# Care for Rare Diseases & Orphan Drug Provision

## An economic analysis of current incentives in orphan drug development in the U.S. and the EU

Seminar paper of the "Advanced Seminar Economics, Policy & Econometrics: Health Economics" Module


**Supervised by:** Dr. Christian Feilcke

Department of Economics

**Submitted by:** Jonathan Palm

Merianstraße 8, 80637 Munich

03766521

Tian Tang

Kirchenstraße 6, 81675 Munich

03756155


**Submitted on:** 11.08.2024 in Munich

# List of Abbreviations

COMP..... *Committee for Orphan Medical Products*
EU.....*European Union*
FDA.....*Food and Drug Adminstration*
HTA.....*Health Technology Assessment*
ODA ..... *Orphan Drug Act*
ODD .....*Orphan Drug Designation*
OMAR.....*Orphan Maintenance Assessment Report*
OMP ..... *Orphan Medical Products*
PRV .....*Priority Review Voucher*
WHO .....*World Health Organization*

# List of figures

# 1. Introduction

With the introduction of the Orphan Drug Act (ODA) in 1983, the Food & Drug Administration (FDA) has shed a global limelight on the treatment of rare diseases. Once an underrepresented area of drug development, recent incentivization has led to a stellar rise in the number of orphan drugs. This paper examines the current state of care for rare diseases and discusses the current state of legislative support under the aspect of economic theory.

The key aspect which distinguishes "rare" diseases from "normal" diseases is the prevalence in the population. In WHO regions, a disease is commonly defined as rare if it affects fewer than five in 10,000 people (0.05% of the population), a definition adopted by most jurisdictions with slight variance (The Lancet Global Health, 2024). According to EUROSTAT, approximately 36 million people in the EU, or one in twelve of the 448 million population, are likely to suffer from a rare disease. By estimation, the EU region has over 6,000 types of rare diseases, with around 80% having a genetic cause (*Orphan Medicines in the EU*, n.d.), of which 95% lack approved treatments, and 70% affect children. Notably, 30% of afflicted children die before the age of five, and it takes an average of 4.8 years for a patient to receive an accurate diagnosis (The Lancet Global Health, 2024). These statistics highlight the lethality and prevalence of rare diseases, which significantly impact the population yet remain largely untreatable. Due to the lack of hope for many patients, particularly children, drugs targeting rare diseases are often referred to as orphan drugs.

Given the share of affected population and the lethality of rare diseases, one might expect that pharmaceutical companies would have an inherent interest in developing orphan drugs. Historically however, without external incentives, pharmaceutical companies have avoided developing orphan drugs due to their lower profitability compared with that of non-orphan drugs. The refusal of pharmaceutical companies to develop orphan drugs without external stimuli can be attributed to two key complications in the development process:

The development of a drug is by design a risky venture with low success rates. For most drug development projects, the low probability of success is offset by high potential revenue for a long period of time. For orphan drugs, the payoff in case of a successful development process is much smaller than for other drugs, even considering much higher prices for them due to the very low prevalence. For example, for new drugs approved by FDA in 2017-2021, the median cost of orphan drugs is over $200,000, over 15x of non-orphan drugs (Althobaiti et al., 2023). Health technology assessments (HTA) in many EU countries, where average incomes are high,

set price caps based on the additional benefits a drug provides over existing alternatives, further limiting revenue potential (Kelly et al., 2020).

But not only is the revenue potential lower but developing them is arguably more complicated. While capitalized costs are on average lower than non-orphan drugs (Jayasundara et al., 2019), demonstrating drug efficacy using traditional clinical trial designs is more complicated due to the low patient size[1]. Instead, n-of-1 trials are gaining popularity: Individual patients are their own control groups and treatments (drug under development and existing alternatives/ placebo) are tested over multiple, crossover, randomized periods, to determine the optimal treatment option for each individual patient (Defelippe et al., 2023). Additionally, to achieve significant benefit or clinical superiority, orphan drugs often have strong effects, which can result in severe side effects, necessitating extensive testing and revisions (Rana & Chawla, 2018).

Due to the skewed risk-reward ratio for developing orphan drugs, governmental incentives were introduced. In the following paper, we first discuss the economic reasoning for incentivizing orphan drug development. In subsequent chapters, we examine current incentives for drug developers in more detail, with a special focus on market exclusivity and priority review vouchers as two examples of inducements. To conclude this seminar paper, we note the limitations of current incentives and discuss future policy implications.

## 2. Economic Reasoning for Orphan Drug Incentives

A market failure in resource redistribution exists where there is a clear need for orphan drugs, but the supply side is under-incentivized to meet the demand (Figure 1, right side). Government incentives should be implemented to shift the supply curve due to the positive spillover effects of orphan drugs (Gruber, 2018b). Beyond benefiting the patients, orphan drugs also benefit the patients' families (e.g., by alleviating the loss of income for family members who must care for a sick child, which subsequently reduces the government's loss of tax revenue). Additionally, orphan drugs can lower healthcare costs associated with treatments that do not cure but are necessary to manage patient care (e.g., the cost of painkillers to manage the disease). Therefore,

[1] Large scale trials are often not possible, as the total patient pool is too small to find an adequate number of patients to set up a “control group”.

we argue that the development of orphan drugs should be incentivized by the government to push the supply and demand to intersect more favorably (Figure 1).

