Regulation 141/2000/EC on Orphan Medicinal Products: A Critical Perspective

Master thesis

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Abstract

Phrase “living from day to day” is well known among patients suffering from rare diseases. The understanding of most of rare diseases is still very limited. Thus, the patients lack access to adequate treatments. Although rare diseases have a very low prevalence individually, they collectively cover 7-10% of EU population. Either way, low prevalence should not be used as an excuse to deny treatments to patients, suffering from rare diseases. In European Union (EU) it is widely acknowledged that people suffering from rare diseases are entitled to the same quality of treatments as other patients. However, research, development and marketing of medicines requires high investments. Whereas, pharmaceutical industry is inclined to undertake production of a medicine, only if its return on investments is foreseeable. This is almost never a case with treatments for rare diseases. Due to the low prevalence of target patients and lack of economic viability of a medicine, the pharmaceutical industry is reluctant to produce such medicines. The described problematics of treatments for rare diseases named them orphan medicines.

Since initial pharmaceutical incentives as well as patent law did not induce production of orphan medicines, there was a need for further legislator’s intervention. The legislator had a task to put in place incentives that are capable of spurring development and marketing of orphan medicines. However, this was all but an easy task. Namely, such legislation pursues objectives of innovation, competition and accessibility of safe medicines. However, the latter objectives are hardly ever achieved complimentary and therefore a legislator needed to conduct a complex trade-off. The result of this legislative process was Regulation 141/2000/EC on Orphan Medicinal Products. Regulation 141/2000/EC was attributed tremendous success and by the end of 2015, gave birth to 117 orphan medicines.

In its 15 years Regulation 141/2000/EC brought considerable benefits to patients suffering from rare diseases. At the same time, the years of its application also uncovered some of its pitfalls. Many patients’ advocates criticize the extensive length of market exclusivity period. On the other side, pharmaceutical industry cries for a greater clarity of certain blanket terms under Regulation 141/2000/EC. Last but not least, there is also a threat deriving from a newly emerged field of pharmacogenomics. The thesis examines these and other critical points of Regulation 141/2000/EC from a legal perspective. Bearing in mind the upper described legislative objectives, the thesis proposes certain legislative solutions, which would remove current pitfalls and prevent misuses of the incentives under Regulation 141/2000/EC.

**Key words:** orphan medicinal product, orphan medicine, Regulation 141/2000/EC, market exclusivity, revocation clause, pharmacogenomics, disease salami slicing
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>COMP</td>
<td>Committee for Orphan Medicinal Products</td>
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<td>ECJ</td>
<td>Court of Justice of the European Union</td>
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<td>EEC</td>
<td>European Economic Community</td>
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<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>Etc.</td>
<td>Et cetera</td>
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<td>EU</td>
<td>European Union</td>
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<td>EURORDIS</td>
<td>Rare Diseases Europe</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GMP</td>
<td>Good manufacturing practice</td>
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<td>Ibid.</td>
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<td>IP</td>
<td>Intellectual property</td>
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<td>IPRs</td>
<td>Intellectual property rights</td>
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<td>J.L.</td>
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<td>OJ L</td>
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<td>SPC</td>
<td>Supplementary protection certificate</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. Introduction

1.1. Background

Medical profession and medical research have made tremendous progress in the treatment of many diseases. However, there are still diseases for which there is no satisfactory treatment available. Moreover, it is estimated that there are approximately 5000 to 8000 rare diseases.\(^1\) The pharmaceutical industry is unwilling to develop appropriate treatments for the rare disorders, since their economic profitability is insignificant or even null. On the other hand, in contemporary modern society it is not acceptable to deny treatment to certain individuals, simply due to the fact that they suffer from a condition that affects only a small proportion of people.

It was United States of America who first recognized the need for regulatory intervention, and in 1983 adopted Orphan Drug Act, with an aim to provide for incentives for development of orphan medicines. The approach was later followed also by other states. In 2000 the European Union introduced Regulation 141/2000/EC on orphan medicinal products.\(^2\) Since the adoption of Regulation 141/2000/EC and till 25 September 2015, 1544 medicines were granted designation as orphan medicines. The number of designations is in principle increasing every year, however it is still far from the actual number of existing rare diseases.\(^3\) Yet, the Regulation 141/2000 has been considered as a tremendous success and has been praised by all relevant stakeholders, patients, governments and pharmaceutical companies.

It is more than 15 years since the adoption of Regulation 141/2000/EC and, in this time, some of its deficiencies have come to the surface. Moreover, the pharmaceutical science has evolved and in certain aspects surpassed the scope of Regulation 141/2000/EC. These deficiencies gave rise to certain practices that could prove to be malicious to patient’s benefits. Such practices, although in line with Regulation 141/2000/EC, go against its aim. Therefore the thresholds and incentives could be improved and Regulation calls for an amendment. When amending, the legislator should restore/correct the balance between unmet patients’ needs and encouragement of research, development and marketing of orphan medicines.\(^4\) In this

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3 Commission Inventory (n 1) 3, 19
regard, it is the legislator’s role to find most appropriate solution for striking such balance. However, certain attributes of orphan medicines make the process of achieving this balance a rather difficult task.

1.2. Central research question and sub-questions

The thesis aims to assess specific provisions and incentives for research, development and marketing of orphan medicines under Regulation 141/2000/EC. It begins with an explanation of the need for incentives, which is later followed by evaluation of the effectiveness and proportionality of the main incentives. Finally the thesis aims to provide advice on possible legislative solutions. With this purpose the thesis pursues the following research questions:

What are contentious legislative aspects of Regulation 141/2000/EC on orphan medicinal products?

What is the purpose of the incentives under Regulation 141/2000/EC and is their purpose achieved in practice?

Which legislative measures can be used to correct the problematic aspects?

Within the scope of “contentious legislative aspects”, the thesis examines aspects that have been expressed as critical either by scholars, EU and Member states authorities, patients’ advocates or pharmaceutical industry. Additionally, it should be noted that the assessment is centered on the Articles 3, 5, 7 and 8 of the Regulation 141/2000/EC, leaving out the remaining articles. Additionally, the scope of the thesis does not cover pricing of orphan medicines.

1.3. Significance

The rise of worldwide orphan medicine market is significant and it is set to reach $127 billion by 2018. It has been 16 years since the adoption of Regulation 141/2000/EC and since, it has not been subject to any substantial amendments. Moreover, in Europe only a few legal scholars have briefly touched upon the text and functioning of the Regulation 141/2000/EC. The thesis, thus, aims to provide some guidance on points of improvement and could serve as guidance tool for the legislator.

1.4. Methodology

The thesis follows the descriptive, evaluation and conceptual analysis, with the emphasis on the latter two. The descriptive analysis is used to present the phenomenon of orphan medicines and the state of play in regard to applicable legislation, Regulation 141/2000/EC. The legal research underlying the thesis consists

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of academic literature research, legislation research and research on relevant case law. The legal research consists of a close examination of Regulation 141/2000/EC and legal acts deriving from it. The academic literature research expands to European and US publications. Whereas the case law research is based solely on the relevant jurisprudence of ECJ. Here, the greatest attention is given to the recent ECJ judgment C-138/15, *Teva Pharma and Teva Pharmaceuticals Europe v EMA*. While the other case law is used to assess further interpretation of terms in Regulation 141/2000/EC and to outline the purpose of its adoption. The thesis in not based on any empirical research however it includes data from already conducted quantitative and qualitative empirical researches e.g. EU Commission reports, reports from various organizations in the field of pharmaceuticals and financial reports of some developers of orphan medicines. For the purposes of better evaluation, the thesis is also grounded on a comparative research. The latter is however limited to the comparison between implications and text of the US Orphan Drug Act and EU legislation and excludes research of any other similar legal act.

1.5. Overview

The thesis examines the contentious aspects of Regulation 141/2000/EC, by pointing out its provisions that tend to be problematic or can be subject to exploitation. In this regard the emphasis is given on the assessment of incentives for research, development and marketing of orphan medicines. Further on, the thesis examines possible legislative measures that could correct current deficiencies and failures of Regulation 141/2000/EC.

In Chapter 1 the thesis sets out brief historical, economical and legal backgrounds of orphan medicines’ legislation. These backgrounds serve as an outline of the purpose of Regulation 141/2000/EC. In addition, they also present some initial policy-making issues, which are more in detail addressed in the following chapters of the thesis.

Chapter 2 outlines the main definitions under Regulation 141/2000/EC and their points of weakness. In this regard, the text in centered on the designation criteria as set in Article 3. Further on, the thesis discusses the main incentives for research, development and marketing of orphan medicines. Each incentive is presented by its definition and purpose.

Based on the previous two chapters, Chapter 3 examines contentious aspects of Regulation 141/2000/EC, as they have emerged over the years. A gross part of this chapter deals with the most highly debated incentive of market exclusivity and to it related review procedure. Moreover, Chapter 3 also addresses implications of the recent ECJ judgement *Teva v. EMA* (C-138/15). And, finally, the thesis looks into the newly emerged field of pharmacogenomics and its effects on the Regulation 141/2000/EC. Each of those
parts is accompanied with some possible legislative measures that could serve as a solution to the described problems.
2. Placing Regulation 141/2000/EC in-to a bigger picture

2.1. Historical introduction

After the 1960s the pharmaceutical sector has become one of the most highly regulated sectors within the EU. Before 1960 several European countries recognized the potential negative effects of medicinal products and enacted legislation. However the latter acts were primarily administrative, they regulated mainly quality, advertising and promotion of the products. It was the thalidomide tragedy of that led to a more complex pharmaceutical regulation in Europe. As a result, quality, safety and efficacy became widespread authorization criteria. More, because of it, pharmaceuticals today are the most regulated consumer good. However, even today there is still no single European medicines market despite the fact that there is a growing number of products which benefit from the centralized marketing authorization which is valid throughout the EU/EEA. Some European countries historically followed the US model and enacted laws that pose stricter liability on the medicines manufactures and established special regulatory bodies. In addition, European countries saw a need for a cross-border control and as a result the European Community put in place Directive 65/65/EEC on common authorization requirements for new medicines.

Directive 65/65/EEC ensured the availability of safe and efficient pharmaceuticals. In the aftermath of Directive 65/65/EEC the EU legislator enacted several acts governing pharmaceuticals, which were later, due to the adverse effects of fragmentation joined in the single Directive 2001/83/EC. Although the legal

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7 Ibid 1 The drug was first placed on the West German market in 1957 and four years later it was removed due to its severe and adverse effects on newborns and pregnant woman. After the travesty brought by thalidomide, European legislators recognized the vital need for the safety evaluation of the medicinal products. At the same time, the tragedy lead to development of clinical pharmacology in the 60s.
8 Ibid 1,2. On contrary to Europe the US had in place a legislation since 1950s, which obliged medicines manufacturers have been obliged to provide reliable and accurate information about a medicine on its package. Additionally, the US had established an specialized a federal regulatory authority, the Food and Drug Administration (FDA), which was empowered to license manufactures based on prescribed safety standards. On these grounds thalidomide was prevented to enter the US market. The reason why Europe was lacking an effective pharmaceutical regulation, can be seen in the fact that in US patients were the direct payers of the medicines and therefore the proof for safety and efficacy was stronger.
9 Ibid 2
10 Ibid 3
11 Ibid 2. The United Kingdom (UK) for example, created Committee on Safety of Drugs (CSD) in 1963. And although companies were required to submit their data to the CSD for assessment, there was little direct government control until the 1968 Medicines Act. And in the Germany the 1961 drug law was accompanied by the compulsory registration of all new medicines with the Bundesgesundheitsamt (Federal Ministry of Heath).
13 Ibid 2
framework governing pharmaceuticals provided for incentives for economic operators for development of medicines e.g. data exclusivity,\textsuperscript{15} it did not foster the availability of treatments of rare diseases. Before 1983, people suffering from rare diseases, had no real availability and accessibility of adequate treatments. The development of such a cure requires high expenditures that due to limited volume of consumption would hardly ever be reimbursed.\textsuperscript{16} Therefore pharmaceutical companies were not inclined to explore and enter into research and development of medicines and devices for rare disorders. 

Then in the 80s these diseases raised a greater public awareness which triggered the adoption of policies that provided incentives for pharmaceutical companies to develop medicines for rare disorders. Surprisingly, it was also an US TV show “Quincy”, hosted by Jack Klugman that added to the process. In episode “Seldom Silent, Never Heard” from 1981 Klugman brought to spotlight a patient suffering from Tourette syndrome. The story touched the public and lead to extensive news coverage.\textsuperscript{17} It is claimed that this episode was instrumental for the final adoption of the Orphan Drug Act in 1983, the first of its kind.\textsuperscript{18}

Following US and Japan, in 1999 European Union adopted the Regulation 141/2000 on orphan medicinal products.\textsuperscript{19} The Regulation in general followed the name and wording of its US counterpart. Additionally, it took into account the early US experiences and tried to find a proper solution for the issues.

2.2. Economic perspective - medicines’ market failure

"Lacking economic return as a viable prospect, some useful drugs sat on the shelf without hope of normal commercial investment in the costs of premarketing approval."\textsuperscript{20}

Nowadays there is a predominant view that markets should be a self-regulating phenomenon, since as such they lead to a greater welfare.\textsuperscript{21} Although the statement seems at first glance contradictory, it was proven to be true in places of well-functioning market mechanism.\textsuperscript{22} Moreover, this view is also embedded in law.

\textsuperscript{15} Article 10 of Directive 2001/83/EC
\textsuperscript{16} Gina M. Cavalier, ‘Pushing parentless pharmaceuticals: toward an international home for »Orphan drugs« and a cure for »zebra diseases«’ (1996) 27 Law and Policy in International Business 447, 449
\textsuperscript{17} Henkel J., Orphan drug law matures into medical mainstay, (1999), 33(3) FDA Consum. 29-32
\textsuperscript{20} James T. O’Reilly, ‘Orphan Drugs: The Strange Case of Baby M’ (1987) 42 Food Drug Cosm. L.J. 500, 517
\textsuperscript{21} Paul A. Samuelson, William D. Nordhaus, \textit{Economics} (19\textsuperscript{th} edn McGraw-Hill 2010) 40 In 19th century laissez-faire doctrine emerged as a leading market regulation approach in Western Europe. The doctrine has its grounds in liberalism and it proclaims principles such as free trade and free competition as the main principles governing states economics.
\textsuperscript{22} Ibid 29
On the Union level this principle is attained in Article 120 of the Treaty on the Functioning of the European Union.\textsuperscript{23}

Due to issues such as information asymmetry, uncertainty and inconsistent expectations market forces sometimes dictate unfair distribution of goods and services.\textsuperscript{24} In economic terms, such situations where distortions provoke the “invisible hand” to allocate the resources inefficiently is called market failure.\textsuperscript{25} The result of it is decreased social welfare. However, today’s developed democratic countries recognized the negative outcome of \textit{laissez-faire} as unacceptable and unfair and had taken steps to regulate the distribution of goods and services.\textsuperscript{26} This approach is, among economists, regarded as welfare state, under which markets direct activities of day to day life, while the government regulates certain social conditions, among others health care.\textsuperscript{27} In situations where the \textit{laissez-faire} doctrine collapses, the states need to intervene with otherwise free market and put in place certain regulatory instruments. Although governmental solutions are claimed to be controversial, people in general believe that societies must provide basic necessities to everyone, including health services.\textsuperscript{28} In the regard of the above, the lack of accessibility of medicines for rare diseases is a market failure and Regulation 141/2000/EC is a form of state intervention.

