A COMPARISON OF THE PRE-MARKET ORPHAN DRUG LEGAL FRAMEWORKS IN THE UNITED STATES AND THE EUROPEAN UNION

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INTRODUCTION

Drugs developed to treat rare diseases are like fine gems: they are highly sought after, have large research and development costs, and come with a high price tag. In the case of a rare disease treatment, the patient has no alternative but to mine for that gem often at a cost upwards

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of $100,000 more than a patient with a common disease would spend on treatment.[1] Rare diseases are estimated to affect nearly 400 million people worldwide and about 30 million people in Europe and 25 million people in the United States.[2] In the pharmaceutical world, rare diseases and the drugs used to treat them are called "orphan diseases" and "orphan drugs" based on regulations of the same name. This paper will focus on the pre-market legal frameworks of these orphan drugs in the United States and the European Union in order to understand how these frameworks may impact the cost of treatment.

In the United States, an orphan disease is a disease that affects less than two hundred thousand people or is a disease where a drug sponsor is unlikely to recover the cost of development once the drug is marketed in the United States.[3] In Europe, an orphan disease is one that affects less than five in ten thousand people.[4] It is estimated that of the more than six thousand orphan diseases, only five percent have an approved treatment in either the United States or the European Union.[5] Access to these orphan drugs is not guaranteed for the fortunate five percent of patients that have an approved treatment option. This may be because of cost. For example, patients in the United States end up paying 20–40% more on average for drug treatments than their European Union counterparts.[6] This difference can be cost prohibitive. One study found

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1 "Per capita spending on prescriptions in 2011 was highest for central nervous system agents ($170), those ages 55–64 ($1,711), and those in the South ($838)." Gregory Stanton et. al., *Spending on Prescriptions in 2011*, ISSUE BRIEF #4 (Health Care Cost Institute, Washington, D.C.), Sept. 2012, at 1, http://www.healthcostinstitute.org/files/HCCI_IB4_Prescriptions.pdf. A different report found that on average, a patient pays 5.5 times more for orphan drugs versus non-orphan drugs. ANDREAS HADJIVASILIOU, ORPHAN DRUG REPORT 2017, 6 (4th ed. 2017), http://www.evaluategroup.com/public/Reports/EvaluatePharma-Orphan-Drug-Report-2017.aspx. The average cost per patient in 2016 for an orphan drug was $140,443 compared to $27,756 for a non-orphan drug. *Id.* at 9.

2 WARREN KAPLAN ET AL., PRIORITY MEDICINES FOR EUROPE AND THE WORLD (2013 UPDATE) 148, http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf.

3 21 C.F.R. § 316.10(8) (2017).

4 Commission Regulation 141/2000, art. 3.1, 2000 J.O. (L18) 1.

5 *About Rare Diseases*, ORPHANET (Oct. 25, 2012), http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN; Birgitta Miyamoto & Emil Kakkis, *The Potential Investment Impact of Improved Access to Accelerated Approval on the Development of Treatments for Low Prevalence Rare Diseases*, 6 ORPHANET J. RARE DISEASES 49, 1 (2011).

6 IMS INST. FOR HEALTHCARE INFORMATICS, INNOVATION IN CANCER CARE AND IMPLICATIONS FOR HEALTH SYSTEMS 3 (2014), http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global-oncology-trend-report-2014.

that the lifetime cost of orphan drug treatment of cystic fibrosis was €858,604 in Germany compared to €1,907,384 in the United States.[7]

It is this difference in cost—and the high cost of the orphan medications in general—that prompted the author to further explore this topic. The main question explored in this article is whether, and to what extent, the legal frameworks that provide incentives to sponsors impact the cost of orphan drugs and how these legal frameworks compare to each other. The goal of this analysis is to identify areas where regulations may be amended to have a positive outcome on the cost for patients while not jeopardizing the success of the orphan drug programs. Finally, this article will use examples from other countries to begin a discussion about possible changes and/or alternatives, all while keeping in mind that the question of drug pricing is much broader and touches many more disciplines beyond pre-market regulation.

To begin this analysis, the remainder of the introductory section will provide the reader with a basic outline of how drugs are approved in the United States (US) and the European Union (EU), irrespective of whether the drug has an orphan designation or not. Section I will then explore the pre-market regulations for orphan drugs in both the US and the EU. Section II will outline current legal and regulatory developments in both frameworks in order to establish the current landscape of the legal frameworks. Section II will also analyze the current incentives included in each regulatory framework in an effort to answer the article's main question. Finally, Section III of this article will conclude with possible changes based on efforts to reduce drug prices currently underway across the world.

