited for this study, therefore this research lacks their perspective. Given the two-way relationship between private pharmaceutical companies and public payers, the payer perspective regarding these changes to regulatory protection periods is crucial. Understanding how the payers will respond to the changes in combination with the response from the private sector would better inform the impact the changes to regulatory protection will have on the direction of the pharmaceutical industry in the EU. Further research should include the payer perspective. Future research could take this same interview protocol and interview payers and representatives from public healthcare systems, and then compare results to this research. Alternatively, these results could be taken to the payers and representatives from public healthcare systems to gain their response to this and understand how their perspective connects into private industry stakeholder perspective.

A final limitation of this research is that it focused on the proposed changes to regulatory protection periods in isolation. However, there are a variety of other proposed changes to EU pharmaceutical legislation which may impact the direction of the pharmaceutical industry and previous research demonstrates various factors influence pharmaceutical R&D and market entry, and therefore patient access to medicine. None of these factors exist in isolation. Intellectual property in the form of regulatory protection periods is a vital asset for pharmaceutical companies, however it displays synergistic relationships with other areas of pharmaceutical R&D such as early stage science, funding and investment, and commercial decisions. While this research touches on some of these relationships, none are explored in-depth leaving a gap in literature and providing an area for further research.

7. Appendix One: Interview Protocol

These questions provide a starting point for each theme of the interview. The interviewer will be flexible in their approach and probe deeper based on participants response to gather in-depth insights into the participants perspective.

Section 1: Participant contextual factors

What is your professional background and current role in your organisation?

- What are your primary responsibilities?

In your opinion what is your organisation's role in the pharmaceutical industry?

Section 2: Opportunities presented by the regulatory incentive changes

In your opinion what opportunities do you see emerging because of the proposed changes to the regulatory incentives in the pharmaceutical industry?

- What other factors compliment these opportunities?

Can you tell me about how you see these opportunities to benefit the industry?

- What are any specific benefits or advantages you see for your organisation or area in the industry?

How do you see regulatory protection periods to be of benefit?

- In your opinion, how do these changes impact this?

Section 3: Challenges the regulatory incentive changes propose

From your perspective, what are some of the challenges that may arise due to the proposed regulatory incentive changes?

- How do you expect industry to respond to these challenges?
- What barriers to drug development or market access do these regulatory protections periods bring?

In your opinion, are there any risks or unintended consequences surrounding the regulatory incentives changes you think are important to consider?

Section 4: Impacts of changes on the industry

How do you believe these proposed changes to regulatory protection periods will influence the strategic direction of industry?

- Can you tell me more the role regulatory incentives play in decision making?
- What other factors influence these decisions?

How do you see the pharmaceutical industry evolving over the next few years in response to these regulatory incentives?

- How do you expect to see shifts in the research and development priorities within the industry?
- Can you tell me more about how the regulation protection periods influence innovation?
- Is there an area of the industry you expect to see impacted more strongly due to the changes? How so?

How might the changes shape the competitive landscape and market dynamics in the long term?

- How will the incentives impact market access?

Is there anything you would like to add to this discussion that you feel I may have missed?

8. Appendix Two: Information and questions provided to the participants before the interview

Background

The two EU pharmaceutical legislative proposals are:

1. New directive repealing and replacing directives 2001/83/EC and 2009/35/EC, and incorporating relevant parts of the paediatric regulation.

2. New regulation repealing and replacing regulation (EC) No 726/2004, repealing and replacing orphan regulation, and incorporating relevant parts of the paediatric regulation.

Although drug development and access to medicines depends on factors beyond the scope of EU legislation, the legislation can have an impact on these issues through regulatory protection periods that act as incentives. To achieve the overarching aim the proposed revision involves several incentives in the form of regulatory protection periods to boost innovation, access, and address unmet medical needs. These changes incentivise and reward innovation that meets public health needs as the protection periods shift from a 'one size fits all' approach towards targeting patient access and address unmet medical needs.

In the EU, regulatory protection periods compliment intellectual property rights (patents and supplementary protection certificates (SPC)) to incentivise innovation. Regulatory protection includes data protection, market protection, and market exclusivity periods. Currently, from the time of marketing authorisation standard innovative medicines are provided 10 years of regulatory protection (8 years data protection and 2 years of market protection), which can be extended by 1 year (data protection) if a new therapeutic indication is added after marketing authorisation (EC 2023). Orphan medicines are granted 10 years of market exclusivity (EC 2023).

Under the proposed reform, the period of regulatory protection for standard innovative medicines is reduced from 10 years to 8 years, however the maximum is extended from 11 years to 12 years to incentivise improved patient access and drive development towards areas

of unmet medical need (EC 2023). For orphan medicines the standard duration of market exclusivity will be 9 years, a reduction from the current 10 year period (EC 2023). However, this period can be extended under certain conditions to a maximum of 13 years (EC 2023). These proposed changes for regulatory periods including conditions for extension are further demonstrated in figure 1, and definitions of key terms in table 1.