There are several reasons which can be seen as a cause for the market failure of orphan medicines. The specific and unique features of the pharmaceutical market and even more so the orphan medicines market hinder the existence of many essential market preconditions.\textsuperscript{29} This leads to severe distortions on the market.\textsuperscript{30} It was due to these distortions that people who suffered from rare diseases did not have access to adequate treatments. The development of orphan medicines is very expensive, their demand insignificant and, thus, pharmaceutical companies' investments could hardly ever be returned.\textsuperscript{31} On the other hand,

\begin{itemize}
\item \textsuperscript{23} Consolidated version of the Treaty on the Functioning of the European Union - Protocols - Annexes - Declarations annexed to the Final Act of the Intergovernmental Conference which adopted the Treaty of Lisbon, signed on 13 December 2007 [2012] OJ L Official Journal C 326/1
\item \textsuperscript{24} Francis M. Bator, ‘The Anatomy of Market Failure’ (1958) 72(3) The Quarterly Journal of Economics 351 at 351
\item \textsuperscript{25} Samuelson, Nordhaus (n 21) 39
\item \textsuperscript{26} Ibid 38
\item \textsuperscript{27} Ibid 40
\item \textsuperscript{28} Ibid 38, 39 Due to coercion powers of government they are most suitable to correct flaws of the market. To avoid the threat of market failure governments regulate health, safety and quality standards. This regulation aims to minimize the information dissymmetry, by giving customers the knowledge of costs and benefits and by enforcing standards to producers to reduce risks of injuries.
\item \textsuperscript{29} Permanand (n 6) 3 Permanand argues that the special nature of pharmaceutical market gives rise to mainly two different regulatory problems. Firstly, the pharmaceutical market differs to great extent from markets of other goods. Mainly, the peculiarities lie in the fact that a consumer generally relies on a doctor’s prescription and the state is the head purchaser. Also, unlike other markets, the pharmaceutical market is heavily regulated since the states are responsible for public health. All these factors lead to unique dynamics on the market, which presents a great challenge to policy makers.
\item \textsuperscript{30} Permanand (n 6) 3
\item \textsuperscript{31} Cavalier (n 16) 449
\end{itemize}
economic operators invest in order to produce a product that will be desirable in future, and more importantly for them, a product which will bring the company profit.\textsuperscript{32}

Firstly, from an economic perspective, prevention methods and treatments of diseases are public goods and services, which market does not provide efficiently. The eradication of smallpox benefited millions, however firms were able to collect only a fraction of revenues. The orientation of companies in R&D of lifestyle-related medicines resulted in the current lack of new and effective antibiotic while the antimicrobial resistance is on the increase. This and other similar examples are common in the field of health care and they lead to underinvestments in health improvements.\textsuperscript{33} Second reason lies in the information asymmetry between patient, doctor and health insurance company/fund and in the lack of private health insurance market. Due to lack of adequate information, patients tend to choose inappropriate insurances, which results in undesired costs.\textsuperscript{34}

Secondly, market failures are mainly caused by scientific deficiencies (e.g. small numbers of subjects for clinical trials, lack of knowledge about the cause of the disease, absence of valid biomarkers), greater regulatory demands on new medicines in terms of safety, efficacy and real world effectiveness, possible obstacles in patenting, and a lack of public awareness of the issue.\textsuperscript{35} Moreover, the orphan medicines must meet demanding quality, safety and efficacy standards and, thus, undergo a rigorous procedure before they are granted market approval.\textsuperscript{36} Further on, marketing approval does not necessary guarantee success. It is estimated that only three out of ten marketed prescription medicines will produce revenues sufficient enough to recoup investment.\textsuperscript{37} Finally, in case of orphan medicines the development barriers are amplified by the low prevalence of the disease that a medicine is associated with.\textsuperscript{38}


\textsuperscript{33} Samuelson (n 21) 220

\textsuperscript{34} Ibid 220 There are information asymmetry between patient and the insurance provider. People may know more about their medical condition than do insurance companies. Low-risk individuals may choose not to buy health insurance. This leads to adverse selection, which increases the average riskiness of the group and subsequently increases the cost for those who do participate.


\textsuperscript{36} Article 8 of Regulation 141/2000


\textsuperscript{38} Rogoyski (n 37) 2
Finally, probably the most likely argument is that the market failure of orphan medicines is a result of inadequate protection of intellectual property. A technological innovation is subject to a market failure, because information is a public, non-rival good, which is expensive to produce, but cheap to reproduce.\textsuperscript{39} Namely, markets may fail to produce and allocate scarce resources in the most efficient way. Because the governments did not offer sufficient incentives, the policies resulted in underproduction of orphan medicines. For this reason the government must enact laws that will provide sufficient and strong intellectual property rights, which will secure innovation of new technologies.\textsuperscript{40}

In this regard the best solution would probably not be enhancement of the traditional patent protection, but rather creation of a tailor-made protection.\textsuperscript{41} The patent protection is an innovation-driven incentive and as such does not directly encourage marketing of an invention. Moreover, marketing of a medicine is further hindered by expensive and otherwise rigorous market authorization procedure. Additionally, patients entirely depend on the marketed medicines. Consequently, access to orphan medicines would be ensured only through a market-driven incentive. This argument is also upheld by the fact that the market failure of orphan medicines existed regardless of the existing incentives provided by standard regulation for medicines and patent protection.\textsuperscript{42} The outcome of described issue is a Regulation 141/2000/EC, which as \textit{lex specialis} provides for incentives for research, development and marketing of orphan medicines. Namely, preceding Regulation 141/2000/EC the incentives were so limited that the large majority of companies withdrawn from these areas and rather concentrated on the lines of research that held greater promise of commercial success.\textsuperscript{43} Nonetheless, the encouragement through IP rights should be approached with care, since strengthening of IP rights may decrease patients’ benefits.

\begin{footnotesize}
\begin{itemize}
\item[\textsuperscript{39}] Samuelson (n 21) 511
\item[\textsuperscript{40}] Ibid 511
\item[\textsuperscript{41}] Ted Sichelman, ‘Commercializing patents’ (2010) 62 STAN. L. REV. 341 Sichelman strongly criticizes the existing IP protection and proposes a \textit{sui generis} model, one that would tie patent holders to commercialization of their invention
\item[\textsuperscript{42}] EURORDIS Rare Diseases Europe, ‘EURORDIS response to the public consultation on Notice from the Commission on aspects of the application of Article 3, 5 and 7 of Regulation (EC) N° 141/2000/EC on orphan medicinal products’ (2016) \textltt{http://ec.europa.eu/health/files/orphanmp/2015_11_pc_orphanmp/replies/2015_11_pc_orphans_eurordis.pdf} > accessed 22 July 2016 In the position paper EURORDIS states that prior to Regulation 141/2000/EC there was only 8 orphan medicines.
\end{itemize}
\end{footnotesize}
2.3. Regulatory perspective – issues of pharmaceutical policy making

EU pharmaceutical legal framework strives to provide high standards of quality, efficacy and safety of medicinal products and intends to promote innovation and competitiveness of the internal market. Unfortunately, all these are contrasting objectives. Therefore legislators are required to undertake a balancing process. The primary objectives in all this are probably the equity and efficiency and meeting patients’ needs. However, the latter objectives must be attained by measures which do not hinder the development of pharmaceutical industry or trade in medicinal products within the Union. To sum up, it rather seems that provision of all this objectives present a considerable challenge to the legislator.

Moreover, the pharmaceutical policy making is especially complex at the EU level. In principle, EU leaves regulation of healthcare systems to the greatest extent to the competence of the Member States. Due to limited competence of EU institutions, it can be argued that the legislation is not as effective as it could be. The EU derives its competence from the Treaty-based public health mandate. The Article is a dissonance between subsidiarity principle and the free-movement principles. Based on the former, the EU has a competence at the lowest level under which it can be effectively undertaken. Member states decide upon the healthcare policy elements when designing and performing pharmaceutical policy. While under the free movement principles, pharmaceuticals are treated as industrial goods and therefore fall under the EU SEM competence. The competence is consequently divided between the Community institutions and Member States competent authorities. However, economic integration is significantly affecting also the healthcare and vice-versa. Thus it is possible to foresee greater integration in the future. Namely, as the theory of neofunctionalism describes – integration in one sector necessitates integration in another in order to ensure that the advantage of integration in the first sector is maximized.

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44 Recital 2 and 3 of Directive 2001/83/EC
45 Elias Mossialos, Monique Mrazek, Tom Walley, Regulating Pharmaceuticals In Europe: Striving For Efficiency, Equity And Quality, (McGraw-Hill Education (UK), 2004) 1. Governments should refrain from uncritically accepting the claims from the industry that any constrain on profits should threaten truly valuable innovation. However, pharmaceutical innovation is valuable to society and, thus, truly innovative medicines should be appropriately awarded.
46 Ibid 1; see also Recital 3 of Directive 2001/83; see also Permanand (n 6) 4. Discussing three policy inputs public health (drug quality, safety, and efficacy), healthcare system (financing and reimbursement) and industrial policy (successful and efficient pharmaceutical sector).
48 Permanand (n 6) 4
49 See Article 168 of the TFEU
50 Permanand (n 6) 4
51 Ibid 4
52 Barnard, Peers (n 47) 539 Discussing the economic impact of public services, where healthcare alone accounts to 10 percent of state’s GDP.
53 Ibid 2,3
As mentioned above, the objectives of EU pharmaceutical policy-making force the authorities to make trade-offs. Due to orphan medicines’ unique features, the trade-off in their respect, is even more complex. To secure the accessibility and availability of orphan medicines a big sacrifice needs to be made on the account of otherwise appreciated competitiveness. Moreover, a balance needs to be established among the safety, efficacy and quality of an orphan medicine.

It was acknowledged that patients suffering from rare diseases should be entitled to the same quality of treatment as other patients. Therefore, the legislator was required to encourage research, development and marketing of orphan medicines. This is already partially ensured through the intellectual property protection. Further on, the sponsors are required to undertake a rigorous market authorization procedure, which is costly and time-consuming. Since market authorization is in the interest of patients, the legislator is required to award developers that put their invention through the market authorization procedure. In this respect, the existing intellectual property protection does not suffice, since it as invention-driven incentive and, thus, only fosters creation of ideas and not their marketing. Acknowledging that patients only benefit from inventions if they are accessible for them, the legislator needs to provide for a sui generis intellectual property protection, one that is in its form a market-driven incentive. Nowadays it is unambiguous that invention is best encouraged by reward of exclusive rights, which grant their holder a monopoly position in the market. For this reason, it is appropriate to use a patent-like incentive for encouraging the marketing of inventions. Because of all the upper reasons, the EU legislator decided for a reward of market exclusivity right.

However, monopoly, especially the one deriving from both IP and market exclusivity rights, is significantly hindering competition on the market. As a consequence patients’ benefits are endangered, since the accessibility is diminished on the account of monopoly prices. Moreover, marketing authorization in itself places no obligation for its holder to actually launch the product on a particular Member State market. This is a fact that further increases the availability risks for patients especially in the smaller Member States.

In addition to the trade-off between the above described objectives of pharmaceutical policy making, there is also a trade-off between safety, efficacy and quality of an orphan medicine. Although a medicine generally requires some extent of a trade-off between the three aspects, this is even more so with an orphan medicines. The market authorization for orphans is in principle given on the basis of lower level of evidence

54 Permanand (n 6)
55 Recital 2 and 3 of Directive 2001/83/EC
56 Recital 8 of Regulation 141/2000/EC
57 Article 8 of Regulation 141/2000/EC
58 Recital 2 and 3 of Directive 2001/83/EC
when compared to the average high-volume medicines. For example, should we provide a patient with an evidently uncovered medical need with a medicine regardless of the notion that its safety can only be established provisionally? Such situation tends to be a frequent, if not usual case with orphan medicines. Clinical trials, by default are facing a statistical issue, due to the small number of patients. Thus, clinical trials do not always provide a finite proof about the safety and/or efficacy. This brings additional risk into the treatments. Most of it can be addressed through the pharmacovigilance systems. However the latter is rather an *ex post* instrument than a preventive measure, which in turn is generally more desirable approach in developing the pharmaceuticals. It is the role of legislator to secure the three requirements to the highest possible level.

Nonetheless, one should not neglect the fact that medicines are produced by private entities, which are primarily governed by market forces. Hence, the pharmaceutical companies generally orientate their production towards profitable products. Since orphan medicines are unprofitable, their R&D can only be achieved through their incentives, provided that they are able of shifting the paradigm. Foreseeability of profit is therefore essential. As Schrumpeter argues, the “major engines of innovation” are companies with monopoly power, since monopoly profits allow for security and such security secures the freedom to innovate. There is a fine line between incentives that spur innovation of orphan medicines and incentives that do not create a promise of profit. For this reason, some argue that the ambit of incentives is an “all or nothing debate”. This meaning that by cutting the incentives to diminish unreasonable profits, we endanger production of orphan medicines itself.

To conclude, in the light of the above, formation of the orphan medicines policy was a complex process. In addition, it is worth bring to attention that the pharmaceutical policy-making arena is characterized by (protracted) negotiation, bargaining, compromise and much-revised policy documents. Most likely, the result of all aforementioned actions is also Regulation 141/2000/EC. It is a compromise between all above described stakes and objectives. However, the question now is, whether the compromise from sixteen years ago is still proper and adequate or should it be readdressed by the legislator.

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60 Arti K. Rai, ‘Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust’ (2001) 16 Berkeley Tech. L.J. 818 Schrumpeter believes that monopoly power also helps companies fully reap the benefits of their efforts by controlling the diffusion of patented knowledge to competitors.