THE BASICS OF PRE-MARKET DRUG APPROVAL

Before any drug can be prescribed in the United States or the European Union, it must be approved by either the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) respectively.[8] This section will outline the approval pathways for a

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[7] Todd Gammie et. al., *Access to Orphan Drugs: A Comprehensive Review Legislations, Regulations and Policies in 35 Countries*, 10.10:e0140002 PLOS ONE, Oct. 9, 2015, at 2, http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0140002&type=printable.

[8] In Europe, each country also has pre-market approval systems that handle the regulation of certain classes of drugs. This paper focuses on the centralized procedure which is orchestrated by EMA, hence the summary sentence. *See Marketing Authorization*, EUROPEAN MEDS. AGENCY,

general drug product in each framework, beginning with the United States.

United States

The FDA, an executive agency under the Department of Health and Human Services, is responsible for drug approval in the United States.[9] The agency is comprised of many offices and centers, including the Center for Drug Evaluation and Research (CDER),[10] which regulates over-the-counter drugs and prescription drugs.[11]

The first step towards marketing approval is to submit an Investigational New Drug Application (IND).[12] The IND must be in effect before the sponsor can begin clinical trials.[13] The phases of investigation include three primary phases (Phases 1–3) and a post-marketing phase (Phase 4).[14] In Phase 1, the new drug is introduced to humans for the first time.[15] The goal of this phase is to determine "the metabolism and pharmacologic actions of the drug in humans" as well as any side effects specific to dosage increases.[16] A secondary goal of a Phase 1 trial is to record any early signs of effectiveness.[17] A Phase 1 trial usually includes between twenty and eighty subjects and patients.[18]

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001595.jsp&mid=WC0b01ac0580b18a3d (last visited Oct. 1, 2017).

[9] *What does FDA regulate?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194879.htm (last visited Sept. 14, 2017).

[10] *FDA Organization*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/AboutFDA/CentersOffices/default.htm (last visited Sept. 14, 2017).

[11] *About the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm (last visited Sept. 14, 2017).

[12] 21 C.F.R. § 312.20.

[13] 21 C.F.R. § 312.20(b). *See generally* 21 C.F.R. § 312.23 (providing information concerning an IND's required content and formatting).

[14] 21 C.F.R. §§ 312.21, 312.85.

[15] 21 C.F.R. § 312.21(a).

[16] *Id.*

[17] *Id.*; *see also Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews*, NAT'L CTR. FOR BIOTECHNOLOGY INFO., https://www.ncbi.nlm.nih.gov/books/NBK44024/ (last visited Sept. 22, 2017) (where efficacy refers to a study under ideal conditions, and effectiveness refers to real-world conditions).

[18] *Id.*

In Phase 2, the sponsor's goal is to evaluate effectiveness for particular indications (diseases, etc.) and to further evaluate short-term side effects and other risks.[19] Phase 2 studies usually involve "no more than" several hundred subjects.[20] A new drug then enters Phase 3 where the primary goal is to gather more data demonstrating safety and effectiveness and to determine appropriate physician labeling information.[21] At this stage, the sponsor will include up to several thousand patients.[22] In each of these phases, the FDA looks at the new drug's safety and efficacy data, and also evaluates the quality of scientific evaluation, including research design.[23] The amount of information required for approval depends on the intended indication and the novelty of the drug.[24] The FDA further requires all sponsors to report any adverse events that occur during any of the clinical trial phases in addition to any serious identified risks.[25]

The final step in the approval of a new drug is for the FDA to evaluate the safety and effectiveness research and to determine the drug's official labeling.[26] If the FDA determines that the new drug is safe and effective for the indicated disease, then the drug will be approved for marketing.[27] If the drug does not pass muster, then the FDA will send a complete response letter detailing why the NDA is not approved.[28] If the drug reaches market, it then enters Phase 4.[29] In Phase 4, the drug is monitored for any unexpected adverse events.[30] If serious unexpected adverse events do occur, the FDA can take action and either issue warnings or withdraw marketing approval.[31]

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[19] 21 C.F.R. § 312.21(b).

[20] *Id.*

[21] 21 C.F.R. § 312.21(c).

[22] *Id.*

[23] 21 C.F.R. § 312.22.

[24] 21 C.F.R. § 312.22(b).

[25] 21 C.F.R. § 312.32.

[26] *Drug Approval Process*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM394845.pdf (last visited Sept. 14, 2017).