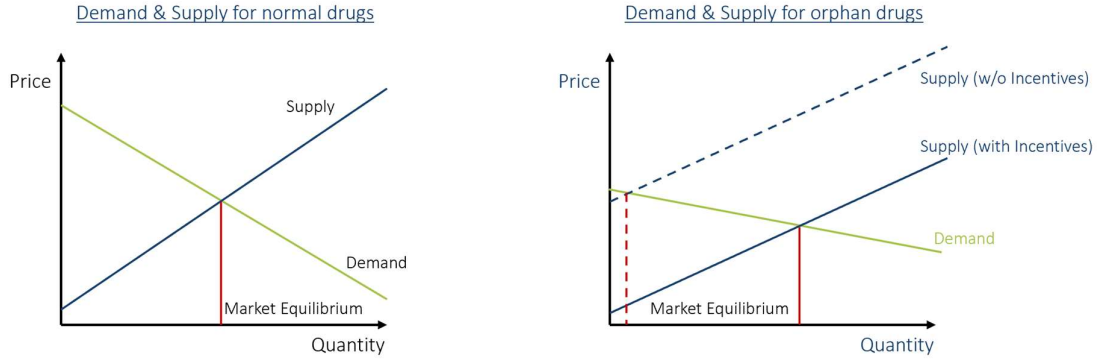


*Figure 1: Demand & Supply Change with Governmental Incentives*

Applications of mainstream arguments in welfare economics also support government incentives both economically and morally. First, utilitarianism aims to maximize overall welfare by redistributing resources efficiently. Assume everyone has the same utility function: total utility might approach its maximum when one segment's utility is zero and the rest's is one. However, utility functions vary among individuals, and society employs safety nets and other measures to redistribute resources (e.g. public health insurance) (Gruber, 2018a). Thus, the focus of argument shifts to the efficiency of redistribution, which is part of our focus in this paper. Second, consider the Rawlsian philosophy: maximize the welfare of the worst of individual in the society. This is given by the veil of ignorance reasoning: If one assumes a purely egoistic and risk-averse perspective, it is in one's interest to fund treatments for rare diseases due to the possibility that oneself or a family member might be affected. Third, a Nozickian perspective emphasizes redistribution of opportunities instead of resources. In this case, patients with rare diseases lack the opportunity to cure because cure does not exist. Finally, commodity egalitarianism underlines that the absolute resources provided to any individual must meet the bare minimum for survival (Gruber, 2018a). Given that there is no cure in most cases, commodity egalitarian principles support government intervention as well.

## 3. Current Incentives on Orphan Drug Development

The financial viability of a drug candidate depends on whether it receives market approval. In "normal" drug development, potential profits must offset the costs of failed candidates as well. Due to the low revenue potential, this becomes (almost) impossible for orphan drugs. Hence, in recent years different incentives were introduced in the Orphan Drug Act by the FDA in the U.S. and the regulation on Orphan Medical Products (OMP) by the EMA in the EU, which aim to improve the situation by supporting companies during their development process and mostly

by ensuring that the financial benefit of getting a drug approved compensates the development risk adequately. Through these legislation drug developers are supported in all three key steps in the drug development, namely pre-clinical discovery, clinical trials and market approval (see Figure 2). To be eligible for incentives, companies must file for an "Orphan Drug Designation" (ODD), which only drugs can receive when fulfilling some (later specified) criteria.

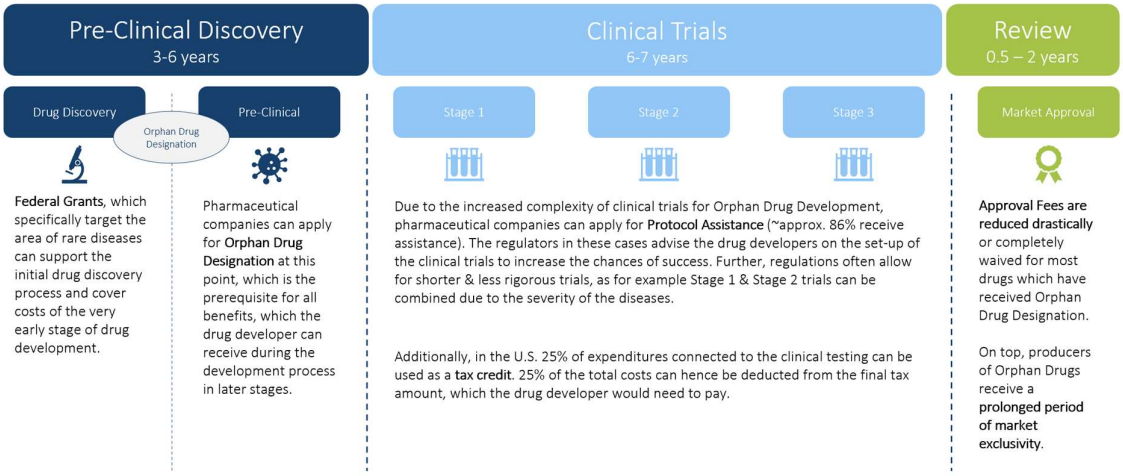


*Figure 2: Incentives throughout the Drug Development Process*

Namely, these incentives include support during the development of the drug through federal grants in the discovery phase as well as assistance during the execution of the clinical trials. Especially, support during clinical trials can range from help on how to set up the proper clinical trials to less rigorous requirements regarding the testing in Stage 1 & Stage 2. Normally, in Stage 1 the efficacy of the drug is tested on healthy people who are not affected by the targeted disease. A drug can only pass through the first stage if the drug shows little to no harmful side effects in healthy people. Since the severity of rare diseases is often so high, side effects become less prevalent in comparison and most regulations are willing to waive the high requirements for Stage 1, e.g. allowing a combined Stage 1 & Stage 2 trial (*From Laboratory to Patient - the Journey of a Medicine Assessed by EMA*, 2019; *Scientific Advice and Protocol Assistance*, n.d.).

While regulators support the companies during development, most of the incentives are aimed at increasing the potential profits in case of a successful market launch of a new drug. As such, some of the strongest incentives governmental agencies promote are tax credits, market exclusivity, and priority review vouchers (PRV). Tax credits allow companies to recoup some of their expenditures throughout the clinical trials once the company becomes profitable[2]. Both market exclusivity and PRVs aim at rewarding the drug developer by providing a stronger financial benefit when a drug receives market approval. As such in the following subchapters,

[2] Companies in the U.S. can deduct 25% (formerly 50%) of their clinical trial expenditures from their tax bill for up to 20 years (Rogers & Sheikh, n.d.).

this seminar paper will go into more detail about the Orphan Drug Designation as well as Market Exclusivity and PRVs.