3. Regulation on orphan medicinal products 141/2000/EC

In 1998, the Commission prepared a proposal for the European Parliament and Council on orphan medicinal products. Regulation 141/2000, as it became following the legislative procedure, entered into force on 28 April 2000. The scope of the regulation is limited to “medicinal products for human use” as defined in the Directive 2001/83/EC.62 The regulation has an aim to establish a community procedure for the designation of orphan medicines and provide incentives for the research, development and placing on the market designated orphan medical products.63 It was acknowledged that the pharmaceutical companies are unwilling to develop medicines for infrequent health disorders under the normal market conditions.64 However, all patients, including those who suffer from rare diseases should be entitled to the equality of treatment. For this reason the European Union recognized the necessity to stimulate development of appropriate medical products for rare disorders.65 In addition, community procedure for designation of orphan medicines seemed to be the most appropriate to determine an orphan medicine and later assign incentives.66

Prior to Regulation 141/2000/EC certain Member States had already put in place measures that encouraged development of orphan medicines, however the Commission concluded that those are low in number and do not lead to significant progress.67 Also, the somewhat dispersed incentives would not suffice to provide equality of treatment for patients, suffering from rare diseases. Additionally, the Commission argued that if such measures were adopted individually and in an uncoordinated manner by the Member States, this would lead to obstacles in Community trade and to the distortion of competition.

Regulation 141/2000/EC also provides for an institutional design of the orphan medicine policy. Article 4 established the Committee of Orphan Medicinal Products (COMP), who has competence over the examination of any application for the designation of a medicinal product as an orphan medicine and the assistance to the Commission on any matter in relation with the Union policy on orphan medicines.68 Its structure also provides for representation of the patients, which ensures greater transparency and democracy.

62 Article 1(2) of Directive 2001/83/EC
63 Article 1 of Regulation 141/2000/EC
64 Recital 1 of Regulation 141/2000/EC
65 Recital 2 of Regulation 141/2000/EC
66 Recital 4 of Regulation 141/2000/EC
68 Article 4 of Regulation 141/2000/EC
Regulation 141/2000/EC tends to reduce the gap between medicine and economics, since it provides for access to medicine regardless of the prevalence and profitability of a medicine. As such it ensures a right for all citizens to a certain level of health protection.\(^6\) Regulation 141/2000 follows the same aim as its *lex generalis* Directive 2001/83/EC that is – to strike a balance between public health protection and the development of pharmaceuticals.\(^7\) Additionally, it can be stated that not only did Regulation 141/2000/EC boost the access to orphan medicines for EU patients but it also encouraged the development of the biotechnology sector.\(^8\)

Regulation 141/2000/EC is complemented by several legal acts and guidelines. Unlike the US Orphan Drug Act, which is part of annual Congress debates, it has never been amended.\(^9\) The following text of the thesis will demonstrate that there is a long pending need for a change.

### 3.1. Orphan medicinal product – designation criteria

Regulation 141/2000/EC under Article 2 does not substantially define an orphan medicine, but rather states that an orphan medicine product is a medicinal product designated as such under the terms and conditions of Regulation 141/2000/EC.\(^10\) Based on Directive 20001/83/EC and as envisaged by the current pharmaceutical EU law, the term medicinal product for human use includes any substance or combination of substances which may be administrated to human beings with a view to making a medical diagnosis or for treating or preventing a disease.\(^11\) Additionally, the definition only applies to medicinal products which are covered by the marketing authorization system and therefore excludes medical devices and nutrition supplements, regardless of the fact they might play a role in diagnosis, prevention or treatment of a rare disease.\(^12\) This definition seems to be complemented with the objective designation criteria established in Article 3 of Regulation 141/2000/EC.\(^13\)

There are two main designation criteria – epidemiological and economic – under which a medicine can be designated as an orphan medicine. The two criteria are not mutually exclusive and can therefore be applied cumulatively were appropriate.\(^14\) In addition to alternative criteria from Article 3(1)(a), the product also

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\(^7\) Recitals 2 and 3 of the Directive 2001/83/EC and Recitals 1 and 7 of the Regulation 141/2000/EC
\(^8\) Many of the orphan medicines are biological medicines, more precisely, in 2009 the share of biological medicines among orphan medicines was 64%, which amounted to 54.6 billion dollars in sales. Aarti Sharma, Abraham Jacob, Manas Tandon, and Dushyant Kumar, ‘Orphan drug: Development trends and strategies’ (2010) 2(4) J Pharm Bioallied Sci. 290, 290-299
\(^9\) Pusinelli (n 18) 302
\(^10\) Article 2 of Regulation 141/2000/EC
\(^11\) Article 1(2) of the Directive 2001/83/EC
\(^12\) Commission Proposal (1999) (n 67) 7
\(^13\) Article 3 and Recital 5 of Regulation 141/2000/EC
\(^14\) Commission Proposal (1999) (n 67) 7
needs to suffice the designation criteria of Article 3(1)(b). Again, there are two alternative criteria – a medicine either needs to bring significant benefit or it is novel in a sense that there is no satisfactory method of treatment for this condition.\footnote{78 Article 3 of Regulation 141/2000/EC}

3.1.1. Medical plausibility

Firstly, the product needs to be “medically plausible” – intended for diagnosis, prevention or treatment of a condition. Following the approach set in the definition of the rare disease, the designation criteria does not distinguish between the concepts of medicinal product intended for treatment of a condition and a medicinal product intended for the diagnosis or prevention of a condition (e.g. vaccines).\footnote{79 Commission, ‘Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products (Communication)’, (2003) OJ L 178/2, ch A.1} Thus, a condition is understood as any deviation from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognized distinct disease or a syndrome).\footnote{80 Ibid A.1; see also Commission, ‘Commission Notice on the application of the Articles 3, 5, and 7 of Regulation (EC) NO 141/2000 on orphan medicinal products, (Consultation Document)’ (2015) at 5 <http://ec.europa.eu/health/files/orphanmp/2015_11_pc_orphanmp/2015_11_06_notice_orphan_medicinal_products _comments.pdf> accessed 5 July 2016} However, the term “population affected by”, when considering a medicinal product intended for the diagnosis or prevention of a condition can be interpreted in several ways. Such medicinal product, if effective, can eventually decrease a number of people suffering from this condition. Here, the Commission clarified that the prevalence calculation of such medicinal product will be based on the expected number of people to which the product will be annually administrated.\footnote{81 Ibid 5,6}

3.1.2. Epidemiological criterion

A medicinal product can be designated as orphan medicinal product based on the prevalence or incidence of the disease concerned within a given population. This is that it is intended for the diagnostic, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the EU. The described criteria is based on the prior Commission Communication concerning a programme of Community action on rare diseases. The latter has proposed to define rare disease as life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them so as to prevent significant prenatal and early morbidity and mortality or a considerable reduction in an individual’s quality of life or socio-economic potential.\footnote{82 Commission, Communication, ‘Programme of Community action on rare diseases (1999 – 2003) Decision No 1295/99/EC of the European Parliament and of the Council (1999) OJ L 155/1, Annual work programme for 1999-2000 (Art. 5(2) of Decision 1295/99/EC)’ (1999) at 2}
threshold is lower than in the US where orphan medicine designation is granted to treatments of diseases with prevalence of 7.5 per 10,000.83

The prevalence is relevant for the EU territory, therefore medicinal products that are intended for the treatment of diseases that are widespread in other parts of the world, can nonetheless be eligible for designation as an orphan medicinal product under Regulation 141/2000/EC (communicable diseases).84 It seems that development of such medicinal product would likely result as a “quasi-orphan buster” for a pharmaceutical firm. In such case the firm would collect high revenues in the EU territory, concurrent with smaller revenues per product, but also collect revenues on larger quantities of product elsewhere. Additionally, the 10-year period of market exclusivity in this case tends to be over-excessive. The marketing authorization would be given to a single sponsor and with market exclusivity in place denied to all others. If in the meantime the communicable disease would increase in prevalence, Europe would have only one supplier. Such situation would have a significantly negative effect on public health.85 Moreover, the market exclusivity would prevent equally good medicines, but less costly, eventually produced abroad and even complying with EU standards of quality, safety and efficacy, to enter the EU market.86

3.1.3. Economic criterion

It was acknowledged that it is also vital to foster development of medical products that do not exactly fit into category of rare disorders. Therefore, the economic criterion is based on the presumption that a prospect medicinal product is not commercially viable. The economic criterion follows the main purpose of Regulation 141/2000/EC, which is to provide for appropriate incentives where needed.87

Therefore a medicinal product can be designated as orphan medicinal product, without fulfilling the prevalence threshold criteria, if it suffices cumulatively two other requirements. Firstly, it needs to be medically plausible. Secondly, a sponsor of an orphan medical product needs to show that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.88

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84 Article 3 of Regulation 141/2000/EC; see also Commission Communication at A.1
86 Ibid
87 Commission Consultation Document (2015) (n 80) 6
88 Article 3(1)(a) of Regulation 141/2000/EC
The economic criterion is less objective than the epidemiological one and therefore to certain extent problematic. Firstly, it relies on two vague notions of “unlikely” and “sufficient return”. The Commission Consultation Document only briefly touched upon these two terms. The only explanation given was that the assessment under the economic criterion will be based on all costs (past and future) and expected revenue. This leaves out decision on any appropriate method. And secondly it tends to be hard for the sponsor to establish that the requirements are met and later the evaluation of the evidence presents a significant burden to the designation committee. Namely it is hard to assess whether it will be possible to obtain a reasonable return at a time point which is years before the product is placed on market. It was consequently proposed that the epidemiological criterion alone would be used initially.

Additionally, it is questionable whether the economic criterion appropriately functions as a ground for incentive for research and development of orphan medicines. The US Orphan Drug Act experience show that this criterion is to certain extent a dead end. Namely, the initial Orphan Drug Act from 1983 relied exclusively on the economic criterion. As such the Act placed a high burden of proof on sponsors and consequently did not lead to an expected outcome.

3.1.4. “Satisfactory method” and “significant benefit” under Article 3(1)(b)

Prospective orphan medicinal products under both epidemiological and economic criterion must fulfill additional requirement set out in the Article 3(1)(b). A sponsor needs to establish that no satisfactory method of diagnosis prevention or treatment of the condition in question has been authorized in the Community, or if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

The Commission in its Communication clarified that under the notion of “satisfactory method” the sponsor is required to provide details on ‘existing methods, which may include authorized medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community.’ The Commission also further clarified that the grant of a marketing authorization establishes that a method is satisfactory. This derives from the Directive 2001/83/EC, which places the assessment of criteria of safety, quality and efficacy at the time of market authorization. Granting of marketing authorization

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89 Commission Consultation Document (2015 (n 80)) 6
90 Commission Proposal (1999) (n 67) 7
91 Ibid 8
92 David Duffield Rohde, ‘The Orphan Drug Act: an Engine of Innovation? At What Cost?’ (2000) 55 Food & Drug L.J. 125, 129. For this reason the Act was amended in 1984 with introduction of the epidemiological criterion – presumption that a drug is unprofitable if it has a prevalence less than 200 000 people in US.
93 Article 3(1)(b) of Regulation 141/2000/EC
94 Commission Communication (2003) (n 82) A.3
depends on the positive outcome of the assessment of balanced risks and benefits related to the use a medicinal product.\textsuperscript{95} As for the matter of “authorized in Community”, the Commission clarified that an authorization in any Member State fulfills this notion.\textsuperscript{96} Additionally, there is a requirement that a satisfactory method needs to have market authorization, meaning that all off-label uses are not regarded as satisfactory methods under Article 3(1)(b).\textsuperscript{97}

There has been much debate on the “significant benefit”, but the term has not yet been fully clarified. Significant benefit is vaguely defined in Commission Regulation 847/2000/EC as ‘a clinically relevant advantage or a major contribution to patient care.’\textsuperscript{98} The Commission noted that the sponsor needs to show significant benefit over existing method rather than proving the existing method is not satisfactory.\textsuperscript{99} The significant benefit can arise also from increased supply/availability of the method, but only if the sponsor can establish that the supply/availability issue with the competitive methods as such presents an unmet need of patients.\textsuperscript{100} Also, the improvement of a pharmaceutical product is an obligation of every sponsor and therefore as such cannot be a basis for the assumption of significant benefit.\textsuperscript{101}

In addition, the ECJ got to rule on the concept of “significant benefit” in the \textit{Now Pharm v Commission}.\textsuperscript{102} In the aforementioned case the ECJ stated that the establishment of significant benefits takes place in the context of comparison with an existing authorized medical product or method and cannot be limited to an assessment of the intrinsic qualities of the product in question, without comparing the qualities with the intrinsic qualities of the authorized methods.\textsuperscript{103} The ECJ also clarified that based on the criteria of “significant benefit” a generic orphan medicines product cannot benefit from orphan designation, since it is lacking improvement from the already authorized medical product.\textsuperscript{104}

\begin{flushleft}
\textsuperscript{95} Ibid A.3; see Directive 2001/83/EC
\textsuperscript{96} Commission Communication (2003) (n 82) A.3
\textsuperscript{97} Ibid A.3
\textsuperscript{98} Article 3(2) of Commission Regulation (EC) 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’, (2000) OJ L 103/5
\textsuperscript{99} Commission Communication (2003) (n 82) A.4
\textsuperscript{100} Ibid A.4
\textsuperscript{101} Ibid A.4
\textsuperscript{102} Case T-74/08 \textit{Now Pharm v Commission} ECR [2010] 376
\textsuperscript{103} Ibid para. 46
\textsuperscript{104} Case T-264/07 \textit{CSL Behring v Commission and EMA} [2010] ECR:371, paragraph 94
\end{flushleft}
In November 2015 the Commission launched a new public consultation for the Communication on the interpretation of Article 3, 5 and 7 of Regulation 141/2000/EC. In it, it acknowledged the lack of clarity of “significant benefit”, its application and demonstration. As outlined above, the “significant benefit” is one of the key criteria for the application of the Regulation 141/2000/EC and as such it should be clearly and transparently defined.

Additionally, the subject of the consultation was also removal of the claim of increased supply as significant benefit.105 The EU Commission is of an opinion that this claim does no longer fits the purpose of EU development and integration. However, such statement is rather contradictory. Preceding the Commission Consultation Document lack of supply was regarded as unmet patient need and as such served as a legitimate claim for orphan designation. Moreover, until today there is no provision in law that would require a sponsor to sell his medicine following the obtainment of the market authorization.106 In this way the provision of access of a medicine is solely the prerogative of a sponsor. Since the state does not have coercion powers over the first sponsor, it can only ensure access to medicines by encouraging other sponsors to place similar medicine on the market. Also this mechanism may not be feasible for a particular state in need of the product, if the supplementing product is eligible for the compulsory Centralized Authorization Procedure and the first product is on the market of a substantial number of Member States. Whereas, the second sponsor can benefit from the orphan designation only if he demonstrates the increased supply. Also, such situation is also favorable from the perspective of competition law, since it would probably decrease the adverse effects of monopoly.