[27] *Id.*

[28] *Id.*

[29] *Id.*

[30] *Id.*

[31] *Id.*

European Union

Marketing approval for new drugs in the EU can take two main routes: a centralized procedure or a national procedure. The centralized procedure is governed by the EMA and is required for human medicines intended to treat HIV, AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, viral disease, medicines from biotechnology processes, advanced-therapy medicines, orphan medicines, and veterinary medicines concerning yield enhancement.[32] The national authorization procedure governs the remainder of drug products and has historically been the more common authorization route.[33] Additionally, drugs that are not required to go through the centralized route may use either the mutual-recognition procedure or the national procedure in order to gain access to multiple EU member states.[34]

A drug that is granted marketing authorization by the EMA through the centralized route is valid for marketing in all EU member states as well as Iceland, Norway, and Liechtenstein.[35] The approval process of a drug through the centralized procedure involves a clinical trial phase process like that of the United States.[36] First, clinical trials must be authorized based on a scientific and ethical review to ensure that their design will result in data that is reliable and robust.[37] In multi-country clinical trials, the regulations require a three-phase process.[38] The

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[32] *Authorisation of Medicines*, EUROPEAN MEDS. AGENCY http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47 (last visited Sept. 14, 2017).

[33] *Id.*

[34] *Id.*

[35] *Marketing Authorisation*, EUROPEAN MEDS. AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001595.jsp&mid=WC0b01ac0580b18a3d#Steps%20involved%20in%20obtaining%20an%20EU%20marketing%20authorisation (last visited Sept. 14, 2017).

[36] Gail Van Norman, *Drugs and Devices: Comparison of European and U.S. Approval Processes*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 399, 401 (2016). New regulations concerning clinical trials will take effect in 2019 for the European Medicines Agency through Clinical Trial Regulation EU No. 536/2014. *See Clinical Trial Regulation*, EUROPEAN MEDS. AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp (last visited Oct. 1, 2017).

[37] Commission Regulation 536/2014, arts. 3–4, 2014 O.J. (L 158) 14 (repealing Directive 2001/20/EC, *id.* at 52).

[38] *Id.*, art. 6.5, at 17.

regulations further require the sponsor to report any unexpected serious adverse reactions.[39]

I. PRE-MARKET REGULATION OF ORPHAN DRUGS

A. UNITED STATES

The US Orphan Drug Act became the first of its kind when it was passed in 1983.[40] The goal of the act is to incentivize sponsors to develop drugs to treat rare diseases and conditions by offering financial and other benefits.[41] The Orphan Drug Designation program governs the approval of orphan drugs in the United States.[42] In order to receive orphan designation, the drug must be intended to treat a disease or condition that affects fewer than two hundred thousand people in the United States or is one where there is no reasonable expectation that development costs will be recouped post-approval.[43] An orphan drug's orphan designation may be revoked if the sponsor provides incorrect prevalence information.[44] However, the orphan designation will not be revoked if the prevalence of the disease becomes more than two-hundred thousand people after designation.[45]

The incentives included in the Orphan Drug Act are market exclusivity, user fee waivers, tax benefits, and approval advantages. The market exclusivity period given to orphan drugs is seven years in the United States.[46] This exclusivity applies only to the approved orphan indication.[47] The current user fee set by the Prescription Drug User Fee Act (PDUFA) is $2,038,100.[48] A new drug that has received orphan

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[39] *Id.*, art. 42, at 37.

[40] Dan Phair, *Orphan Drug Programs: Public-Private Partnerships and Current Efforts to Develop Treatments for Diseases of Poverty*, 4 J. HEALTH & BIOMED. L. 193, 203–04 (2008).

[41] *Id.* at 193; *see also* 21 C.F.R. § 316.1(a); *Developing Products for Rare Diseases & Conditions*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/ucm2005525.htm (last visited Sept. 14, 2017).

[42] 21 C.F.R. §§ 316.20–30.

[43] 21 C.F.R. § 316.20(b)(8).

[44] 21 C.F.R. § 316.29.

[45] 21 C.F.R. § 316.29.

[46] 21 C.F.R. § 316.31(b).

[47] 21 C.F.R. § 316.31(a).

[48] This amount is current until October 1, 2017, when the reauthorized act takes effect. Prescription Drug User Fee Rates for Fiscal Year 2017, 81 Fed. Reg. 49,674–78 (July 28, 2016); *see* FDA

designation is exempted from the user fees so long as the drug does not include a non-orphan indication as well.[49] Further, PDUFA, as amended in 2012, authorizes $30 million for each fiscal year through 2017 to be used for grants and contracts for the development or orphan drugs.[50] These grants are awarded to sponsors to help cover the cost of clinical testing.[51] In addition to these grants, orphan drugs are also eligible for tax credits on the cost of clinical research.[52] These tax credits total 50% and have a 20-year carry forward and a 1-year fall back provision.[53]

Moreover, the FDA offers four special approval systems in addition to the above financial incentives for orphan drugs. These are: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. Each of these programs is available to a drug indicated to address an unmet medical need in the treatment of a serious condition.[54] The fast track designation program was approved to encourage the development and expedited review of drugs to treat serious conditions.[55] The advantages of fast track designation include increased opportunities for interaction with the FDA review teams and periodic review of information prior to the submission of a completed application.[56]

Reauthorization Act of 2017 (FDARA), Pub. L. No. 115-52, § 104(c), 131 Stat. 1005, (2017); *see also* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 105(a), 126 Stat. 993 (2012) (amending the Prescription Drug User Fee Act). The prescription drug user fee amount for FY 2018 was announced on September 14, 2017 and will be $2,421,495 for applications requiring clinical data. 82 Fed. Reg. 82, 43244 (Sept. 14, 2017).