For the remainder of this seminar paper the effect on revenue is calculated using the formula below. Revenue is the product of patient population, drug price, and marketable years[3].

$$Revenue = Patient\ Population \times Price \times Marketable\ Years$$

## 3.1. Orphan Drug Designation

An ODD is an initial qualification set forth in the ODA and OMP regulation, enabling drug developers to unlock associated incentives. To qualify, the drug under development must be intended for the "prevention, diagnosis, or treatment (coverage) of a life-threatening or chronically debilitating disease (seriousness)" so rare that no more than five in 10,000 (0.05%) have it in the EU, or fewer than 200,000 affected individuals in the U.S. (rarity) (*Orphan Designation: Overview*, n.d.; Taruscio & Gahl, 2024). The U.S. absolute number threshold has not changed since 1984 despite a 40% population increase, reducing the coverage from 0.086% to 0.060%. Nevertheless, the U.S. rarity threshold remains 1.2x that of the EU, covering a wider range of rare diseases (Taruscio & Gahl, 2024; *U.S. and World Population Clock*, n.d.).

In connection with the low prevalence, lack of disease natural history mandates the EMA and FDA control the data quality of ODD applications. The FDA prohibits citing previously granted orphan designations, ensuring that latest data and clinical methods are used to prove orphan indication (Srivastava & Winslow, 2024). In the EU, control is implemented differently. Discrepancies have been found among prevalence data across applications for the same orphan designation, even if granted in the same year[4]. To reduce doubts about application validity, from 2018 onwards, ODD prevalence data is cross-checked with figures from the orphan maintenance assessment report (OMAR), eliminating discrepancies Additionally, each newly authorized OMP undergoes a review of its ODD based on data at the time of marketing authorization application to maintain its status (Mariz et al., 2020).

Besides rarity and seriousness, evidence of potential efficacy and unlikelihood of profitability must be shown: the orphan drug needs to demonstrate significant benefit or clinical superiority over existing alternatives, and the return without incentives must be unlikely to justify the necessary investment (*Orphan Designation: Overview*, n.d.; Taruscio & Gahl, 2024).

[3] We acknowledge that the accurate estimation of profit today needs to consider the time value of money by discounting cash flows with the required rate of return (opportunistic cost of capital).

[4] For instance, panobinostat and elotuzumab were both granted orphan designation in 2012 for treating multiple myeloma. Panobinostat reported a prevalence of 3.2 in 10,000, twice as high as elotuzumab's (Bouwman et al., 2024).

## 3.2. Market Exclusivity

Market exclusivity has been widely regarded as the most attractive incentive because it is a "de facto monopoly for a predefined, set period, during which supra-competitive monopoly prices can be charged" (Oronsky et al., 2023).

To understand how market exclusivity functions, we start with the differences between market exclusivity and patent (see Figure 3). A patent is a protection on a technical invention, and it requires three elements: novelty, inventive step and industrial applicability. Market exclusivity in comparison is essentially a monopoly – during this period, no new or renewal application for marketing authorization (MA) will be approved. (Oronsky et al., 2023). It is applied concurrently with the application for MA and is automatically attached to the first MA. (*Market Exclusivity: Orphan Medicines*, n.d.).

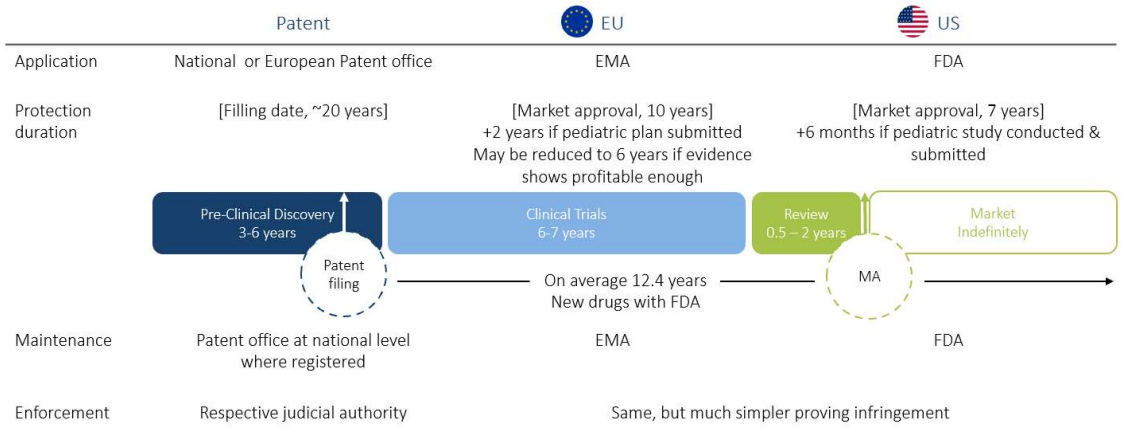


*Figure 3: Comparison of Patent and Market Exclusivity in the EU and U.S.*

Market exclusivity complements patents on better aligning the interests of pharmaceuticals and patients, by merely delaying but not truncating the marketable years. Patent protection begins at the filling date and typically lasts for 20 years with possible extensions to compensate for lengthy R&D (Beall et al., 2021). They are usually filed near the end of the pre-clinical discovery phase, meaning much of the clinical trial phase being counted toward the patent's protection period (Beall et al., 2019). Market exclusivity, in comparison, starts from the date of the first MA and guarantees a fixed period of market monopoly. In the EU, it lasts for ten years; In the U.S., it lasts seven years. A two-year or six-month extension is awarded is a pediatric indication is satisfied in the respective region (*Orphan Incentives*, n.d.; *Patents and Exclusivity*, 2015).

A conflict of interest arises with patents: While longer R&D may boost drug efficacy and significantly improve patient welfare, it does not necessarily lead to proportionate price increases. However, reduced marketable years and additional trial costs are tangible. For example, new drugs in the U.S. take 12.4 years on average from the first patent filing to MA,

leaving only 7.6 years for profitability (not counting patent extension) (Beall et al., 2019). Therefore, to maximize profit, it is preferable for pharmaceuticals to maximize marketable years by obtaining MA as soon as possible, even if it means meeting only the minimal clinical requirements (Beall et al., 2021). Notably, the approval of drugs targeting chronical diseases based on shorter pivotal clinical trials has been criticized, as both the long-term efficacy of the drug and the guidance on optimal dosage provided by trials are questionable (Hemkens, 2018; Hlatky, 2014). Expectedly, such conflict is more pronounced in the case of orphan drugs due to longer journeys from lab to MA, given the challenges highlighted before.