Finally some Member States suggested that medical products prepared in the hospital should be considered in the assessment of the significant benefit.107 This proposal raised a lot of criticism on the account of otherwise established exemption of “hospital use” in the article 3(7) of Directive 2001/83/EC. In its position paper, EMA argued that such provision would go against the aim of Orphan Regulation, since medicines prepared in the pharmacy are generally exempted from the requirement to comply with the GMP standards for industrially manufactured pharmaceuticals... Moreover, potential orphan medicines need to undertake a rigorous designation and market authorization process which provides for the assessment, opinion and decision on the medicine to be actually of good quality, safe and efficacious. Also, the pharmacy regulation and practices differ among member states. If pharmacy prepared medicines would somehow be included in

105 Commission Consultation Document (2015) (n 80) 2
106 This lack of obligation to pale the products on markets is often deemed as the underlying reason for shortages on the markets, especially in the small markets Member states
107 Commission Consultation Document (2015) (n 80) 2
the assessment as an existing satisfactory method, this would considerably hinder the development of industrially produced orphan medicines.108

Despite several guidelines on the interpretation of “significant benefit”, the term is still lacking clarity. In the new Communication the Commission should seek to fill in this gap. Moreover, it should take into account the technical considerations argued by many companies. As described above, the proof of significant benefit tends to be over burdensome and as such it substantially increases the time lag between the development and marketing of a medicine, which again has a negative effect for the treatment outcomes in the specific patient groups.

3.2. Incentives under Orphan Regulation

Regulation 141/2000/EC successfully encouraged the research, development and marketing of previously unprofitable and therefore not existing or inaccessible medicines. Not only there is insufficient return on investments but also the development of orphan medicines is considerably hindered by the required sufficient evidence of effectiveness and safety of a medicine.109 Additionally, the rigorous process of market authorization is both very costly and time consuming. The aim of the incentives is to strike a fair balance between promotion of innovation and competition and pricing – availability and affordability of a medicine. The emphasis should be given to patients’ needs, however, both under-protection and over-protection of the patients is undesirable and should be avoided wherever possible.

There are five main incentives for research and development of orphan medicines, the essential one being market exclusivity. Other incentives are protocol assistance, access to centralized market authorization procedure and fee waivers. The designated product is subject to many waivers from fees associated with the marketing authorization procedure, including fees for protocol assistance, marketing authorization, inspections, and renewals.110

Regulation 141/2000/EC allows for further measures which can be enacted by Member States. This might especially be the case with tax benefits.111 Namely, the EU does not have competence over taxation, other than those related to indirect levies and custom duties and therefore was unable to put in place, otherwise highly valuable tax benefits. Whereas as it is seen from the US Orphan Drug Act experience, tax benefits

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109 Brendan M. Buckley, ‘Clinical trials of orphan medicines’ (2008) 371 The Lancet 2051 at 2051, 2052
110 Articles 3,5,6,7 and 8 of Regulation 141/2000/EC
111 Article 9 of Regulation 141/2000/EC
have tremendous relevance for the development of orphan medicines, perhaps even greater than market exclusivity.\textsuperscript{112} Therefore, if there would be a need for bigger encouragement of development of orphan medicines, the legislators should consider approaching this demand also through tax legislation.

The incentives aim to reduce adverse aspects that hinder development and market authorization of orphan medicines. Firstly, they deal with challenges in the assessment of clinical relevance and cost-effectiveness of a medicine. Secondly they address the issue of lack of information, since data on many rare diseases is inadequate.\textsuperscript{113} The purpose of the following chapters is to outline the purpose and utilization of the main four incentives, whereas all the incentives are discussed throughout the thesis, especially in chapter 4.

3.2.1. The designation procedure

The sponsors who apply for the orphan medicinal product benefit from a designation procedure free of charge. The scientific examination of the application is conducted by Committee for Orphan Medicinal Products (COMP). The Regulation calls for flexible and rapid designation procedure. A sponsor can apply for designation at any stage of the development, provided that designation criteria are met.\textsuperscript{114} Designation procedure is basically a tool to identify candidate products in a transparent way and to make them eligible for financial benefits. However, obtaining a designation approval does not make a sponsor eligible for marketing of the medicine. A medicine can be only placed on the market after it undertakes all relevant steps and it is granted market authorization.\textsuperscript{115}

3.2.2. Protocol assistance

To demonstrate the quality, safety and efficacy of the product for marketing authorization, the sponsor can request protocol assistance, prior to the submission of an application for marketing authorization.\textsuperscript{116} This is a scientific advice for orphan designated products on the conduct of the various tests and trials necessary to demonstrate the upper three criteria.

The rationale behind this incentive is the fact that the sponsor might have difficulties in finding enough patients willing to participate in trials, therefore EMA here offers assistance.\textsuperscript{117} Also, rigid requirements on

\textsuperscript{112} Pulsinelli (n 18) 312; see also O’Reilly (n 20) 518. The economic incentives available to Congress included tax credits and direct federal grant funds. The additional award of exclusivity of sale 16 was viewed as a small additional benefit since the exclusive rights to something no one wanted were virtually meaningless.

\textsuperscript{113} Pieter Stolk, Marjolein J. C. Willemen, and Hubert G. M. Leufkens, ‘Rare essentials: drugs for rare diseases as essential medicines’ (2006) 84(9) Bull World Health 745, 745-751

\textsuperscript{114} Article 5 of Regulation 141/2000/EC

\textsuperscript{115} Fulfillment of designation criteria are examined again at the time of grant of market authorization. Article 7 and 8 of Regulation 141/2000/EC

\textsuperscript{116} Article 6 of Regulation 141/2000/EC

\textsuperscript{117} Commission Inventory (n 1) 9; Buckley (n 109) 2051
the proof of safety, efficacy and quality of a medicine would prevent many orphan medicines from entering the market. For short survival diseases of relatively common incidence, the classical clinical trial models are sufficient. However, this is not the case with rare diseases with low incidence. For example hyperammonaemia associated with N-acetylglutamate synthase deficiency was in the period between 1980 and 2001 detected only on 42 patients in 28 families.\textsuperscript{118} For such disease the normal clinical trial which would require participation of hundreds of patients is impossible.\textsuperscript{119} This leads to a reasonable outcome that the conduct, analysis and interpretation of studies of rare diseases can be limited based on their prevalence.\textsuperscript{120} The EMA Guidelines require the sponsor of a medicine to establish efficacy and safety of a medicines by evidence that is best assembled in a reasonable time.\textsuperscript{121} This meaning, there is no defined form of clinical trials for the prospect orphan medicine. On contrary the medicine is evaluated on a case-by-case basis.\textsuperscript{122} The proof of efficacy and effectiveness of an orphan medicine is very burdensome, but this is even more so for the evidence on safety of a medicine. Due to the small prevalence of a rare disease, a reliable detection of adverse effects is almost impossible. Therefore the safety of an orphan medicine is adequately determined only after the clinical trials through the instrument of pharmacovigilance.\textsuperscript{123} However in practice the lack of adequate information spreads far into the period after market authorization.\textsuperscript{124}

3.2.3. Access to the centralized procedure

Regulation 726/2004/EC established mandatory centralized marketing authorization procedure. This “fast track” measure solved the problem of “regulator lag” i.e. the considerable time gap between designation and market approval, which was generally criticized before adoption of the latter regulation.\textsuperscript{125} Mandatory

\begin{thebibliography}{99}
\bibitem{119} Buckley (n 109) 2051-2053
\bibitem{120} Buckley (n 109)
\bibitem{122} Buckley (n 109) The EMEA lists a detailed summary of all evidence presented to them to support applications for marketing approval (as European Public Assessment Reports or EPARs) on their website. These reports show that the European regulator has taken an eclectic approach to the levels of acceptable evidence for licensing orphan products (table). They show that studies supporting marketing authorisation for orphan drugs consisted of numbers of treated patients ranging from as few as 12 to several hundred.
\bibitem{123} Buckley (n 109) Clearly, the number of patients included in all studies presented for any given authorised orphan drug is far too small to allow reliable detection of adverse effects that occur with a frequency of less than about 1% (a sample size of 500–1000 would be needed).
\bibitem{124} EURORDIS Position paper (n 42) In their position paper they express a burning need for continuous generation of real-world evidence post-authorization; and, on the other hand, the still very fragmented landscape of requirements set by EU Member States when it comes to such evidence generation (registries, comparators, etc).
\bibitem{125} Ibid at 2
\end{thebibliography}
centralized market authorization procedure in principle shortens the average time-to-market, because the product is authorized for all EU Member States (EEA states) at the same time. Again, the actual access on a given national market is dependent on the placing of the product on that market, which is the prerogative of the market authorization holder.

3.2.4. Market exclusivity

The main incentive for availability of the orphan medicinal products is the 10-year market exclusivity for designated orphan medicinal products.\textsuperscript{126} The market exclusivity prevents the EU or a Member State from subsequently issuing or varying a marketing authorization for a similar product (e.g. the same active substance) within the following 10 years.\textsuperscript{127} This incentive is granted under condition that a medicinal product has been designated as an orphan medicine and that the EU has issued a market authorization.\textsuperscript{128} In this regard, it is important to note, that the designation criteria need to be met also at the time of the market authorization.\textsuperscript{129} The market exclusivity period of 10 years is granted equally to orphan medicinal products designated on the basis of prevalence criterion or insufficient return on investment criterion.\textsuperscript{130}

Since the period of 10 years grants the sponsor a considerable monopoly power, Regulation 141/2000/EC established two additional safeguards in the paragraphs 2 and 3 of Article 8 that allow for withdrawal of exclusive rights.\textsuperscript{131} The market exclusivity does not preclude marketing of another product with the same indication, which would constitute an unjust restriction on therapeutic innovation, on the right of third parties and on patient expectations. However, Paragraph 2 allows for reduction of exclusivity period down to 6 years, if at the end of 5\textsuperscript{th} year the prevalence criterion is not met anymore or if the charged price allows for unreasonable profit.\textsuperscript{132}

Paragraph 3 establishes the requirements that allow grant of a marketing authorization to a similar medical product. The derogation can apply at any time if the authorization holder cannot supply sufficient quantity of the product or/and because another medical product has been recognized as safer, more effective or

\textsuperscript{126} Article 8 of Regulation 141/2000/EC: Commission Inventory (n 1) 5
\textsuperscript{127} Article 8(1) of Regulation 141/2000/EC
\textsuperscript{128} Article 8(1) of Regulation 141/2000/EC
\textsuperscript{129} Case T-140/12, Teva Pharma and Teva Pharmaceuticals Europe v EMA [2015] ECR 41 para. 66.

The designation criteria must continue to be met when the medicinal 210 product designated as an orphan product is granted marketing authorization as an orphan 211 medicinal product since, pursuant to Article 5(12)(b) of the Regulation, a medicinal product which, before marketing authorization is granted, fails to meet the criteria laid down in Article 3(1) of the Regulation, must be removed from the register.

\textsuperscript{130} Article 8(1) of Regulation 141/2000/EC
\textsuperscript{131} Article 8(2)(3) of Regulation 141/2000/EC
\textsuperscript{132} Article 8(2)(b) and (c) of Regulation 141/2000/EC
otherwise clinically superior to the initial product.\textsuperscript{133} However, in this case\textsuperscript{134} it is desirable that the margin between similar products is established easily, especially in the cases of macro-molecules (proteins) which differ only very slightly in their sequence of amino acids.\textsuperscript{135} Additionally, market authorization can be also granted on the basis of consent of the initial sponsor.\textsuperscript{136} The latter provision is important, because it allows competitive companies to manage their business on their own.\textsuperscript{137} On the other hand, as discussed in Chapter 4.1., it can give rise to concerns in regard to competition law and accessibility of medicines.

4. Orphan medicines as “niche-busters”

The most highly debated incentive of market exclusivity period enables sponsors of orphan medicines to reap their profits for whole 10 years. In principle, the length of market exclusivity right should not be contentious, since it was acknowledged that such period is generally required to recoup investments of otherwise unprofitable orphan medicines. However, what seems to be the source of all these debates are certain “exploitive” practices that sponsors undertake to increase the profits. The US sources generally speak about the issue of off-label prescriptions, phenomenon of expanding orphan diseases and so-called disease salami slicing methods. All latter contentious practices are also relevant for Regulation 141/2000/EC. Additionally, the recent ECJ judgement \textit{Teva v. EMA} have brought about a questionable interpretation of Article 8, which could endanger the future of generics market.\textsuperscript{138} The following chapters discuss all the upper described issues. But before digging into the issues themselves, it seems proper to closely examine the purpose and relevance of the highly debated market exclusivity incentive. The former analysis will enshrine a better light on the questionable practices and even more so, on the measures that could be used to eliminate them.

4.1. At least 10 years of monopoly revenues

Normally, the way to protect the market for a product or treatment is by obtaining a patent. However, there is another type of protection available for medicines – market exclusivity.\textsuperscript{139} This form of protection is very effective due to special features of pharmaceutical market. Namely, a medicine cannot be placed on the

\textsuperscript{133} Article 8(3) of Regulation 141/2000/EC
\textsuperscript{134} It is necessary to make a different conclusion in regard to products that are similar and share the same indication (practically generic). In these cases, an easily established similarity is not favorable.
\textsuperscript{135} Commission, ‘Communication from the Commission Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorized orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity’ (2008) C(2008) 4077 final
\textsuperscript{136} Article 8(2)(a) of Regulation 141/2000/EC
\textsuperscript{137} Pusinelli (n 18) 311
\textsuperscript{138} Case C-138/15, ‘Teva Pharma and Teva Pharmaceuticals Europe v EMA [2016] ECR 136
\textsuperscript{139} Pusinelli (n 18) 310
market without the approval of EMA or national medicines agency (marketing authorization). The agencies function as market gatekeepers, whereby Regulation 141/2000/EC prevents them to approve similar medicinal products for the period of 10 years.\footnote{Article 8 Regulation 141/2000/EC}

While market exclusivity is the main instrument for encouragement of research, development and marketing of orphan medicines, it is also subject to extensive criticism. Regulation grants monopoly powers to the sponsor of an orphan medicine and with it in principle eliminates any potential competition for 10 years. Interestingly, at the time of adoption of Orphan Drug Act in US market exclusivity was seen as an additional award, since there was a predominant view that exclusive rights to something no one wanted were virtually meaningless.\footnote{O’Reilly (n 20) 518 Discussing the debate underlying Orphan Drug Act, where tax benefits were seen as the main incentive.} It was only when the Act was implemented that the true potential of the market exclusivity incentive.