[49] Additionally, an orphan drug sponsor can only receive the user fee exemption in FY 2018-2022 if "the applicant . . . submits a certification that its gross worldwide revenues did not exceed $50 million for the preceding 12 months before the exemption was requested." *Draft Guidance: Assessing User Feeds Under the Prescription Drug User Fee Amendments of 2017: Guidance for Industry*, US FOOD & DRUG ADMIN. 11 (Oct. 2017); *Frequently Asked Questions on PDUFA*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm#P112_8652 (last visited September 14, 2017).

[50] Food and Drug Administration Safety and Innovation Act, Pub. L. 112-144, § 906, 126 Stat. 993, 1092 (2012).

[51] *Developing Orphan Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/forconsumers/consumerupdates/ucm107293.htm (last visited Sept. 14, 2017).

[52] *Id.*

[53] Enrique Seoane-Vazquez et al., *Incentives for Orphan Drug Research and Development in the United States*, 3 ORPHANET J. RARE DISEASES 33, 2 (2008).

[54] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS (2014).

[55] *Id*. at 9; *see also* Food Drug and Cosmetic Act (FDCA), 21 U.S.C. § 356 (2012).

[56] U.S. FOOD & DRUG ADMIN., *supra* note 54, at 9.

Breakthrough therapy designation requires "preliminary clinical evidence of a treatment effect that may represent substantial improvement over available therapies for the treatment of a serious condition."[57] Similar to fast track designation, the benefits of breakthrough therapy designation include guidance from the FDA beginning as early as Phase 1, interaction with review teams, including senior managers, and rolling review of application material.[58]

The accelerated approval pathway is intended for diseases that have a long course such that an extended period of time would be required in order to accurately measure the drug's intended clinical benefit.[59] A drug will be approved based on accelerated approval if it is determined that the product has a likely clinical benefit based on a surrogate endpoint.[60] The FDA will consider the disease's severity, rarity, and prevalence in addition to the availability or lack of another treatment.[61]

Finally, priority review designation allows a new drug to receive a marketing application decision within six months as compared to ten months with a standard review application.[62] This program applies to drugs intended to treat a serious condition that will improve the safety or effectiveness compared to a pre-existing drug authorized for the same indication.[63]

B. EUROPEAN UNION

The European Union passed its Orphan Drug Act in 2000.[64] Many of the incentives included in the act are modeled off of the US and Japanese versions of the act.[65] In the EU, a medicinal product is considered an orphan product if the intended indication has a prevalence of no more than five in ten thousand persons, or if it is intended to treat a

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[57] *Id.* at 11.
[58] *Id.* at 13–14.
[59] *Id.* at 15 (offering examples such as HIV and many cancers).
[60] *Id.* at 15.
[61] *Id.*
[62] U.S. FOOD & DRUG ADMIN., *supra* note 54, at 24–25.
[63] *Id.* at 24.
[64] Commission Regulation (EC) 141/2000, 1999 O.J (L 18).
[65] *Id.* at preamble ¶8.

disease that would otherwise remain unstudied except for the act's incentives.[66]

The first incentive available for orphan drugs in the pre-market approval process is protocol assistance.[67] Under this incentive, the sponsor is eligible to receive advice from the EMA on "the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product."[68] Next, the EU regulations allow for community marketing authorization.[69] Under this incentive, all fees payable under community rules are waived.[70]

The EU act also provides market exclusivity incentives. The default market exclusivity period is ten years but may be reduced to six years if the product is sufficiently profitable.[71] Further, an authorized drug may receive twelve years of market exclusivity if that drug is approved to treat a pediatric orphan indication.[72] Market exclusivity under this regulation means that the EMA cannot accept or grant another marketing authorization for that indication of a similar medicinal product.[73] Finally, orphan drugs in the EU also get access to the EMA's centralized marketing authorization procedure which approves drugs for marketing simultaneously across all member states.[74]

There are a number of special approval pathways available through the EMA as well. These include compassionate use, conditional approval, and specific adaptive pathways.[75] The EMA bases these adaptive pathways on three principles: iterative development, real-life evidence gathering, and early involvement in a medicine's development.[76] Iterative development means either "approval in stages,

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[66] *Id.* art. 2.

[67] *Id.* art. 6.

[68] *Id.* art. 6, §1.

[69] *Id.* art. 7, §2.

[70] *Id.*

[71] *Id.* art. 8.

[72] *Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products*, EUROPEAN COMM'N, http://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/orphan_inv_report_20160126.pdf (citing Regulation (EC) No. 1901/2006, 2006 O.J. (L 378/4).