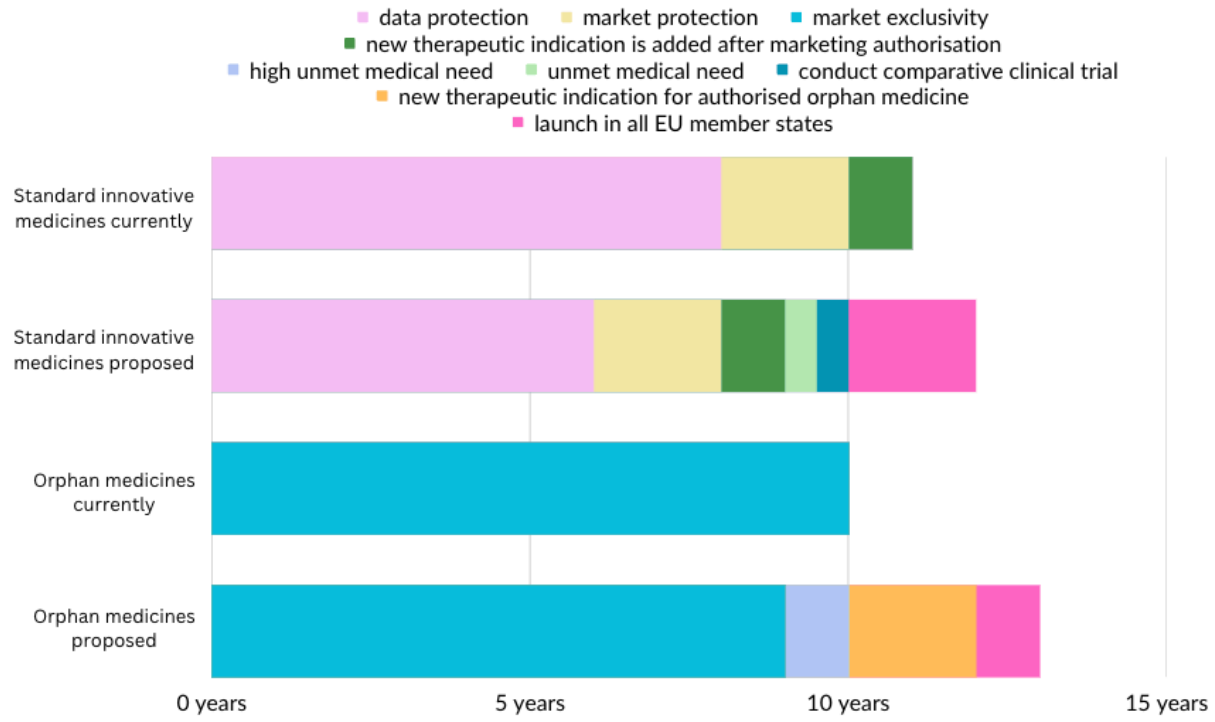


Figure 1. Developed by the researcher. Illustrates the current and proposed regulatory protection periods for standard innovative medicines and orphan medicines.

Table 1: Key definitions

Term	Definition
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings (EC 2023e)
Market protection	Period of protection during which generics cannot be placed on the market (EC 2023e)
Market exclusivity	The period after the marketing authorisation of a medicine for an orphan disease when similar medicines for the same indication cannot be placed on the market and applications for those medicines cannot be validated (EC 2023e)
Orphan (rare) Disease (EU)	Disease with prevalence below 5 in 10,000 people. (Regulation 141/2000)
Orphan medicine (EU)	Intended for diagnosis, treatment, or prevention of a disease with a prevalence below 5 in 10,000 people, or if for a seriously debilitating or chronic condition where in the absence of incentives it is unlikely to generate sufficient returns to justify investment (Regulation 141/2000)
Unmet medical need	As defined in article 83(1) of proposed directive, there is no medicinal product authorised in the EU, or despite an authorised medicinal product morbidity and mortality associated with the disease remains high and the use of the medicinal product results in a meaningful reduction in disease morbidity and mortality for the relevant patient population (EC 2023c)
High unmet medical need	As defined in Article 70(1) of proposed regulation, there is no medicinal product authorised in the EU for the condition, or where a product is authorised the applicant demonstrated the orphan medicinal product will have significant benefit and bring exceptional therapeutic advancement. The use of the orphan medicinal product results in meaningful reduction in disease morbidity and mortality for the relevant patient population (EC 2023d)

Questions

Due to the semi-structured conversational nature of the interview these questions are only a guide.

- What is your professional background and current role in your organisation?
- What is your organisation's role in the pharmaceutical industry?

- In your opinion what opportunities do you see emerging because of the proposed changes to the regulatory incentives in the pharmaceutical industry?
- From your perspective, what challenges for industry may arise due to the proposed regulatory incentive changes?
- How do you believe these proposed regulatory incentive changes will influence the strategic direction of industry?
- How do you see the pharmaceutical industry evolving over the next few years in response to these regulatory incentives?
- From your perspective, how might the changes shape the competitive landscape and market dynamics in the long term?

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