4.1.1. IPR and market exclusivity – to which should the success be attributed?

Historically, the rise of the pharmaceutical industry was founded on intellectual property protection (primarily product patents), which enabled competition based on innovation rather than price.\footnote{PATVAL, ‘The Value of European Patents. Evidence from a survey of European Inventors’, (2005) at 18. As demonstrated by the survey on European Inventors, which was conducted in 6 European countries, 20% of all patent are part of pharmaceutical industry. <http://ec.europa.eu/invest-in-research/pdf/download_en/patval_mainreportandannexes.pdf> accessed 10 July 2016} In this regard, the incentives under Regulation 141/2000/EC are supplements to the patent protection, which are granted to both patentable and unpatentable medicines.\footnote{Article 8(1) Regulation 141/2000/EC} In case a medicine or its development process is covered by a patent right, its sponsor is required to obtain a license from the rights holder in afford to successfully benefit from the market exclusivity protection. Although the patent and market exclusivity might share a common basis, they do nonetheless serve a different purpose. Whereas patent right rewards the creation of innovation, the incentives under Regulation 141/2000/EC reward the commercialization of a product.\footnote{This statement should be regarded without prejudice to SPCs}

Patent rights are regarded as the most appropriate measure for spurring innovation and technical progress.\footnote{Patent rights are granted to an invention which has patentable subject matter, is innovative, new and has industrial applicability. Article 52 of Convention on the Grant of European Patents (1973) 13 ILM 268 (European Patent Convention, as amended) (EPC)} The ambit of patentable subject matter has spread in the last decades, making also sensitive issues, such as biotechnological inventions patentable. On the other hand, the chemical process and products were
recognized as a patentable subject matter even before.\textsuperscript{146} Additionally, the EU legislator enacted a special act on supplementary protection certificates for medicines (SPCs).\textsuperscript{147} The latter grants a patent holder a subsequent 5 years period of patent protection. The idea of SPC is to provide for a mechanism that compensates for the lost years of marketing a medicine, because of the time consuming market approval process.\textsuperscript{148} The scope of the legislative acts in the field of pharmaceuticals shows EU’s inclination to create a larger market of pharmaceuticals and eventually catch up or overcome the US one.\textsuperscript{149}

Patent protection, in combination with massive industry growth, is crucial for the research and development of orphan medicines.\textsuperscript{150} On the other side, patent protection does not contribute much to the marketing of an invention. However, only commercialization of an invention ensures satisfaction of unmet patients’ needs. Meaning that patients can only benefit from a medicine, when it is accessible to them – placed on the market. This justifies the existence of market exclusivity, as a market-driven incentive. As Sichelman concludes, the patent system is substantially retarding the commercialization of valuable inventions.\textsuperscript{151} This is upheld by data from EU Survey, which shows that 37\% of the patents were never commercialized.\textsuperscript{152} To ensure commercialization of the orphan medicine states enacted social acts which provided incentives for both patented and unpatentable medicines. Orphan medicine incentives do not only strive to induce discovery of a medicine, but also encourage risky and costly post-invention testing.\textsuperscript{153} In this way Regulation 141/2000 can be seen as \textit{ex post} IP regime that directly incentivizes commercialization of orphan medicines.\textsuperscript{154} Moreover, in words of Sichelman Regulation 141/2000/EC can be seen as a correction of failure of the Kitch’s prospect theory and on it based contemporary patent system.\textsuperscript{155}

\begin{footnotesize}
\begin{enumerate}
\item Ibid 87
\item Ibid 144-148
\item Ibid 145 US was the first to have a SPC type of mechanism called patent term restoration. The mechanism was introduced already in 1984
\item Rogoyski (n 37) 1-22 In his article Rogoyski argues that a recognition of market exclusivity as a key component of encouragement of R&D is a myth. Rather, the attributes go to patent protection. He bases this argument on the fact that the majority of approved orphans have some patent protection. Secondly he argues that if the market exclusivity were the only factor affecting incentives, the number of designations should at least increase steadily as the population size approaches 200,000.
\item Sichelman (n 41) 345
\item Survey of European Inventors (n 142) 41
\item Sichelman (n 41) 387
\item Ibid 388 Yet, from a different angle, one could view the Orphan Drug Act as validating prospect theory. In particular, if an orphan drug is patentable, then the Act allows a patentee that does not gain early market approval for a drug embodying its patent to extend the effective term of the patent.
\end{enumerate}
\end{footnotesize}
Nonetheless it is argued that market exclusivity has only provisional powers and, thus, the main force of R&D of orphan medicines is patent protection. Patents are in certain ways potentially broader that market exclusivity, both substantially and temporary. In particular, market exclusivity is a disorder-specific protection, meaning it is granted for an active substance in combination with an indication. On the other hand patent protection is granted in regard to a product or process in a way this product is produced, and therefore the patent holder can prevent competitors from marketing the product in any way. Finally, patent protection has also a temporal advantage over market exclusivity, since it lasts 20 years with the possibility of 5 years extension. Nonetheless, Rogoyski concludes that a nuanced analysis of the Orphan Drug Act supports a view that although market exclusivity is not the dominant incentive, it remains a substantial factor.

Whether the patent system actually hinders or fosters pharmaceutical development is an ongoing debate. On one hand, the impact of patents in practice is less invasive than it appears. Inventors generally patent their inventions in a very early stage of the development process. From this point on the inventor undertakes a time consuming and costly process of making his invention commercially viable. Since the viability of commercialization of a product, at the time of patent application, is uncertain and associate with many risks, it might not even occur. Additionally, some of patent protection deficiencies are in practice corrected by the so called Bolar provision, also known as the experimental use exemption. The provision grants manufacturers of generics and biosimilars an exemption to patent infringement for pre-marketing testing. This is a boost for generic market, since the companies are in principle free to use patented invention for the development of their product. The Bolar provision, thus, is a safe harbor for generic companies, since

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156 Rogoyski (n 37) 1-22
157 Ibid 7,8 (using the example of Chemical X)
159 Rogovsky (n 37) 21
161 John F. Duffy, ‘Rethinking the Prospect Theory of Patents’, (2004) 71 U. CHI. L. REV. 439, 442 (2004) Duffy argues that the prospect of patents shift patent filling to a very early stage of innovation process and consequently they expire earlier than otherwise; see also Sichelman (n 41) 343; EFPIA, ‘The Pharmaceutical Industry in figures, Key Data’ (2014) 6. Due to extensive time lag between patent application and market approval, patent protection might even expire before the data exclusivity period, in average 12-13 years after market authorization.
162 In order to harmonize the law in this area and to put the European pharmaceutical industry the EU introduced a new exemption in article 10(6) of Directive 2004/27/EC amending Directive 2001/83/EC: “Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.” It should be noted that this provision is not identical to its mother provision, which originates from Canada and is therefore only a “Bolar-type” provision.
163 10(6) of Directive 2004/27/EC
it enables them to place their product on the market soon after the data exclusivity of the originator medicine expires. Moreover, patents by encouraging innovation provide access to medicines. However, access comes with a price, since patent rights allow its sponsor to set high prices and thus make the medicine unaffordable for most of the patients.164

To conclude, the answers to upper issues should be sought through a complex balance test, as described in Chapter 2.3. Whether this issue should be solved by, either **sui generis** patent protection,165 a complete abolishment,166 or retaining **status quo**, is an extensive debate, which is not subject of this thesis. To prevent double protection, it is possible to argue that market exclusivity should be granted only to unpatentable orphan medicines. However, the US experience shows that market exclusivity as a stand-alone incentive for development of orphan medicines does not function effectively. The US Orphan Drug Act initially contained a provision which secured incentives under this act only for the unpatentable orphans. However this provision incurred high administrative costs167 and common situations where patents expired before the market exclusivity period.

There is perhaps but one point of this debate, which is unanimous. Due to the rigorous market authorization procedure, the incentives should not encourage only R&D, but also commercialization of orphan medicines. High costs are, thus, associated with all three stages. Therefore, encouragement of innovation through regulatory incentives is most certainly essential. Unfortunately, this only comes with a price on account of accessibility of safe and efficient medicines.

### 4.1.2. The “All or nothing debate”

As outlined above market exclusivity is to certain extent contradicting the principles of availability, accessibility and affordability of medicines.168 It has been argued by civil society organizations and generic manufactures, that data exclusivity incentives hinder entry of generics to the market, and thus access to

164 Sichelman (n 41) 386, 387
165 Sichelman (n 41) patents in pharmaceuticals would be granted for the commitment to make and sell a substantially novel product; see also Dan L. Burk, ‘Biotechnology and Patent Law: Fitting Innovation to the Procrustean Beed’, (1991) 17 Rutgers Computer & tech. L.J. 1
167 Rogovsky (n 37) Second, while it was easy to determine which drugs were "unpatented," it could be quite difficult to determine whether a drug was "unpatentable," even with the assistance of the Patent and Trademark Office.
168 EURORDIS position paper (n 42) EURORDIS claims that access to orphan medicines is sometimes hindered in certain MS countries, which is profoundly undermining the value of the market exclusivity. Even after authorisation and reimbursement may be granted, about one third of European patients living with a rare disease still have no access whatsoever to the orphan medicinal products they require for their condition. And yet another third may obtain access but only after further substantial delays of several more years (far later than foreseen by the EU Transparency Directive!) as a given product may end up being introduced first in major EU Member States and only later, years after authorization, in other, smaller EU Member States.
medicines. This is even more so with the market exclusivity, which tends to be even more invasive that data exclusivity, since the latter allows, following the expiry of data exclusivity period, the entrance of a generic product, as long as its market authorization is not based on the data of the originator. Nonetheless, formal reliance on originators clinical tests is generally an essential feature of generics business model and therefore the two incentives are de facto the same. However, the notions of access and innovation go hand in hand only if innovation is incentivized. Additionally, due to the negative effect of market exclusivity on the access of medicines, it is of an utmost significance that the market exclusivity is set in a proportional and appropriate manner.

However:

"If drug companies are told there will be no winners, these companies are unlikely to enter a game in which they cannot offset their losses."172

As already noted before the need for incentives for R&D of orphan medicines consists of a trade-off between having expensive medicines or no medicines at all. This statement alone, provides for a big enough justification for market exclusivity. As Pulsinelli concludes: “Thus, large profits for a few drugs might be something to embrace, rather than avoid.”174

Another reason for accepting the profitability is the nature of pharmaceutical research, which is highly unpredictable. In practice, only one to every 10 medicines in development is granted market approval. This means that successful medicines must subsidize the failed ones.176

One of the advantages of market exclusivity is that it is an industry-specific incentive and as such recognizes some important needs of a particular area. The field of healthcare depends heavily on the availability of products. As such it benefits only to a limited extent from creation of invention, but rather entirely depends on marketing of the invention. Since market exclusivity is a market-driven incentive it appropriately suffices this need. This issue is subject to greater examination in Chapter 4.1.1.

One of the upsides of market exclusivity is also that it tends to function in the disease’s prevalence-neutral way. Economically speaking, the market exclusivity should first and foremost incentivize the research,
development and marketing of orphan diseases with the highest prevalence, since they in principle secure higher revenues. However, a study conducted by Rogoyski suggest the contrary, rather than looking at big populations, the companies develop orphans for the scarcest disease.\textsuperscript{177} In fact, by 2014 there were 18.7% orphan designations for ultra-rare diseases.\textsuperscript{178}

Final and most important reason in favor of market exclusivity as a main incentive for R&D of orphan medicine is the tremendous success of the Regulation 141/2000/EC. Until the end of 2015, the number of orphan designations has exceeded 1500 and almost 120 medicines were granted market authorizations. This is substantial in comparison to mere 8 medicines prior to Regulation 141/2000/EC.\textsuperscript{179}

4.2. Some contentious practices

The most significant critique of Regulation 141/2000/EC is existence of enormous revenues of certain sponsors which benefited from the incentives.\textsuperscript{180} These sponsors although fulfilling the statutory requirements, got their R&D investments returned in a first few years after market authorization of the product. Such cases might be seen as an exploitative practices, however it is Regulation 141/2000/EC which grants monopoly power and with it to a large extent eliminates any potential competition for 10 years. Nonetheless, the practice goes against the purpose of the Regulation – to incentivize production of medicines, which otherwise would not be developed and manufactured.\textsuperscript{181}

Experts have pointed out two main situations which lead to over-profitable orphans – “expanding orphan diseases”\textsuperscript{182} and “off-label prescriptions”\textsuperscript{183} The latter is more in detail discussed in the Chapter 4.3. The most common example of the former is treatment of AIDS. While the situation predates the European Regulation, it is none the less relevant, especially in today’s cases such as Zika virus. Many of the initial AIDS treatments were granted protection under the US Orphan Drug Act, due to at that time low prevalence of the disease. Later the disease spread and in 1993 it reached the cap of the 200,000 people criterion.\textsuperscript{184}

\begin{itemize}
\item \textsuperscript{177} Rogoyski (n 37) 11, 12 Of 26 designations, 18 (69\%) were for populations of 50,000 or less. Of the designations in the 0-50,000 category, 14 (54\% of the total) were in the 20,000-50,000 range. However, the study is based on medicines that were designated and it is unknown whether they also obtained market approval.
\item \textsuperscript{178} EMA, ‘Orphan medicines in numbers, The success of ten years of orphan legislation’, (2010) <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/05/WC500090812.pdf> accessed 30 May 2016 By 2010 orphan designation by prevalence conditions was the following: 11.2\% less than 1 in 10,000, 53.2 between 1 and 3 in 10,000 and 35.6\% for more than 3 in 10,000
\item \textsuperscript{179} EURORDIS Position paper (n 42)
\item \textsuperscript{180} See for example Pulsinelli (n 18)
\item \textsuperscript{181} Recital 2 of Regulation 141/2000/EC
\item \textsuperscript{182} Pulsinelli (n 18) 320
\item \textsuperscript{184} Rohde (n 92) 135
\end{itemize}
continuing extension of prevalence brought high profits to the sponsors of the initial medicines. However, to secure the availability of medicines for such diseases, it is nonetheless important that the initial medicines qualify under the orphan medicine designation. This approach was also followed by the Commission which in its Communication clarified that communicable diseases may benefit from orphan designation, if their prevalence in Community is not more than 5 in 10 000.

Finally, in the last two decades pharmaceutical companies show tendencies to concentrate a significant part of their investments towards research and development of orphan medicines. Pharmaceutical companies are shifting their business model from classical essential medicines towards contemporary niche busters – orphan medicines. From the perspective of pharmaceutical companies the incentives for orphan medicines provided by both US and EU ensure more secure and certain investments. Commercial viability of conventional medicines is usually significantly reduced with entrance of generic medicines following the expiry of data exclusivity and patent protection. On the other hand, orphan medicines have longer market exclusivity protection, which comes in hand with several other beneficial measures.