[73] EUROPEAN COMM'N, *supra* note 72, at 2.

[74] EUROPEAN MEDS. AGENCY, *supra* note 30.

[75] *Adaptive Pathways*, EUROPEAN MEDS. AGENCY (2017) http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp.

[76] *Id.*

beginning with a restricted patient population then expanding to wider patient populations," or "confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) considered predictive in important clinical outcomes."[77] Real-life evidence gathering is intended to be used to supplement clinical trial data which may be particularly useful in the area of orphan diseases. The third principle is tangential to the agency advice incentive provided by the FDA.[78] Compassionate use regulations allow a patient to use a drug that is still in the development stages. The EMA explains that "under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorized therapies and who cannot enter clinical trials."[79]

The final specialized pathway offered by the EMA is conditional marketing authorization. Under this program, a sponsor's drug "may be granted a conditional marketing authorization . . . where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in legislation and guidelines."[80] All of the following requirements have to be met in order for a drug to be granted conditional approval:

> the benefit-risk balance of the product is positive; it is likely that the applicant will be able to provide comprehensive data; unmet medical needs will be fulfilled; the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.[81]

The EMA has only approved thirty drugs through this pathway but has had a remarkable 100% success rate meaning that no conditional authorizations have been revoked or suspended.[82]

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[77] *Id.*

[78] *Id.*

[79] *Compassionate Use*, EUROPEAN MEDS. AGENCY (2017), http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c.

[80] *Conditional Marketing Authorization*, EUROPEAN MEDS. AGENCY (2017), http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b.

[81] *Id.*

[82] *Id.*

II. CURRENT LEGAL AND REGULATORY DEVELOPMENTS CONCERNING ORPHAN DRUGS

Orphan Drugs are big business. Studies have found that orphan drugs are expected for account for 21.4% "of worldwide prescription sales by 2022 (excluding generics)."[83] The same study found that the "median cost per patient differential [is] 5.5 times higher for orphan drugs compared to non-orphan [drugs]."[84] Limited access to these orphan drugs continues to be one of the largest barriers to treatment for patients suffering from a rare disease.[85] In the United States, the issue often exists because the patient lacks either health insurance or because the drug is not included in the patient's insurance company's covered prescription formulary.[86] In either scenario, the patient may be priced out of access to the treatment in the US. Along the same theme, the problem of access in the EU is often due to inadequate funding under a single-payer system.[87]

It has been theorized that drug prices are high

> because of three main fundamental aspects of drug development: 1) Drug development is risky. Costly R&D has to be incurred years before any return can be realized. 2) Despite patent protection of new pharmaceuticals, most branded products have high competition on the market with products that provide similar benefits. 3) For breakthrough products, product usually without obvious competition,

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[83] HADJIVASILIOU, *supra* note 1, at 6–8 (further stating that orphan drug sales are forecasted to reach $209bn by 2022).

[84] *Id.*

[85] RARE DISEASE DAY: PATIENTS FACE BARRIERS TO CRITICAL THERAPIES, CELGENE (Feb. 27, 2015), http://www.celgene.com/rare-disease-day-patients-face-barriers/.

[86] *Id.*; *see also* Aris Angelis et al., *Socio-economic burden of rare diseases: A systematic review of cost of illness evidence*, 119 HEALTH POLICY 964, 969 (2015).

[87] The single payer system common in Europe forces governments to look closely at cost-benefit ratios, particularly of new orphan treatments.

> In many cases, the cost is several hundred thousand dollars/Euros per patient per year. With ever-increasing pressures on health budgets, the reimbursement bodies have started to look very critically at the cost-benefit ratio for orphan drugs, leading to a situation where many orphan drugs, although approved throughout Europe, are not available in some countries due to lack of funding. In the US, patient access to expensive orphan drugs is limited by the patient's own lack of health insurance or their inability to pay the portion of the cost of their treatment not covered by their insurance plan.

Anthony K. Hall & Marilyn R. Carlson, *The current status of orphan drug development in Europe and the US*, 3(1) INTRACTABLE & RARE DISEASES RES. 1, 6 (2014).