The situation is alleviated when market exclusivity is in play – its protection either approximates (seven vs. 7.6 years in the U.S.) or exceeds (ten vs. 7.6 years in the EU) the average effective post-MA period under patent, ensuring the marketable years of orphan drugs are comparable to the average of non-orphan drugs (Beall et al., 2019, 2021; *Orphan Incentives*, n.d.; *Patents and Exclusivity*, 2015). A guaranteed exclusivity period, which merely delays the revenue but not reducing it, encourages pharmaceuticals to prolong the R&D without immediate threat of generics entering the market after patent expiration.

Market exclusivity also offers a broader geographical coverage with central supervisory agencies, granting a stronger enforcement against infringement than patent. While patents are centrally managed by the federal government in the U.S., in the EU they must be maintained on a country-by-country basis. Conversely, market exclusivity is centrally managed by FDA and EMA. Thus, disputes over market exclusivity are less costly, time-consuming and uncertain than those over patents, because regional courts are more reluctant to challenge EMA than national patent offices (Oronsky et al., 2023).

Although market exclusivity is widely regarded as the principal incentive, it is criticized, for the length of exclusivity is neither tied to the drug's public health value (even with pediatric extensions) nor to its price (Beall et al., 2021). First, an orphan drug classified with high degrees of additional benefits should receive a longer exclusivity period than one with a lower ranking, given its higher anticipated public health benefits[5]. A uniform duration does not motivate drug developers to conduct more R&D. Statistics also highlight the need for high-efficacy drugs: among all oncologic orphan drugs introduced in Germany during 2011-2023, only 13 out of 70 (18.6%) are categorized as “major or considerable benefit” (Watt, 2024). Secondly, a lower price could maximize impact by reducing the burden per patient, allowing statutory insurers to cover more drugs. The extended duration would also enable consistent clinical adoption of the new drug, making it financially rewarding for developers in the trade-off between price and

[5] For example, the prevention of an infectious disease onset, curing a deadly disease, or achieving therapeutic intent across multiple conditions should all qualify (Beall et al., 2021).

marketable years. Therefore, the extension of exclusivity term can stimulate the development of high-efficacy drugs and boost the cost-effectiveness of healthcare spending (Beall et al., 2021).

Since market exclusivity is a de facto monopoly, it's logical to ask the question: Can orphan drug developers arbitrarily set the prices to maximize revenue in the predefined market exclusivity period? The answer is it depends on the pricing mechanism of a country.

In the EU, after EMA issues a recommendation for the MA, the European Commission must officially authorize the MA, and the drug's actual market entry then depends on negotiations with authorities in each Member State (*From Laboratory to Patient - the Journey of a Medicine Assessed by EMA*, 2019). All EU Member States adopt health technology assessment (HTA), which sets an upper limit on pricing. However, HTA process for orphan drugs varies across Member States, complicating market entry, pricing and reimbursement for pharmaceuticals (Kelly et al., 2020).

In Germany, any orphan drug with MA is automatically granted an abbreviated HTA process, provided the drug's gross revenue from statutory insurer (GKV) do no exceed €30m for the past 12 months (previously €50m) (Engelke et al., 2023; Pownell, 2022). An abbreviated HTA dossier may be submitted instead of a full one. Although the likelihood and the extent of additional benefit still need to be assessed, additional benefit is automatically assumed, giving the marketing authorization holder a strong position in negotiation with GKV. Reassessment of additional benefits and price renegotiation are required once the revenue threshold is passed or orphan status is no longer maintained (Pownell, 2022).

The U.S. has in theory no price cap on prescription drugs, which in turn can lead to very high out-of-pocket costs for individual patients (Vincent Rajkumar, 2020). For orphan drugs, the pricing is more focused on the negotiation between the pharmaceutical companies and the insurance companies to strike a balance so that orphan drugs are covered by insurance providers (Lopata et al., 2021). For this often times the U.S., similar to European countries, uses External Reference Pricing and Therapeutic Equivalency Pricing (Bipartisan Policy Center, 2019). Hence, even though in theory the U.S. has no price cap on orphan drugs, it can be assumed that the price is roughly in line with the pricing in other regions, such as the EU.

Despite that, studies have shown U.S. has a much higher prices on orphan drugs than EU without conclusive factors determined. One study has found that VAFSS U.S. prices[6] were

[6] Prices used by U.S. Department of Veteran Affairs, representing the lower bound of prices in the U.S. (Żelewski et al., 2022)

1.64x of the average list prices[7] of six EU Member States. Specifically, VAFSS U.S. prices are on average 1.46x of Germany's (second highest), and 2.11x of Poland's (lowest). We cannot rule out the possibility that the price differences on orphan drugs are due to traditionally higher drug prices the U.S. compared with the EU, or other contributing factors.

For new drugs approved in the U.S. alone in 2017-2021, orphan drug prices are 1.8x of non-orphan, after controlling for application type (Biologic License Applications vs. New Drug Applications), country of incorporation (U.S. vs. non-U.S.), treatment intent (prevention vs. treatment), therapeutic area (genetic disorder, oncology, or others vs. infection), and treatment duration (single use vs. more than one year). The overall impression of high prices on orphan drugs could be more likely owing to the combination of multipliers instead of on rarity alone (Althobaiti et al., 2023). While prices for some are indeed high as a result of small patient populations, most prices are relatively moderate. Additionally, orphan drug prices exhibited slower growth than the overall branded market from 2003 to 2017, though the growth was faster before (Aitken & Kleinrock, 2018).

Among the six selected Member States, list prices are rather homogeneous because external reference pricing is adopted: 57% of all list prices fall within +/-10% range of the average and 82% fall within +/-20%. Nevertheless, regression indicates the number of reimbursed orphan drugs is positively correlated to GDP/capita in the EU countries (Germany reimbursed 91 drugs while Poland 26), suggesting pharmaceuticals' unwillingness to make market entry when price flexibility is limited (Żelewski et al., 2022).