Regulation 141/2000/EC does not govern a subject of additional indications. Thus, this could give rise to yet another contentious practice, where a sponsor would firstly limit his medicine to only one indication and only later on extent the scope of indications to cover a bigger target group of patients. However, EMA seems to be well prepared for these situations. Based on the FAQ published on EMA website a sponsor cannot add a non-orphan indication to the existing one. A new non-orphan indication can only be added if it is subject to a separate market authorization under Directive 2001/83/EC or if the orphan designation is withdrawn.

4.2.1. Answer one, answer them all

The main objective of Regulation 141/2000/EC is to strike a fair balance between the innovation, availability of medicines, and monopoly prices. It is argued by some that this is an “all or nothing” debate,
whereas the main goal is protection of the patients. Most simply, the problem of over-profitable orphans could be solved through reduction of the market exclusivity period, however such solution would neglect medicines that actually depend on the period of 10 years.

One of the possible solutions to achieve this aim would be a cumulative application of the economic criterion, in cases where sponsor applies for designation under the epidemiological criterion. However such solution would pose several difficulties in the examination of the designation application. The objectivity of the economic criterion is rather vague and therefore its examination could lead to a wrong conclusion. A special kind of standardization would be needed and processed normatively. Not to mention that this solution would be very much time consuming. Nonetheless, it could be applied to clear-cut cases, where the large revenues can be clearly foreseen.

Another optional solution would be also amendment of the revocation clause, by shortening the time of the review procedure to 3 years instead of 5 and to conduct it every consequent 3 years. Then the revocation clause would be triggered in the events, which depend upon objective criteria. Firstly, it should be required to examine whether the number of patients have surpassed the margin of 5 per 10,000. The second revocation event would be exceeding the set amount of the revenues, whereas the amount should be set differently for biological and conventional medicines. Since the production costs vary among industries, it might be even a better solution to examine revenues on case-by-case basis. The sponsor would be required to demonstrate his development costs relatively early, e.g. twice, firstly at the application of the designation procedure and secondly at the time of the review procedure when they would be compared with the profits. The reporting and evaluation of the latter present another challenge in itself and therefore the feasibility of this solution is questionable.

Nonetheless, there is a threat that such views neglect a great part of complexity of “all-or-nothing debate”. Whereas the real trade-off underlying the incentives for development of orphan medicines is between having expensive medicines and having no medicines for these diseases. Additionally, one should bear in mind, that enormously profitable orphan medicines are rather an exception than a rule. Therefore perhaps most appropriate solution would not seek to per se eliminate all profitable orphans, since this is not an

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191 Pulsinelli (n 18) 318-319
192 See Chapter 3.1.3.
193 For instance the US in the 1992 amendment of the orphan act proposed a revenue cap of 200,000 million USD
194 Pulsinelli (n 18) 318 As Robert K. Dresing, head of the Cystic Fibrosis Foundation, said, "[P]aying even $300,000 a year for an effective drug against cystic fibrosis would be preferable to having no drug at all!"; Cavalier (n 16) 447, 457 (quoting testimony before the Subcommittee on Antitrust, Monopoly, and Business Rights, quoted in Rex Rhein & Tony Delamothe, Orphan Drugs, (1992) 304 BRIT. MED. J. 465).
ongoing and serious threat. Any such solution would make marketing of orphan medicines more burdensome and consequently unappealing to future producers of orphan medicines. The balance that orphan medicine policy is striving for, could be best achieved by a simple amendment of the existing revocation clause. Under existing provision review procedure can be initiated only by Member states. However, since Member States do not grant market authorizations to orphan medicines, they cannot be expected to possess the relevant information. Consequently the review procedures are in practice very rare. All this could be improved by making review procedure mandatory and, thus, placing the burden of proof to sponsors, who not only possess all the relevant information, but also have an interest for their medicine to retain the orphan status.

In any event, provisions of EU competition law can be applicable to such contentious practices. Namely, pharmaceutical company that undertakes one of the practices, could find itself in a breach of Article 102 of TFEU or adherent national anti-trust legislation. Having a monopoly position on the market, on the account of market exclusivity, the sponsor must refrained from any abusive practices, which fall under the scope of abuse of dominant position. Until now, there is no case law regard to abuse of dominant position of a sponsor of orphan medicine. Nonetheless, it can be claimed that nothing precludes the scrutiny of competition authorities in these cases.

4.2.1.1. Just how effective the existing revocation clause actually is?

Article 8(2) of the Regulation 141/2000/EC provides for a revocation clause from a full 10 years period of a market exclusivity. The market exclusivity period can be reduced to 6 years, if it is shown, at the end of the 5th year, that the medicine no longer meets the designation criteria laid down in Article 3, \textit{inter alia}, where it is shown on the basis of available evidence that the product is sufficiently profitable to remove any justification maintenance of market exclusivity. Once either positive or negative decision is made, the review procedure cannot be initiated again. Consequently, the contested medicine benefits from the whole market exclusivity, without the possibility of reexamination.

The aim of this provision was to withdraw the incentives for medicines that gained unreasonable profits in the first few years of marketing. While the review procedure tends to be solution for the all possible abusive practices of the Regulation 141/2000/EC, it proved to be ineffective in practice. This problem can be attributed to many reasons.

\footnotesize
\begin{itemize}
  \item[196] Article 8(2) of Regulation 141/2000/EC
\end{itemize}
Firstly, the review procedure is not intended to be a systematic conduct. On the contrary it is undertaken only on the initiative of a Member State.\(^{197}\) Once triggered, there is a two-step procedure led by COMP in accordance with Article 5(4) to 5(8) of the Regulation 141/2000/EC. At the end the COMP provides an opinion whether the period should be reduced or maintained.\(^{198}\) Finally, the Commission adopts a decision on the basis of Article 5(8). Where the decision is to reduce the period of market exclusivity, the product concerned will be removed from the Community Register of Orphan Medicinal Products, in accordance with Article 5(12) of Regulation 141/2000/EC.\(^{199}\)

Additionally, the burden of proof lies on the Member States. Based on the Commission Guidelines Member States are required to submit “appropriate evidence”.\(^{200}\) The evidence is required to demonstrate that at least one of the designation criteria is no longer met. However, in practice member states often lack overview and data to justify the application of Article 8(2).\(^{201}\) Additionally, COMP assesses the criteria solely on the basis of evidence provided to it by member state and a sponsor. If the available evidence is insufficient to establish with “reasonable confidence”, there is a presumption in favor of a sponsor. If the fulfillment of the designation criteria is ambiguous, COMP will recommend that the period of market exclusivity is not reduced.\(^{202}\)

The Commission Guidelines provide for some clarity on what is “appropriate evidence”. It is important that the Commission obliged COMP to follow the same standards and calculation methods as were used at the time of designation.\(^{203}\) It is the sponsor, who is required to provide evidence on the alleged change of designation criteria. The set of evidence depends on the initial designation criteria – economic criterion.\(^{204}\)


\(^{198}\) Ibid 5 The review of market exclusivity by COMP will be based, in a first step, on the same set of criteria on which designation was granted according to Article 3 of the same Regulation. The period of market exclusivity will not be reduced to six years, if at the end of the fifth year the original designation criteria are still met. If the original criteria are no longer met, COMP will also review, in a second step of its assessment, the situation of the product concerned as regards the other designation criteria of Article 3(1) of Regulation No (EC) 141/2000.

\(^{199}\) Ibid 5

\(^{200}\) Ibid 6

\(^{201}\) Dutch Government, Position Paper (n 85)

\(^{202}\) Commission, Communication on aspects of the application of Article 8(2) (n 197) 7

\(^{203}\) Ibid 7

\(^{204}\) The corresponding test at the time of the review of market exclusivity would use the same principles. Therefore, the criterion would still be fulfilled if the marketing of the medicinal product in the Community, without the incentive, would not generate sufficient return on investment to balance the risks already taken or still to be taken by the sponsor. If, after subtraction of the financial benefits gained as a result of the incentives under the Regulation, the return on investment is insufficient, market exclusivity will not be reduced.
or prevalence criterion. A for the matter of inexistence of satisfactory method or significant benefit the sponsor is required to provide a critical review of its product, thus they are not required to generate new comparative data.

If the initial designation criteria are no longer met, the sponsor is given the opportunity to demonstrate the applicability of the other designation criteria, either under 3(1)(a) or 3(2)(b). This meaning that if a medicine was designated on the basis of prevalence criterion, the sponsor can still maintain the market exclusivity right, if he shows that economic criterion is met. And the same applies for the interchangeability of the significant benefit and satisfactory method.

The upper brief outline of the procedure and Commission Guidelines raises certain concerns. Firstly, there is a lack of clarity on what “appropriate evidence” actually is. The guidelines only set a frame definition on the evidence. Secondly, it is possible to question the objectivity and accuracy of the evidence presented by sponsors. This is especially problematic in regard to demonstration of the economic criterion. Namely, the companies are in general reluctant to share commercial success of their products. Finally, it is also possible to contest the initiation phase of the review procedure. As already stated Member States lack sufficient information and are therefore not able to justify the fulfillment of designation criteria. In this regard COMP would be in much better place to provide such evidence. Since the Regulation 141/2000/EC provided for unified procedure for designation and market authorization of orphan medicines, the COMP is the only specialized body in this field. It would be therefore easier and more efficient if also COMP would be given the competence to initiate the review procedure.

As discussed throughout the thesis much of the unjustified use of incentives can be addressed and prevented through the review procedure, the Commission should strive to design an easy and effective process. Since it has been already 16 years since the adoption of the Regulation 141/2000/EC the Commission should assess the experience and knowledge gathered to date and enact a more clear Guidelines for the review procedure.

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205 The sponsor will be requested to provide a critical review of possible changes in the estimated prevalence of the condition, including a discussion on the impact of the product on the prevalence in comparison with the natural development of the prevalence of the condition.
206 The critical review will include any available data, for instance:
   - results of any comparative studies performed;
   - a comprehensive and balanced bibliographic review;
   - marketing studies; or
   - patients’ surveys.
207 Ibid 8
208 Ibid 8,9
209 Pulsinelli (n 18) 307
In US there were several debates about the introduction of revocation clause. Many of them proposed that the revocation clause would be based on a sales cap.\textsuperscript{210} Such a solution would depend on introduction of company’s obligation to release development costs. However the demonstration of costs and profits is very difficult to compute. This is even more so when a medicine has market authorization for more than one indication and it is being sold in more than one country.\textsuperscript{211} Additionally pharmaceutical companies prefer to keep information on sales and profits secret.\textsuperscript{212} If revocation clause would be set with regard to a sales cap, it should be based rather on sales than on profits. The former are much easier to track and companies are less reluctant to provide information.\textsuperscript{213} Nonetheless such provision should take into account the differences between different medicines, such as biological medicine, the development of which is often significantly more expensive than production of conventional medicine (ie. chemical).\textsuperscript{214}

Another solution, perhaps the most appropriate one, would be done through modification of market exclusivity form. The period of market exclusivity should be set to a time frame which is generally required for the recoup of investments, e.g. 5 years.\textsuperscript{215} After this period the sponsor would have a chance to extend the market exclusivity for a subsequent 5 years period. The extension would depend on sponsor’s ability to demonstrate “limited commercial potential” or “low prevalence” of his medicine. Such provision would solve many of the current issues of the review procedure. Most importantly it would place the burden of proof to companies, who are in possession of all adequate information. Also the companies would be encouraged to provide such information, since they would benefit for another 5 years of monopoly.\textsuperscript{216}

\textsuperscript{210} Pulsinelli (n 18) 332 An approved orphan drug was guaranteed exclusivity for a period of two years. After two years, if at any time during the next seven years, the total revenue from the orphan drug exceeded $200 million, the exclusivity term would be revoked.

\textsuperscript{211} Pulsinelli (n 18) 333

\textsuperscript{212} Pulsinelli (n 18) 334

\textsuperscript{213} Pulsinelli (n 18) 334

\textsuperscript{214} In principle, the biological medicines are more complex in structure then the conventional medicines. The latter consist of pure chemical substances and their structures can be identified. On contrary, the biological medicines are made of mixtures of molecules or the molecules have a complex macromolecular stricture and are as such more difficult to identify or characterize. This specific structure led to many regulatory problems; Arezzo, E. Ghidini, G.,Gustavo Ghidini (ed.), Biotechnology and Software Patent Law: A Comparative Review of New Developments, (Edward Elgar Publishing, 2011) 31; EFPIA, The Pharmaceutical Industry in figures, (n 161) 6. Due to the specific structure of biological medicines, the research and development of biologics is not only significantly longer and more complex than production of conventional medicines, but also far more expensive. In this regard the highest percentage of the R&D investments goes to the costs of clinical trials; Pharmaceutical Research and Manufacturers of America, ‘2015 biopharmaceutical research industry profile’ (2015) <http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf> accessed 12 July 2016 The estimated average costs of developing a biological medicine is 2,6 billion US dollars (the amount also includes the costs of the failed medicines.)

\textsuperscript{215} Pulsinelli (n 18) 333, (discussing Biotechnology Industry Organization proposal)

\textsuperscript{216} Council Regulation 1768/92/EEC
Moreover, such revocation clause would in general address the over-profitable orphans, irrelevant if they are a product of so-called disease salami slicing method, an expanding orphan disease or other practice.

4.3. “First come-first served”

The exclusive rights are granted to the sponsor who first obtains the market authorization. This means that a sponsor who is second to submit an application is automatically shut off for the period of 10 years. In practice the pharmaceutical companies are racing each other for the orphan market authorization. However this situation is argued on two different bases.

Firstly, it questions the orphan status of such medicines, since true orphan should lack prospective companies fighting for them. The fighting indicates profitability of such medicines and therefore incentives are unnecessary, hence, abused. However Pulsinelli discards this argument on the ground that this is actually a race for incentives, rather than a race for a medicine. This meaning, that finally the legislations are serving their purpose. Secondly, the issue with the “racing” is claimed to the waste of resources and its consequent negative effect on the loser.

Surely, the principle of first-come-first-served leads to increased competition in the development stage, since it allows the winner to rip monopoly revenues for 10 years. It can be argued that a promise of monopoly and consequent competition in the pre-marketing stage better encourages availability of a medicine than a promise of duopoly. However after the medicine is on the market, the patient’s benefits are significantly decreased.