> the price charged must generally be supported by the economic and clinical value or the product will not be purchased.[88]

In the United States, orphan drugs have a starting cost between $50,000 and $500,000 annually, per patient.[89] These prices in Europe are, on average, 20–40% lower.[90] Some have concluded that this difference in price is a result of the inability of US insurers (including the government) to negotiate or mandate certain prices.[91]

Worldwide, orphan drugs make up close to 20% of all prescription sales.[92] In the United States, the top-selling orphan drug reported sales of $3.65 billion in 2016.[93] Rituxan is the top-selling orphan drug and the twelfth best-selling drug all-time in the United States.[94] The successes of the orphan drug acts are not limited to profit. Since 2010, there has been a sharp increase in the number of orphan drugs being developed each year. The FDA cites that "nearly 200 orphan drugs enter development each year and approximately one third of new drugs approved by the FDA are for the treatment of rare diseases."[95]

The profitability of orphan drugs, as evidenced by the data above, indicates that there may be changes in regulations that could decrease the cost of treatment to patients while not hampering the development of new orphan treatments. To address this topic, this article will first analyze the differences between the legal frameworks in order to better understand why price differences exist between jurisdictions. Second, this article will introduce recent developments affecting orphan drug regulations in both the US and EU. With this knowledge, the article

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[88] Liselore van Ekdom, *Price Setting Orphan Drugs: Identifying the influential factors on the price setting of orphan drug* 28 (Dec. 2006), http://doczz.nl/doc/322949/price-setting-orphan-drugs—-academy-of-managed-care-phar. . . (internal citations omitted) (citing N. Gregson, *Pricing Drugs: Theory and Practice, Challenges and Opportunities*, NATURE REVS., 4, 121–30 (2005)).

[89] It is not uncommon for an orphan drug treatment to have a starting cost of over $200,000. SANJAY BAJPAI & GEMMA SHIELDS, CURRENT TRENDS IN US & EUROPEAN PRICING OF UNIQUE BIOPHARMA PRODUCTS, (May 2015), https://www.ispor.org/research_pdfs/49/pdffiles/PHP111.pdf.

[90] *Id.*

[91] *Id.*

[92] Crystal Kuntz, *How Drug Companies Game The Orphan Drug Act*, AHIP BLOG (Nov. 20, 2015), https://www.ahip.org/how-drug-companies-game-the-orphan-drug-act/.

[93] *Id.*; *see also* HADJIVASILIOU, *supra* note 1, at 11.

[94] "Roche, the company that makes Rituxan makes $55,000 in revenue for each patient who takes this drug." Kuntz, *supra* note 92.

[95] Shannon Gibson & Barbara von Tigerstrom, *Orphan drug incentives in the pharmacogenomic context: Policy responses in the US and Canada*, July J. L. & BIOSCIENCES 263, 264 (2015).

will then explore possible alternatives to the existing legal frameworks based on current practices in the EU and developments that are underway in the US and EU. These current events will inform possible alternatives and contribute to the understanding of whether proposed alternatives are reasonable and/or feasible.

A. ANALYSIS OF THE LEGAL FRAMEWORKS

It is widely reported that drug prices are higher in the United States than elsewhere in the world.[96] The UK Department of Health found that manufacturer prices for primary care products are 2.81 times more in the US as compared to the UK in 2010.[97] However, another study found that the difference in price is smaller for high-cost therapies that treat small patient populations.[98] One goal of this article is to explore whether—and to what extent—the pre-market approval frameworks regulating orphan drugs explain why drugs are more expensive in the US compared to the EU. In an attempt to answer this question, this section of the article will analyze the differences in the incentives provided in the pre-market orphan drug approval frameworks outlined above.[99]

1. Data Requirements: Prevalence & Safety/Efficacy

The first topic discussed is differences in data and evidentiary requirements. Developing an orphan drug implies that there is not a large population of patients to draw from. This simple fact is one reason the treatment of rare diseases differs from the treatment of common diseases: access to enough data for clinical trials is more challenging and the amount of data required varies based on the indication. Further, the United States and the European Union differ in views on data for prevalence determinations that impact the orphan status of a drug.

When determining whether a condition is a rare disease, the United States emphasizes "demonstrating the scientific rationale and disease prevalence, whilst in the EU there are two additional

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[96] Jesper Jorgensen et. al., *A price comparison of recently launched proprietary pharmaceuticals in the UK and the US*, Sep. J. MKT. ACCESS & HEALTH POL'Y 4:32754, 1 (2016).

[97] *Id.* at 2.

[98] *Id.* at 6.

[99] *See supra* Section I.

requirements: *i)* that the condition is life-threatening or seriously debilitating, and *ii)* that there is currently either no satisfactory method . . . or that the new product will be of significant benefit."[100] In the EU,

> [the] criteria require demonstrating prevalence *in the European Community* and it is not enough to cite prevalence figures for one or two countries only. . . . It is not considered adequate to state that the prevalence 'obviously' meets the criterion, nor to simply quote sources such as OrphaNet. Instead, it is necessary to provide a properly referenced analysis and, if the prevalence figure is close to the cut-off of 5 per 10,000, some sensitivity analyses may also be needed to convince the COMP that the true prevalence is really within the limits.[101]

In the United States,

> [the] application requires documentation with authoritative references of the prevalence of the disease or condition. . . . If the basis for the application is that there is no reasonable expectation of recovering the costs of development, justification must be provided for production and marketing costs the sponsor has incurred and expects to incur during the first seven years after the drug is marketed in the US.[102]

Prevalence does not have to be shown in each region of the United States nor in each individual state.