### 3.3. Priority Review Vouchers

To better understand how the issue of market uncertainty was handled in the U.S. in the following chapter we look at Priority Review Vouchers (PRV). Even after the introduction of Market Exclusivity for orphan drugs the number of new indications for pediatric orphan diseases was not sufficient. To offer pharmaceuticals a compensation for potentially lower revenue and increase the number of pediatric orphan drugs, tradeable PRVs were introduced. They were vouchers, which could be traded on a secondary market and be redeemed at the FDA for an accelerated review process (Mease et al., 2024).

Usually, when a pharmaceutical company has completed a Stage 3 clinical trial successfully, they file for market approval with the FDA, which usually approves the drug within 12–18 months (Wong et al., 2019). Since the developer must file the patent during the discovery stage, the time that the developer has to wait for approval is the time that the company would have

[7] List prices are set as target prices in the EU by the pharmaceutical companies and exclude rebates, representing the higher bound of prices in the EU (Żelewski et al., 2022).

exclusive rights to market and sell its product. A PRV is a voucher, which can be used by companies to shorten the timeline to get a drug to market to less than 6 months[8]. Since this reduction in the timeline is directly linked to the time that a drug has market exclusivity, the PRV has a value to pharmaceutical companies, which is defined by the potential sales of the drug with the "accelerated" approval (Mease et al., 2024).

To incentivize the development of orphan drugs for pediatric diseases the FDA grants a tradeable PRV to each company that has an orphan drug approved for pediatric use. This PRV is tradeable so that the developer can potentially sell the voucher to the highest bidder, recouping a large portion of the development costs. The issuance of PRVs hence supports Orphan Drug Development by ensuring developers that when their drug gets approval, a revenue baseline is guaranteed which is independent of market uncertainties and population size. Historically, PRVs were traded at prices between $50m and $350m (Mease et al., 2024).

As PRVs are used to stimulate the development of drugs with not enough market power to be developed normally, the FDA also grants PRVs to drug developers, which produce drugs for tropical neglected diseases (Aerts et al., 2022). While the program to reward the development of tropical neglected diseases remains intact, the sunset of the PRV program for pediatric orphan diseases was announced in 2024 (Mease et al., 2024). The decision to not further continue with PRVs for orphan drug development leads to the impression that the guaranteed revenue baseline is no longer necessary to incentivize pediatric orphan drug development.

## 4. Conclusion & Limitations

Throughout this seminar paper, we have examined the current legislative support in the treatment of rare diseases. Due to the small patient population, drug developers cannot aim to sufficiently benefit from the development of orphan drugs without governmental support. We continue to argue that from an economic perspective there is a societal value to develop treatments, and such endeavors should be incentivized to reach a social optimum.

Congruent to our analysis of market forces one can see in Figure 4 below that the number of drugs targeting rare diseases has been very low historically, before various incentivization programs were introduced. In line with our thesis, in 1983 the Orphan Drug Act was introduced, directly supporting the treatment of rare diseases in the U.S., which was followed on by the regulation on Orphan Medicinal Products in the EU, in 2000 (Mariz et al., 2020). The legislations assist the development process by providing protocol assistance and reducing

[8] A PRV does not necessitate approval of the FDA, but only that a decision has to be made in 6 months, although historically no drug has failed to receive market approval with a PRV.

administrative costs, but predominantly provides a framework for financial viability of orphan drugs through market exclusivity.

As can be seen in the Figure 4 the incentivization program in the U.S. had an noteworthy impact – the number of Orphan Drug Designations has increased from 38 designations in 1984 to 340 in 2019, and 14% (724) of total 5,099 designations have at least one approval (Miller et al., 2021). The statistics from Figure 5 show a similar trend in the EU attributable to the legislation; Previously undesignated conditions represent 18-20% of new designations per year, a positive sign of increasing interest in untapped field (Mariz et al., 2020). The number of approvals is growing in both regions as well, with the increase being more apparent in the U.S. The comparison reflects the time required for R&D efforts to mature into qualified treatments, again underlining the riskiness of orphan drug development.

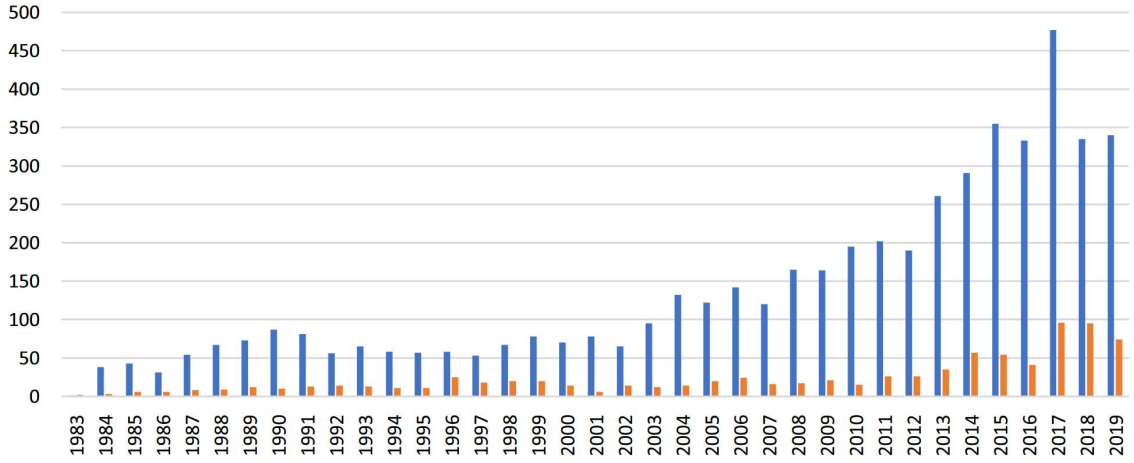


*Figure 4: Number of Orphan Drug Designations and Approvals in the U.S. 1983-2019 (Miller et al., 2021)*