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217 Pulsinelli (n 18) 320
218 Pulsinelli (n 18) 320
219 O’Reilly (n 20) 516 Analogizing these popular orphan drugs to Baby M, whose biological parents and adoptive parents fought over her custody).
220 Pulsinelli (n 18) (quoting Abbey S. Meyers, ‘The Impact of Orphan Drug Regulation on Patients and Availability’ (1992) 47 FOOD DRUG & COSMETIC L.J. 9, 9) A drug should not be designated as an orphan unless the incentives of the Act are "absolutely essential to ensure its development," and indicating that multiple companies were unlikely to be interested in a drug that was truly of "limited" commercial value).
221 Pulsinelli (n 18) 320, 321 The market exclusivity makes the market potentially profitable, and thus makes the drug worth racing for. Races for approval may thus be interpreted as a sign that the Act is serving its purpose by giving drug companies incentives to develop otherwise unprofitable drugs. In most cases, distinguishing a race for orphan drug incentives from a race for a drug that would have been developed anyway is almost impossible, again pointing out the dangers of changing the Act. The effects on the races of any changes to the Act cannot be foreseen in advance. An amendment that changes the incentives could have adverse consequences for a highly successful piece of legislation.
222 Pulsinelli (n 18) 321
Possible solution to prevent abuses deriving from upper described “races”, is “shared exclusivity”, which was subject of many unsuccessful amendments in the US. Additionally, shared exclusivity might also prove to be an effective measure to address high profits, since it encourages competition. Under this concept, two sponsors which develop a medicine “simultaneously” are granted an authorization to share the market exclusivity. While in the US this was considered the most popular solution, it was highly opposed by the industry, since it provided for the division of benefits.

The EU legislator did not decide for such solution. Also, the effectiveness of this solution is limited to certain cases only. Namely, such provision would affect any sponsor, regardless the prospect profitability of the orphan medicine. The fact that there is a scarce spread of the over-profitable orphans, makes this provision seem disproportionate. Finally it would disincentive the development of majority of still needed new orphan medicines. Moreover, the shared exclusivity is entirely dependable on the possible existence of patent rights. This meaning, that a patent right can preclude application of shared exclusivity, regardless the fact its requirements are fulfilled. In this way the effectiveness of this measure is entirely diminished.

Further on, there is an issue of the effects of cooperation. It is questionable whether the companies would still perceive development of orphan medicines as profitable, in situations where the profits might end up being shared. This decreased foreseeability and uncertainty of profits would pose a risk to innovations. On the other hand, in practice, joint ventures, licensing-out and -in and other types of corporate collaboration have been commonly used between companies to reduce the risk of investment. Additionally, the collaboration would help solve certain structural differences of orphan medicines and so increase innovation and efficiency. Moreover, the cooperation might fall under preview of competition law and might be proclaimed as incompatible. All this uncertainty could influence company’s decisions, whereas development of orphan medicines would be perceived as risk.

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223 Ibid 321 This proposal was underlying the reform initiatives of the Orphan Drug Act presented in 1986, 1987 and 1990, however the measure was never enacted.
224 Pulsinelli (n 18) 324
225 Ibid 326
226 Ibid 329 Since successful companies would be forced to divide up the benefits reaped once the products are on the market, and that allegedly would disturb the initial financial risk assessment that producers make when deciding whether to begin to develop a drug or not; Ibid 331 Pulsinelli generally aligns with the industry positions and rejects the introduction of shared exclusivity concluding that “[...] while a change in the Orphan Drug Act to allow shared exclusivity might enhance cooperation and seem more ‘fair’ to losers, the severe damage to the Act’s incentives and the enormously increased administration costs weigh against enacting such change”.
227 Clissold (n 183) 145
228 Pulsinelli (n 18) 328
Finally, there is a risk that shared exclusivity would encourage companies to undertake abusive practices in the phase of designation. In effort to secure their position the companies would file designation applications, without an actual aim to further pursue for market authorization. This manipulations would result in increased administration costs and would be hard to detect.\textsuperscript{229}

On the other hand, the EU legislator should re-examine this measure at the time of next reform. The reach of shared exclusivity has many advantages that result in increased patients’ benefits. It encourages competition and therefore leads to reduced prices. Secondly it prevents the waste of resources that occur when only one company is a winner. And finally, it secures the reward for both companies and thus prevents the possible bankrupt of a company.\textsuperscript{230}

The legislator should undertake a balancing test and find a solution appropriate for the European market. If decision is made in favor of shared exclusivity, the legislator should take into account the experience learned by the US.\textsuperscript{231} Namely, it is of utmost importance to decide on the adequate time frame in which two competing companies are considered for the application of shared exclusivity. The narrow interpretation of “simultaneous development” would render feasibility of the use of shared exclusivity in practice. An eventually too extensive time frame of the notion “simultaneous development” would allow grant of the reward to copycats. For achieving the desired effect, the legislator could also consider lengthening the exclusivity period.\textsuperscript{232}

\textsuperscript{229} Ibid 329 Under the proposed shared-exclusivity regime, designation assumes an entirely new importance. The mere grant of designation starts a six-month clock running for all other potential designees. If a company does not file within this time, it is essentially barred from pursuing the designated drug for that indication. Once the six-month window is closed, any later company faces a losing position: if it loses the race to develop the drug, it will be excluded from the market; if it wins the race, the original designee still has a year to catch up and share the exclusive market. The original designee is thus under very little pressure to proceed quickly, since it knows that another company is unlikely to start a development program under these conditions.

\textsuperscript{230} Pulsinelli (n 18) 326 Pulsinelli questions the actual effect of shared exclusivity on the prices, pointing out the example of hGH. The hHG is subject to shared exclusivity between Genetech and Eli Lily but it is nonetheless one of the highest priced medicines in US.

\textsuperscript{231} Ibid 325 As early as 1986, Congress proposed to change the Act so that it would allow sharing of exclusivity when two drugs were developed "simultaneously." “Simultaneously” was defined as the later company submitting its application for approval before the earlier company’s application was approved. This bill failed to pass. The next attempt to provide for shared exclusivity occurred in 1990.154 The Orphan Drug Amendments of 1990 proposed a more rigorous standard for simultaneous development. The later companies had to: (1) file the requests for designation within six months of the publication of the leader's designation; (2) start their clinical trials within twelve months of the leader; and (3) file for approval and request exclusivity within twelve months of the leader's filing for approval. 155 These strict requirements were intended to prevent copycat generic companies from appropriating the work of the leaders and then forcing the leaders to share their exclusivity. The requirements could help guarantee that the two companies were in fact simultaneously developing the orphan drug.

\textsuperscript{232} Ibid 328
4.4. *Teva Pharmaceuticals* v *EMA* ECJ Case – is future of orphan generic market endangered?

The recent *Teva Pharma and Teva Pharmaceuticals Europe v EMA* (*Teva v EMA*) case heard before the General Court and ECJ raised quite some concerns about similar orphan medicines, which are granted market authorization on the basis of sponsor’s consent. The issue being situations when the sponsor of the original orphan medicine and similar orphan medicine is the same pharmaceutical company. Regulation 141/2000/EC has an aim to incentivize research, development and marketing of new orphan medicines. Hence, the incentives are not granted to similar products, unless one of the three derogations of Article 8(3) apply. Based on the judgement, Article 8(3)(1) of Regulation 141/2000/EC is interpreted in a way that regardless of the similarity of the second product, the latter benefits from a separate market exclusivity incentive (provided it fulfills the criterion of “significant benefit”). Such interpretation, (unintentionally), encourages sponsors of brand named orphan medicines to produce and market a second, similar product. This is an appealing practice, since it allows sponsor to close the doors for competitors for yet another 10 years. Since such practices will significantly hinder the availability and especially affordability of orphan medicines, one can argue that this is hardly something that Regulation 141/2000/EC was intended to encourage.

As for the matter of the background of the case, in 2001 Novartis was granted a market authorization for Glivec, a cancer treatment. Later in 2007 Novartis obtained market authorization for Tasigna, a medicine with the same indication as Glivec. Tasigna being a similar medical product, it was able to obtain a marketing authorization on the basis of consent of the Novartis, without being “clinically superior” to the initial medicine. In 2012 Teva applied for a market authorization for its generic version of Glivec, whose

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233 C-138/15, *Teva Pharma and Teva Pharmaceuticals Europe v EMA* [2016] ECR 234 Article 8(1) and Article 8(3) of the Regulation 141/2000/EC; As described above, according to the Article 8(3) contains three types of derogations from the market exclusivity provided under Article 8(1) of that Regulation: (a) consent of the original marketing authorization holder; (b) inability of the original marketing authorization holder to supply sufficient quantities; (c) the second medicinal product is safer, more effective or otherwise clinically superior.

235 Case T-140/12, *Teva Pharma and Teva Pharmaceuticals Europe v EMA* [2015] ECR 41; see also corresponding appeal C-138/15, *Teva Pharma and Teva Pharmaceuticals Europe v EMA* [2016] ECR 136

236 Several legal professionals commented on the topic e.g. Maynak Dixit, blog. Dixit calls the judgement bizarre and it denotes that it goes against the purpose of the Regulation 141/2000. However Dixit ignores the designation criteria from Article 3 and therefore wrongly presupposes the disastrous misfortune for the generics. The new brand name medicine needs to demonstrate significant benefit over the initial one and thus is not equivalent to the generic medicine, which is generally an exact copy of original. Also for this reason Teva did not apply for an orphan marketing approval, but rather generic market approval. This does nonetheless question whether the criterion of the significant benefit is sufficient enough to provide an appropriate boundary between a generic and similar medicine with a significant benefit in its right purpose.

237 Para. 10 of Case T-140/12

238 Para. 13-17 of Case T-140/12
market exclusivity period expired in 2011. EMA refused the application on the basis that it covered the same therapeutically indication as Tasigna and its market exclusivity precludes application approval.\textsuperscript{239}

Teva contested EMA’s decision at the General Court of EU in March 2012. Main defense of the Teva laid in argument that the interpretation of Article 8 as advocated by EMA would have perverse effects, by encouraging the initial sponsors to develop similar medicinal products in order to evergreen on the market exclusivity period of the first orphan medicine.\textsuperscript{240} The General Court firstly referred to the designation criteria from Article 3 and concluded that an existing treatment can be designated as orphan medicine, if it presents “significant benefit” to those affected by the disease.\textsuperscript{241} More importantly, the General Court outlined that the criterion of “significant benefit” is interpreted strictly and as such precludes a designation of a merely similar product.\textsuperscript{242} The General Court concluded the judgment by upholding the decision and the interpretation of Article 8 as proposed by EMA, which in the General Court’s view attains the purpose of the regulation.\textsuperscript{243} The outcome of the judgement was also upheld by the ECJ.\textsuperscript{244}

In Paragraph 28 of the Teva v EMA judgement ECJ stated that the criteria of “significant benefit” is such precludes designation of a merely similar product. ECJ based its reasoning on Recital 8 of Regulation 141/2000, which states that Regulation 141/2000/EC does no prevent the marketing of a medicinal product similar to the orphan product which could be of “significant benefit” to those affected by the condition in question. Whereas ECJ’s reasoning would be proper if the legislator’s aim was to eliminate similar product with solely one step (such interpretation, however, goes in hand with the Recital 8). Nonetheless, the legislator introduced a second tool – “clinical superiority” – with even higher threshold. Thus, it rather seems unjust that a second medicine which would benefit from sponsor consent could skip scrutiny of otherwise stricter “clinical superiority”, while other similar medicine should be bound by its requirements.

On the basis of the judgement, the measure that hinders the grant of market authorization, on the ground of the derogation of consent, to an orphan generic or biosimilar is the designation criterion “significant benefit”.\textsuperscript{245} In other words the sponsor does not need to demonstrate “clinical superiority” of the second

\textsuperscript{239} Para. 19.20 of Case T-140/12
\textsuperscript{240} Para 60 of Case T-140/12
\textsuperscript{241} Para. 64 of Case T-140/12; the same in para. 28 of Case C-138/15

“As is apparent from recital 8 of Regulation No 141/2000, that regulation nevertheless seeks to circumscribe that period of exclusivity in order not to prejudice existing intellectual property rights and, in the interests of patients, not to prevent the marketing of a medicinal product similar to the orphan product which could be of significant benefit to those affected by the condition in question.”

\textsuperscript{242} Para 65 of Case T-140/12
\textsuperscript{243} Para 80 of Case T-140/12
\textsuperscript{244} See Case T-140/12
\textsuperscript{245} Article 3 of Regulation 141/2000/EC; If a similar medicinal product does not pass the significant benefit test, then it cannot benefit from orphan designation and can be granted market authorization only on the basis of the
medicine, since derogations under Article 8(3)(a) are alternative. Whereas, a sponsor that would be pursuing a market authorization without consent of the first sponsor, would need to demonstrate, both, that his product provides a “significant benefit” and is “clinically superior” in relation to the first. Moreover, it can be argued that the first sponsor is in better position to suffice criterion of “significant benefit”, since he holds all relevant data on the first product. In particular, data on research and development and its use in practice. This information advantage makes market approval process less rigorous and thus questions the justification of the grant of orphan incentives.

However, “significant benefit” and “clinical superiority” are entirely different notions. The former can be, in principle, fulfilled on a rather technical basis, e.g. an ease of self-administration may be considered a benefit. On the other hand, the latter is examined exclusively from a scientific point of view, since “clinical superiority” requires an advantage of quality, safety or efficacy for the initial medicine. Therefore, thresholds of the two notions are distinct.

The Recital 8 of Regulation 141/2000/EC lacks a notion of “clinical superiority”, but this is not a good enough reason to ignore it in the reasoning. In this regard, ECJ’s reasoning is in line with the text of Regulation 141/2000/EC, however it can still be regarded as misconception of its the aim, which is to reward novel products. Although the ECJ made a reference to Recital 8 with a purpose to outline the aim of elimination of similar products, it neglected the purpose of Article 8(3)(1). The purpose of the sponsor’s consent derogation, was probably in the encouragement of collaborations among competitors and not to serve to a first sponsor to evergreen on his first invention.

The negative outcome created by the judgment can only be restored through the mechanism of review procedure. However, as described above, this is not something one cannot count on. Regardless this, one can rely on the preview of competition law, more precisely on Article 102 of TFEU. While ruling in favor of Teva would perhaps be a step to far, the ECJ could, nonetheless, condemn such practices and warn the legislator about this failure. To conclude, the outcome of the Teva v EMA judgment is a cry to the EU legislator to amend the provision and prevent further exploitations. Due to the possibility of a long-lasting monopoly position, it is possible to predict that this will be a practice undertaken by many

Directive 2001/83/EEC. For this reason Teva did not apply for an orphan marketing approval, but rather generic market approval.