The EU and the US have recently come together in an effort to align their processes to make it easier for companies to develop treatments for rare diseases by allowing more international data usage. For example, a recent development is the common application.[103] The FDA and the EMA both recognize the importance of minimizing duplicative efforts in order to ensure that new drugs are authorized as quickly as possible. In this vein, the FDA and the EMA recently agreed to and published general principles concerning parallel scientific advice in human medicinal products.[104] The stated goal of the program is to "provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues

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[100] Hall & Carlson, *supra* note 87, at 3.

[101] *Id;* COMP stands for "Committee for Orphan Medicinal Products." *Id.*

[102] *Id.* at 4.

[103] *Id.*

[104] EUROPEAN MEDS. AGENCY, GENERAL PRINCIPLES EMA-FDA PARALLEL SCIENTIFIC ADVICE, EMA/309801/2017 (2017), http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf.

during the development phase of a new medicinal product" in order to avoid unnecessary testing replication.[105]

The EU and US frameworks are similar when it comes to clinical trial processes but they differ in how each governing organization (FDA or EMA) approaches data standards relating to safety and efficacy. No drug is considered for approval in either framework until it has gone through each system's clinical trial process, which largely mirror one another. The EMA's guidelines for clinical trials are outlined in Directive 2001/20/EC.[106] In the EU,

> Commission Regulation (EC) No. 507/2006 of 29 March 2006 foresees, in the case of certain categories of medicament, i.e. medicinal products for seriously debilitating or life-threatening disease, emergency situations in response to public health threats and for orphan diseases, to grant marketing authorizations on the basis of less complete data than is normally the case, said authorizations being called 'conditional marketing authorizations.'[107]

The EMA also has a clinical trial directive based on the regulations adopted in the United States.[108] This directive accomplishes four things. First, it "provides specific time scales for ethics review."[109] Second, it "requires submission to the Licensing Authority of an application for authorization."[110] Third, the directive "regulates manufacturing of the investigational medical product."[111] Finally, this directive authorizes audits similar to those found in the US regulations.[112]

Additionally, the EMA may approve drugs under conditional authorization so that unmet medical needs are addressed as quickly as possible. The EMA's criteria when approving a conditional authorization are:

- The benefit-risk ratio must be positive
- "Unmet medical needs" (i.e., conditions for which there are no available satisfactory methods for diagnosis, prevention or treatment

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[105] *Id.*

[106] Council Directive 2001/20, 2001 O.J. (L 121) 34 (EC).

[107] 1-7 International Pharmaceutical Law and Practice §7.04 [4][b] (2016).

[108] BIOTECHNOLOGY AND THE LAW, 479, 500 (Hugh B. Wellons ed., 2007) (citing to Council Directive 2001/20/EC, art. 2, 2001 O.J. (L 121/34)).

[109] *Id.* at 501.

[110] *Id.*

[111] *Id.*

[112] *Id.*

> or the product is of significantly major therapeutic advantage than a similarly listed product must be fulfilled.)
>
> • High likelihood that comprehensive clinical data will be provided within an agreed timeframe
>
> • Additional data are required, but the benefit(s) to public health of immediate availability must outweigh the risk(s).[113]

This process appears equitable and advantageous to patients who want some hope of treatment; however, this sort of structure comes with numerous risks. The United States has allowed this process through similar programs such as right to try laws and compassionate use guidelines.[114] Under these programs, the United States allows patients suffering from serious or life-threatening diseases to access drugs that are currently in development.[115] Patients assume the totality of the risks once they request access to a drug that has not been approved. What is disadvantageous about these programs from the perspective of a drug manufacturer is that, in the United States, adverse events that occur to a patient using a new drug under the compassionate use program must be reported and this could adversely impact the final market approval of the drug.[116]

Conversely, the European system treats their compassionate use equivalent as a form of post-market clinical trial similar to a Phase 4 FDA-governed study.[117] There are numerous policy considerations that arise when discussing right-to-try regulations. For example, in the United States, because of the adverse reporting requirements, drug sponsors do not want outside patients involved in their data because the petitioning patient's condition may not meet the intended use of the new drug, or the patient's treatment may be unsatisfactorily monitored. In addition, these concerns could also include the impact of other drugs the patient is taking that are not part of the clinical trial protocol, and any number of other control factors that may impact the adverse event data of a new

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[113] Rapulu Ogbah, *Orphan medicinal products – A European process overview*, 12 REG. RAPPORTEUR 2, 7 (2015), https://embed.topra.org/sites/default/files/regrapart/1/6038/2015-2-regulatory-rapporteur-orphan-process-overview.pdf.