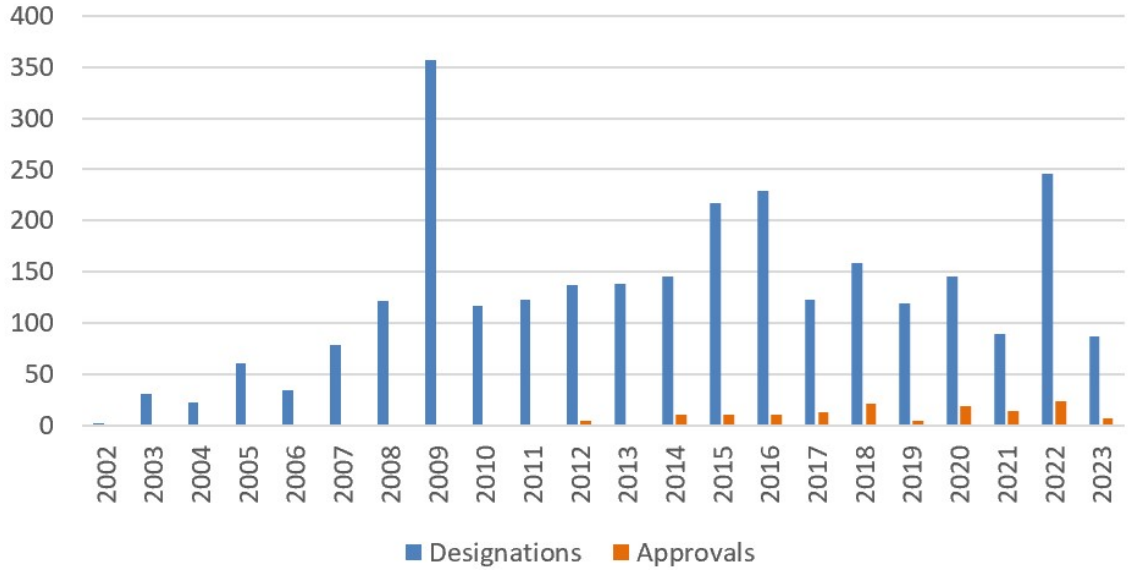


*Figure 5: Number of Orphan Drug Designations and Approvals in the EU 2002-2023 (*Download Medicine Data*, n.d.)*

Nevertheless, orphan drug incentives spike ongoing discussions, and some criticisms are less reasoned than others. ODD applicants have been accused of exploiting the provisions with "salami slicing" – maintaining the drugs' orphan status by applying for one indication each time. Such allegation reflects a misunderstanding of heterogeneity of rare diseases and oversimplification of incremental innovation (Horgan et al., 2022).

A more credible argument is on the criteria of ODD: While the 0.05% rarity threshold is commonly accepted, the binary implementation of incentives based on this threshold is disputed. Drugs targeting diseases with prevalences just above 0.05%, yet still rare, are not incentivized, leading pharmaceuticals to avoid developing them. Moreover, in the EU, review for maintenance of ODD and the Committee for Orphan Medicinal Products' (COMP) efforts to adapt the classification of rare diseases yearly further suggest the possibility of a drug losing its designation at the time of marketing authorization (MA). Although this loss does not revoke MA, it wipes out the most lucrative incentive—market exclusivity[9]. Thus, drug developers demonstrate a tendency to avoid rare diseases with prevalences close to the threshold as well. A study on OMPs approved in the EU from 2010 to 2022 shows that the number of approvals per prevalence segment (each one in 10,000) is steady above 25 but drops to 12 when disease prevalences rise to between four to five in 10,000 (Bouwman et al., 2024). While this drop might just reflect a decrease of the total number of rare diseases in the segment, we believe it is at least partially due to the fear of losing incentives.

Although it might seem logical to base incentives on rarity, this approach is challenging for two reasons: First, rarity cannot be the sole variable; other factors, such as seriousness, must also be accounted for[10]. However, quantifying the seriousness of rare diseases is difficult due to their rarity and heterogeneity. Second, while a progressive incentive system is possible, it could introduce misaligned interests. A more thorough study could diagnose more patients, yet researchers might lose funding the more patients are discovered; Healthcare providers might exaggerate patient suffering to increase budgets, and drug developers could manipulate data on prevalence and seriousness, making verification costly. Hence, while the binary implementation has clear drawbacks, we believe that currently a progressive incentive system would unintentionally create motivations, lowering the overall welfare.

Further discussions are more closely tied to the more recent regulatory activities scaling back incentives: With the FDA, tax credits on R&D costs are reduced from 50% to 25%, and the

[9] In 2015, interstitial cystitis was reclassified to bladder pain by COMP, raising its prevalence above 5 in 10,000, leading the developer to withdraw its ODD (Mariz et al., 2020). Fortunately, such instance is rare; only one example was found across sources.

[10] As an example a rarer but less lethal disease should not receive more incentives than a less rare but more lethal disease.

PRV is no longer issued. The former provides a direct financial benefit to drug developers in the moment they turn a profit; the latter does so when their drugs acquire MA (Aerts et al., 2022; Mease et al., 2024; Rogers & Sheikh, n.d.). The EU Pharmaceutical Reform aims to modify the terms of market exclusivity from a uniform ten-year to ten years for first-in-kind or high-efficacy drugs, five years well-established drugs, and nine years for the rest. A one-year extension (maximum two years) may be granted on the development of a new indication for an already authorized drug (*Document 52023PC0193, COM/2023/193 Final*, 2023). As mentioned, in Germany, the new GKV Financial Stabilization Act (GKV-FinStG) slashed the HTA privilege threshold from €50m to €30m (Engelke et al., 2023).

We believe the legislative adjustments are directly linked to the historical cost-effectiveness of incentives. While the overall uptick on the number of orphan designations and approved drugs is impressive, the growth is uneven among diseases: a considerable share of designations aim for oncologic intent and target adults only, as the risk-return profile is most lucrative (Bouwman et al., 2024; Miller et al., 2021). Further, some incentives are not necessarily associated with more patient welfare, failing to legitimizes the cost. As mentioned previously, an orphan status is not a guarantee for high-efficacy rating in HTAs. For all orphan drugs introduced in Germany since 2011, the Independent Institute for Quality and Efficiency in Health Care (IQWiG) has found 54% of them should be reclassified as "no additional benefit" in subsequent regular assessment, prompting the doubts on their assessment and pricing privilege (Bernardini, 2022). For incentives like tax credits and PRVs, cash is rewarded even the pharmaceuticals choose not sell the approved drugs at all (Mease et al., 2024).