Communication to Commission Regulation A.4

“Clinical superiority” means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorized orphan medicinal product Article 3(3)(d) of the Commission Regulation 847/2000

Article 102 of TFEU Until now, there is no relevant case law, however, it can be argued that such practices could fulfill all the requirements of Article 102 and, thus, qualify as abuse of dominant position.
brand name companies. Now, there are two elimination measures of similar medicines, which application unequally differs. One of the possible solutions would be making the “clinically superior” and consent derogation provisions cumulatively applicable. Although this would probably discourage companies to collaborate, it would also prevent free riding of sponsors on their own already existing orphan medicines. Second solution would be in removal of both consent and “clinical superiority” derogations and leave out the elimination of similar orphan medicines solely to designation criterion of “significant benefit”. Such solution would be following the text of Recital 8, however is it not necessarily better, since the scope of similarity would be much narrower. Meaning, a product that would ease administration would be granted market authorization, without necessarily being scientifically improved from the first one. On the other hand, the latter solution would increase the amount of orphan medicines in the Union.

4.5. Disease “salami slicing”

“Salami slicing” is the peer-community denomination of a method used for describing situations when a pharmaceutical firm subdivides a disease indication relative to target patient population into smaller subgroups, finally making it fit into category of rare diseases. If a sponsor is successful in pursuit of this approach, he may acquire market exclusivity for multiple approvals for the same medicine for treating what are essentially facets of the same disease.\(^\text{249}\)

In practice this phenomenon is best described with the example of Amgen’s Epogen medicine in the US. Amgen was a small biotechnological company in California. In 1886 they applied for designation of a promising new medicine, epoetin alpha. In the application the medicine’s indication was treatment of anemia associated with end-stage renal disease. Amgen later obtained a market authorization for an Epogen orphan medicine. However, soon after the medicine proved to have a tremendous potential for treatment of anemia, not only the one caused by end-stage renal failure. Epogen consequently became a blockbuster medicine, bring its sponsor over billion dollars of annual revenue. Moreover, it was claimed by many, that Amgen intentionally subdivided the disease in afford to avoid normal investments.\(^\text{250}\)

The practices such as the one of Amgen highly depend on off-label prescriptions.\(^\text{251}\) The medicines are in principle used for particular conditions – indications which are stated on the medicines’ label. The medical community generally recognizes doctor’s discretion to prescribe medicine for off-label use. However, in

\(^{249}\) Pulsinelli (n 18) 321-22.
\(^{250}\) Ibid 321.
EU doctors are not heavily inclined to prescribe a medicine outside its approved indications, since this act transfers the burden of liability on them.

However, there are several considerations in regard to regulatory solution of this problem. In some cases dividing the disease and thus market makes sense. For example, a medicine might have severe side effects, which would show only in some parts of population. Therefore, as Pulsinelli argues, devising a regulatory measure that would prevent “salami slicing” and not discourage appropriate submarketing would be almost impossible, since the two situations are hard to distinguish even with a detailed analysis\textsuperscript{252}

EMA attempts to prevent this issue are conducted on a case-by-case basis. The Commission Communication outlines the solution in assessment based on the term of “Medically plausible”.

4.5.1. High-tech “salami slicing” – a threat of a flood of orphan medicines

Although the epidemiological criterion for designation of orphan medicines is generally regarded as objective and unproblematic, it is ill-prepared for the newly emerged field of pharmacogenomics.\textsuperscript{253} Pharmacogenomics presents an interaction between pharmacology and individual’s specific genetic structure. Whereas patient’s genes dictate his inclination towards a medicine, therefore patients are put into different genetic classes, which provide for different ways in which medicines are delivered.\textsuperscript{254} The pharmacogenomics science is a solution to currently very problematic issue of adverse side effects, which generally result from patient’s genetic predispositions.\textsuperscript{255} Nowadays the sciences and technologies are moving towards development of more effective, tailor-made individual treatments. Such treatments will almost eliminate the occurrence for adverse medicine reactions. Therefore it is reasonable to expect that pharmacogenomics will in the following years provide for customized medicines on an individual level. Thus, a doctor will be able to administer an adequate quantity of a medicine based on the genetic screen of a patient.\textsuperscript{256}

\textsuperscript{252} Pulsinelli (n 18) 322 (discussing the effectiveness of US solution in regard to EPO example) The FDA has attempted to resolve this problem in the Regulations by stating that disease subsets must be “medically plausible.” The effect of this rule on the EPO designation is not clear. The end-stage renal disease patients may be a medically plausible subset, or they may instead be the result of salami slicing. The same holds true for the other forms of anemia. To a large degree, this is a medical decision, with a dollop of policy thrown in. In the case of EPO, the obvious profitability of the drug should probably have been weighed against the grant of designation.

\textsuperscript{253} Loughnot (n 251) 371

\textsuperscript{254} William E. Evans, Mary V. Relling, ‘Moving Towards Individualized Medicine with Pharmacogenomics’(2004) 429 NATURE 464, 466 (Discussing genetic screen employed to identify patients with a high risk of abacivir hypersensitivity).

\textsuperscript{255} Loughnot (n 251) 372

\textsuperscript{256} Ibid 372
Notwithstanding the fact this will secure more effective treatments, it will also pose a great threat to current Orphan Regulation.\textsuperscript{257} Pharmacogenomics allow for high-tech “salami slicing”, with a difference that slicing is move from the area of medical judgment to area of a scientific fact.\textsuperscript{258} Such customize treatments would allow pharmaceutical companies to subdivide otherwise widely spread diseases to small groups that fit in the definition of a rare disease. For instance for some conditions affect millions of European citizens, it would be possible to divide them based on the genetic make-up of specific group and in this way reach the designation criteria for orphan medicine. Additionally, each genetic variation could be regarded a separate disease and therefore be awarded an individual orphan medicine designation.\textsuperscript{259} Later the pharmaceutical firm could promote it as a cure for entire population and benefit from exclusive rights and consequently enormous profit for 6 years.\textsuperscript{260} While this clearly goes against the aim of the Orphan Regulation, its provisions on the designation criteria and market authorization are ill-prepared for this issue.\textsuperscript{261}

Pharmacogenomics give room for additional exploitation in regard to similarity of products. A similar product could apply for designation and manipulated the clinical trials by selecting patients based on their genetic structure. The patients would show adverse inclinations towards the initial medicine, while favorable reactions to his medicine. In this way the new medicine would, wrongly, be regarded as more effective and clinically superior and benefit from orphan medicine protection. While the new medicine is actually similar to the old medicine and therefore its designation should be denied. The upper issue would lead to a failure of the “more safe, efficient and clinically superior” exception.\textsuperscript{262}

Pharmacogenomics is only one of the numerous contemporary technological developments that pose problems to legislators. Here it is the role of the legislator to make sure the regulation does not become obsolete and does not provide room for abuses. The Current Regulation lacks sufficient measures that would provide protection against abuses on the basis of pharmacogenomics. However, we are still far from the full application of pharmacogenomics, it is of utmost importance that the Orphan Regulation does not continue to neglect the effect of pharmacogenomics. Namely once this science reaches its potential, it will trigger an avalanche of orphan medicine designation applications, the refusal of which although fair would be unlawful. Namely, the medicinal product fulfills the conditions set by the regulation, but actually the

\textsuperscript{257} Ibid 366
\textsuperscript{258} Ibid 374
\textsuperscript{259} Ibid 374
\textsuperscript{260} Ibid 366
\textsuperscript{262} Loughnot (n 251) 366
Therefore it is essential that European legislator takes a preventive step and alters the definition of a rare disease, by making it immune to impact of pharmacogenomics.

Article 3(1)(b) of Regulation 141/2000/EC prevents designation of methods that have already been authorized in the Community. In relation to pharmacogenomics this provision is effective only in situations where subdivision of treatment is made after the initial authorization. On contrary, the article is open for abuses, when division of a cure based on genetic structure of individuals is made prior to indication that treatment is good for entire population. The amendment could be done by changing the definition of the “similar medicine” in Article 8(3)(c), making it apply only to certain types of medicines. Namely, with the emergence of biotechnology the distinction between similar and different became more blurry. One of the solutions would be also decreased period of market exclusivity or diminished other incentives, especially financial. The latter approaches would not directly prevent exploitation, however they would disincentive sponsor to apply for designations. Additionally the regulation should also oblige medicine developers to submit reports on the pharmacogenomics researches. Finally, such abuses could also be prevented by close examination of pharmacovigilance reports, which could detect what adverse reactions are results of specific genetic structure.

Further on, Regulation 141/2000/EC needs to solve a problem what happens if a new medicine that treats population, which was not able to be treated with the initial medicine based on their genetic predispositions. For example, SmithKline Beecham marketed a vaccine for preventing Lyme disease called LYMErix. However 30% of the vaccinated patients were predisposed to develop an incurable autoimmune disorder called treatment resistant Lyme arthritis. Pharmacogenomics in such situation would both help prevent these outcomes as well as help with development of an appropriate vaccine for the remaining 30% of the patients. In latter case the new vaccine might fulfill the designation criteria of the orphan medicine. The EU legislator therefore needs to decide whether a sponsor of such medicine should benefit from the orphan medicine designation.

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263 Pulsinelli (n 18) 332-36; Loughnot (n 251) 367
265 Loughnot (n 251) 367
266 Ibid 367
267 Loughnot (n 251) 375 (citing Marc Wortman, ‘Medicine Gets Personal’ (2001) 104 TECHNOLOGY REVIEW 71, 72)
268 Loughnot (n 251) 375
The Commission recognized the potential of the emerging field of personalized medicine in the Commission Consultation Document. Similarly to US it decided to solve the issue of pharmacogenomics with interpretation of the term “medical plausibility.” It concluded that patients in the subset should present a distinct and unique evaluable characteristics with plausible link to the condition and that such characteristics would have to be essential for the medical product to carry out its action. Further they specifically pointed out that genetic profile should be closely linked to the treatment in a way that absence of these genetic characteristics would render the medicinal product ineffective. Additionally, the Commission condemned sub-setting a condition with the use of biomarkers, with a derogation in situations where a sponsor can sufficiently establish that the activity of the product should not be shown on a larger population. However, the aforementioned derogation could be significantly endangered and as such should not hinder the unwanted artificial disease sub-division, because of the otherwise common information asymmetry between sponsors and the EMA. The proposed Commission approach seems to sufficiently limit the adverse effects of pharmacogenomics. This is additionally safeguarded with the burden of proof placed on the sponsor. However there is still room for manipulation of the clinical trials.

269 Commission Consultation Document (n 80) 6-7
270 Ibid 7
271 Ibid 7
272 Gibson, Tigerstrom (n 260) 8
5. Conclusion

It is unanimous that Regulation 141/2000/EC can be attributed tremendous success. Since its application, patients suffering from rare diseases benefited from a considerable number of orphan medicines. In this regard, Regulation 141/2000/EC is diligently following its aim of ensuring equality of treatment to people suffering from rare conditions. However, the 15 years of application of Regulation 141/2000/EC uncovered quite some of its pitfalls. These contentious aspects show that Regulation 141/2000/EC is falling behind with securing the second aim – encouraging research, development and marketing of otherwise unprofitable orphan medicines.

In regard to Article 3 of the Regulation 141/2000/EC the biggest issue seems to be insufficient clarity of certain terms. Consideration should especially be given to the term of “significant benefit”, which has a vital role in the assignation of orphan status to a medicine.

Given the fact that market exclusivity incentive is subject to the greatest criticism the EU legislator should examined it from a close perspective. However, in the latter examination the legislator should perhaps bear in mind that research, development and marketing of orphan medicines is highly dependable on provided incentives, in particular the incentive of market exclusivity. Should this be an “all or nothing” debate, the legislator should leave the period of market exclusivity intact and tackle with the issue of over-profitable orphan medicines through other instruments under Regulation 141/2000/EC.

Certain phenomes (e.g. expanding orphan diseases) or contentious practices (e.g. disease salami slicing) tend to lead to over-profitable orphan medicines. To attain the purpose of Regulation 141/2000/EC to provide incentives to otherwise unprofitable medicines, such practices should be prevented by implementation of certain legislative instruments. Perhaps the best solution lies in the amendment of revocation clause in Article 8(2). Hence, most of the issues could be addressed in the review procedure. However, the existing review procedure proved to be ineffective in practice. This is, especially, because revocation clause can only be triggered by Member States, which, in general, lack adequate EU-level information for a positive decision of the Commission. For these reasons, it seems appropriate to transfer the burden of proof to the sponsor, by modification of the market exclusivity period. The period should be set to 10 years, provided that at the end of the fifth year the sponsor demonstrates applicability of designation criteria. As for the matter of the thread of newly emerged field of pharmacogenomics, it is debatable whether the issue is adequately addressed with the text of the draft of Commission Consultation Document.
Further, the *Teva v EMA* judgment outlined a vital need for modification of Article 8(3). The decision practically encouraged sponsors of orphan medicines to develop a second similar orphan medicine. This is due to the substance of applicable provision, which allows the sponsor to free-ride on its own orphan medicine, provided that the second medicine meets the requirement of “significant benefit”. This has adverse effects on generics market and consequently on patients’ benefits. To prevent the ever-greening on initial invention the legislator should consider a cumulative applicability of the “clinically superior requirement”, when granting a second orphan market authorization on the basis of consent.

Another question is the role of patent protection and the questionability of necessity of its existence. Regulation 141/2000 aims to provide access to orphan medicines, whereas the access is ensured only through marketing of a medicine. On the other hand, patent protection as an invention-driven incentive does not directly spur commercialization of an orphan medicines. On contrary, some argue that the patents actually hinder marketing of a product. This deficiency is corrected by market exclusivity incentive, which, in principle, functions as a reward for undertaking a rigorous marketing procedure. In this regard, the joint existence of both protections is questionable. Nonetheless, patent protection can be attributed a considerable role in development of orphan medicines, one even greater than market exclusivity right. However, this still does not silent the idea of a *sui generis* patent protection in the field of orphan pharmaceuticals. A protection that would encourage equally research, development and marketing of orphan medicines.

Finally, in case of any amendment or implementation of any new legislative instrument, the legislator should respect the objectives of pharmaceutical policy-making. Unfortunately, the objectives go hand in hand only to a limited extent. Therefore, the legislator is required to conduct a complex balancing test. In this regard, the legislator strives to provide equality of treatment by ensuring access to safe and efficient orphan medicines. At the same time the legislator’s role is to encourage pharmaceutical innovation and competitiveness in pharmaceutical industry. However, achieving one objective is only possible on the account of another one. Whereas, innovation ensures access to orphan medicines and the former is only possible through incentives on the account of extensive interference with competitiveness. And, yet again, the legislator should answer the question whether this balancing process is truly an “all or nothing” debate.
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