Hence, it can be concluded that the development of orphan drugs was "over-incentivized" in some areas and adjustments are desired – such as the updated terms of market exclusivity in the proposed EU Pharmaceutical Reform (*Document 52023PC0193, COM/2023/193 Final*, 2023).

In this paper we have mainly focused on the support introduced by ODA and regulation on OMP. The government has also established other efforts to combat rare diseases: conditional approval and expedited review programs (not solely for orphan drugs but highly relevant), proposal for joint HTA to simplify market entry in the EU, and more (Bouwman et al., 2024; Dajka, 2023). We find that the legislative and administrative bodies are working towards a balance where the incentives are sufficient, but not overreaching to better address the unmet medical needs in a more precise, cost-effective way to maximize social welfare.

## Declaration of Authorship

Hereby, I declare that I have composed the presented thesis/seminar paper independently on my own and without any other resources than the ones indicated. All thoughts taken directly or indirectly from external sources are properly denoted as such.

I am aware that the digital form of the thesis/seminar paper can be examined for the use of unauthorized aid and in order to determine whether the thesis/seminar paper as a whole or parts incorporated in it may be deemed as plagiarism. For the comparison of my work with existing sources.

I agree that it shall be entered in a database where it shall also remain after examination to enable

comparison with future works. However, further rights of reproduction and usage are not granted.

This thesis/seminar paper has neither been previously submitted to another authority nor has it been

published yet.

**Munich, 11 August 2024**

| | |
|---|---|
| Jonathan Palm | Tian Tang |

Bibliography

Aerts, C., Barrenho, E., Miraldo, M., & Sicuri, E. (2022). The Impact of the Priority Review Voucher on Research and Development for Tropical Diseases. *Pharmaceutical Medicine*, *36*(3), 189–197. https://doi.org/10.1007/s40290-022-00427-x

Aitken, M., & Kleinrock, M. (2018). *Orphan Drugs in the United States Exclusivity, Pricing and Treated Populations* (pp. 11–16). IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-exclusivity-pricing-and-treated-populations.pdf

Althobaiti, H., Seoane-Vazquez, E., Brown, L. M., Fleming, M. L., & Rodriguez-Monguio, R. (2023). Disentangling the Cost of Orphan Drugs Marketed in the United States. *Healthcare*, *11*(4), 558. https://doi.org/10.3390/healthcare11040558

Beall, R. F., Hollis, A., Kesselheim, A. S., & Spackman, E. (2021). Reimagining Pharmaceutical Market Exclusivities: Should the Duration of Guaranteed Monopoly Periods Be Value Based? *Value in Health*, *24*(9), 1328–1334. https://doi.org/10.1016/j.jval.2021.04.1277

Beall, R. F., Hwang, T. J., & Kesselheim, A. S. (2019). Major Events in the Life Course of New Drugs, 2000–2016. *New England Journal of Medicine*, *380*(11). https://doi.org/10.1056/NEJMp1806930

Bernardini, A. (2022, January 24). *Winds of change blowing over Germany for Orphan Drugs*. Partner4Access. https://partners4access.com/blogs/winds-of-change-blowing-over-germany-for-orphan-drugs/

Bipartisan Policy Center. (2019). *Examining Two Approaches to U.S. Drug Pricing:* Bipartisan Policy Center. http://www.jstor.org/stable/resrep35486

Bouwman, L., Sepodes, B., Leufkens, H., & Torre, C. (2024). Trends in orphan medicinal products approvals in the European Union between 2010–2022. *Orphanet Journal of Rare Diseases*, *19*(1), 91. https://doi.org/10.1186/s13023-024-03095-z

Dajka. (2023, September 18). *The EU regulation on health technology assessment: What's in it and why it matters?"*. European Commission. https://health.ec.europa.eu/system/files/2023-10/hta_20230918_co01_en.pdf

Defelippe, V. M., J.M.W. Van Thiel, G., Otte, W. M., Schutgens, R. E. G., Stunnenberg, B., Cross, H. J., O'Callaghan, F., De Giorgis, V., Jansen, F. E., Perucca, E., Brilstra, E. H., & Braun, K. P. J. (2023). Toward responsible clinical n-of-1 strategies for rare diseases. *Drug Discovery Today*, *28*(10), 103688. https://doi.org/10.1016/j.drudis.2023.103688

*Download medicine data*. (n.d.). European Medicines Agency. Retrieved 30 May 2024, from https://www.ema.europa.eu/en/medicines/download-medicine-data

Engelke, C., Kiss, G., & Gottswinter, A. (2023, February 24). *Germany: How the GKV-FinStG law is transforming the pharma P&R landscape*. Simon Kucher. https://www.simon-kucher.com/en/insights/germany-how-gkv-finstg-law-transforming-pharma-pr-landscape

*From laboratory to patient—The journey of a medicine assessed by EMA*. (2019). European Medicines Agency. https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

Gruber, J. (2018a). *21. Efficiency and Equity*. MIT 14.01 Principles of Microeconomics. https://www.youtube.com/watch?v=osaVeUBA0Qk

Gruber, J. (2018b). *23. Market Failures I: Externalities*. MIT 14.01 Principles of Microeconomics. https://www.youtube.com/watch?v=RJi1GsObmWQ

Hemkens, L. G. (2018). How Routinely Collected Data for Randomized Trials Provide Long-term Randomized Real-World Evidence. *JAMA Network Open*, *1*(8), e186014. https://doi.org/10.1001/jamanetworkopen.2018.6014

Hlatky, M. A. (2014). A Long-Term Perspective on Short-Term Outcomes∗. *Journal of the American College of Cardiology*, *64*(20), 2109–2110. https://doi.org/10.1016/j.jacc.2014.08.038

Horgan, D., Koeva-Balabanova, J., Capoluongo, E., Jagielska, B., Cattaneo, I., Kozaric, M., Tumiene, B., El Ahl, J.-P., Lal, J. A., Kalra, D., & Malats, N. (2022). Making Sure That Orphan Incentives Tip the Right Way in Europe. *Healthcare*, *10*(9), 1600. https://doi.org/10.3390/healthcare10091600

Jayasundara, K., Hollis, A., Krahn, M., Mamdani, M., Hoch, J. S., & Grootendorst, P. (2019). Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet Journal of Rare Diseases*, *14*(1), 12. https://doi.org/10.1186/s13023-018-0990-4

Kelly, S., Stefani, I., Poon, C., & Raj, N. (2020, August 4). *How does HTA for orphan drugs differ across Europe?* PharmaPhorum. https://pharmaphorum.com/views-analysis-market-access/how-does-hta-for-orphan-drugs-differ-across-europe

Lopata, E., Terrone, C., Gopalan, A., Ladikos, N., & Richardson, T. (2021). Meeting the affordability challenges posed by orphan drugs: A survey of payers, providers, and employers. *Journal of Managed Care & Specialty Pharmacy*, *27*(6), 706–713. https://doi.org/10.18553/jmcp.2021.20553

Mariz, S., Westermark, K., & Sepodes, B. (2020). Designation of orphan conditions in Europe: Regulatory observations and considerations after

implementation of regulation 141/2000. *Expert Opinion on Orphan Drugs*, *8*(6), 189–196. https://doi.org/10.1080/21678707.2020.1784720

*Market exclusivity: Orphan medicines*. (n.d.). European Medicines Agency. Retrieved 18 May 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/orphan-designation-post-authorisation/market-exclusivity-orphan-medicines

Mease, C., Miller, K. L., Fermaglich, L. J., Best, J., Liu, G., & Torjusen, E. (2024). Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: Designations, diseases, and drug development. *Orphanet Journal of Rare Diseases*, *19*(1), 86. https://doi.org/10.1186/s13023-024-03097-x

Miller, K. L., Fermaglich, L. J., & Maynard, J. (2021). Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: Substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. *Orphanet Journal of Rare Diseases*, *16*(1), 265. https://doi.org/10.1186/s13023-021-01901-6

Oronsky, B., Caroen, S., Brinkhaus, F., Reid, T., Stirn, M., & Kumar, R. (2023). Patent and Marketing Exclusivities 101 for Drug Developers. *Recent Patents on Biotechnology*, *17*(3), 257–270. https://doi.org/10.2174/1872208317666230111105223

*Orphan designation: Overview*. (n.d.). European Medicines Agency. Retrieved 1 May 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview

*Orphan incentives*. (n.d.). European Medicines Agency. Retrieved 15 May 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/orphan-designation-research-development/orphan-incentives

*Orphan medicines in the EU*. (n.d.). European Medicines Agency. Retrieved 20 May 2024, from https://www.ema.europa.eu/en/documents/leaflet/infographic-orphan-medicines-eu_en.pdf

*Patents and Exclusivity*. (2015, May 19). FDA/CDER SBIA CHRONICLES. https://www.bing.com/ck/a?!&&p=563a405941c69e05JmltdHM9MTcyMjIxMTIwMCZpZ3VpZD0xZDg0NTA0Zi1iZTkxLTZmODgtMzIyZC00MmQwYmYxYTZlMTQmaW5zaWQ9NTE3Ng&ptn=3&ver=2&hsh=3&fclid=1d84504f-be91-6f88-322d-42d0bf1a6e14&psq=patents+and+exclusivity+fda+cder+sbia+5%2f19%2f2015+pdf&u=a1aHR0cHM6Ly93d3cuZmRhLmdvdi9tZWRpYS85MjU0OC9kb3dubG9hZA&ntb=1

Pownell, A. (2022, February 28). *Regular and abbreviated early benefit assessments – Is this the end of orphan drug privileges?* German Market Access Simplified. https://germanmarketaccesssimplified.com/orphan-drug-benefit-assessments/#3-special-status-of-orphan-drugs

*Reform of the EU pharmaceutical legislation—Commission proposal for the Pharmaceutical Regulation*. (2023, April 26). European Commission. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en#consultation-activities-related-to-the-revision-of-the-orphan-and-paediatric-legislation

Rogers, H.-A., & Sheikh, H. Z. (n.d.). *The Orphan Drug Act: Legal Overview and Policy Considerations*.

*Scientific advice and protocol assistance*. (n.d.). European Medicines Agency. Retrieved 15 May 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance

Srivastava, G., & Winslow, A. (2024, April). *Orphan Drugs: Understanding the FDA Approval Process*. Academic Entrepreneurship for Medical and Health Scientists. https://academicentrepreneurship.pubpub.org/pub/einr3b30/release/5

Taruscio, D., & Gahl, W. A. (2024). Rare diseases: Challenges and opportunities for research and public health. *Nature Reviews Disease Primers*, *10*(1), 13. https://doi.org/10.1038/s41572-024-00505-1

The Lancet Global Health. (2024). The landscape for rare diseases in 2024. *The Lancet Global Health*, *12*(3), e341. https://doi.org/10.1016/S2214-109X(24)00056-1

*U.S. and World Population Clock*. (n.d.). United States Census Bureau. Retrieved 10 June 2024, from https://www.census.gov/popclock/?ref=cecna-io.ghost.io

Vincent Rajkumar, S. (2020). The high cost of prescription drugs: Causes and solutions. *Blood Cancer Journal*, *10*(6), 71, s41408-020-0338–x. https://doi.org/10.1038/s41408-020-0338-x

Watt, A. (2024, April 26). *The privileged status of orphan medicines in Germany*. Pharmaceutical Technology. https://www.pharmaceutical-technology.com/analyst-comment/the-privileged-status-of-orphan-medicines-in-germany/?cf-view&cf-closed

Wong, C. H., Siah, K. W., & Lo, A. W. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics*, *20*(2), 273–286. https://doi.org/10.1093/biostatistics/kxx069

Żelewski, P., Wojna, M., Sygit, K., Cipora, E., Gąska, I., Niemiec, M., Kaczmarski, M., Banaś, T., Karakiewicz, B., Kotwas, A., Zabielska, P., Partyka, O., Pajewska, M., Krzych-Fałta, E., Bandurska, E., Ciećko, W., & Czerw, A. (2022). Comparison of US and EU Prices for Orphan Drugs in the

Perspective of the Considered US Orphan Drugs Act Modifications and Discussed Price-Regulation Mechanisms Adjustments in US and European Union. *International Journal of Environmental Research and Public Health*, *19*(19), 12098. https://doi.org/10.3390/ijerph191912098