[114] *Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers Guidance for Industry*, U.S. FOOD & DRUG ADMIN. (2016), https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf.

[115] *Id*.

[116] *Id*.

[117] EUROPEAN MEDS. AGENCY, *supra* note 79.

drug.[118] Each of these elements could impact a drug's initial market price because adverse events can be detrimental to a drug's safety and effectiveness data and may disrupt the flow of a clinical trial phase.

Guidance documents from the EMA and the FDA also differ concerning language related to clinical trial participant numbers. The "overall goals of drug development programs are to evaluate whether a drug is effective in treating or preventing a disease or condition, assessing the magnitude and frequency of that effect, and to assess the risk of the drug, thereby enabling a benefit-risk comparison and appropriate labeling."[119] One way the FDA helps drug sponsors in the approval process is by publishing guidance documents. These guidance documents are not legally binding but they explain the FDA's thought process on a range of topics including orphan drug data requirements and can be very helpful for industry sponsors. For example, the FDA has explained through guidance documents that specific numbers of study participants are not required.[120] FDA guidance states that "[t]here is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease."[121] The FDA will take a "case-by-case" approach to determining whether safety and efficacy are proven based on the data provided.[122] The factors the FDA looks at when making this determination are: "the persuasiveness of the data (e.g., comprehensiveness and quality), the nature of the benefit provided (or expected in the case of surrogate endpoints), the length of treatment or exposure, the patient population that would be treated after marketing approval, and the concern for potential of harm from the treatment."[123] Additionally, the FDA has also noted that

> treatment duration should also be appropriate for the disease under study (e.g., chronic as compared to acute conditions). When conducting a benefit-risk assessment for a drug for a serious or life-

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[118] For more of a discussion on compassionate use, see BIOTECHNOLOGY INNOVATION ORG., BIO STATEMENT ON COMPASSIONATE USE, (Mar. 26, 2017), https://www.bio.org/articles/bio-statement-compassionate-use.

[119] U.S. FOOD & DRUG ADMIN., RARE DISEASES: COMMON ISSUES IN DRUG DEVELOPMENT: GUIDANCE FOR INDUSTRY 11 (2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf.

[120] *Id.* at 12.

[121] *Id.*

[122] *Id.*

[123] *Id.* at 12–13.

> threatening illness, FDA also recognizes that greater risks may be accepted for a treatment that is an advantage over available therapy.[124]

Finally, the FDA's guidance emphasizes

> FDA's commitment to expediting the availability of drugs for serious diseases as soon as it can be concluded that the benefits of the drugs exceed their risks, while preserving appropriate standards for safety and effectiveness, especially when these patients have unmet needs, as is often the case with patients with rare diseases.[125]

Efficacy endpoints are crucial to fulfilling the FDA's commitment of making drugs available for people with rare diseases who have no other treatment options. Efficacy endpoints are defined endpoints in a clinical trial.[126] The goal of the endpoint is to signal the end of a clinical trial that has met the objectives.[127] Like legal research, it is sometimes hard to decide when the effectiveness research is complete. Because of this, the FDA encourages sponsors to consider the following factors when determining an efficacy endpoint:

> • An understanding of the disease, including the likelihood, range, and course of clinical manifestations associated with the disease (disease definition). Sponsors can often obtain this knowledge, along with disease characteristics of patient subsets, from a natural history study of the disease.
>
> • An understanding of the clinical characteristics (manifestations and timing) of the specific population targeted by the drug (which may be a subset of the total population with a disease).
>
> • An understanding of which aspects of the disease are meaningful to the patient and might also be affected by the drug's activity. This evaluation is influenced by knowledge of the pathophysiology of the disease and prior experience (if any) with the drug or related drugs, including nonclinical and clinical effects and pharmacology.

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[124] *Id.* at 13.

[125] *Id.* (emphasis added).

[126] U.S. FOOD & DRUG ADMIN., GUIDANCE: CLINICAL TRIAL ENDPOINTS FOR THE APPROVAL OF CANCER DRUGS AND BIOLOGICS 2–5 (2007), https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

[127] *Id.* at 4.

> • Knowledge of what patient assessments exist or might be refined or developed for use as outcome assessment tolls to measure selected aspects of the disease.[128]

The FDA continues to guide sponsors on characteristics an assessment tool must have. Factors of reliability and resistance to bias are particularly important. For example, "reliability is especially important when clinical trials assess small numbers of patients" like with orphan drugs.[129] On the factor of resistance to bias, the FDA comments that "although treatment-assignment blinding is important to lessening the potential for bias in study results, ensuring perfect blinding is difficult for many treatments. An assessment that is less readily influenced by a patient's or investigator's knowledge of treatment assignment can improve confidence in the study results."[130] These guidances are important because they state what the FDA is looking for which can save sponsors time and money in the protocol design phase.

In Europe, the EMA will grant a conditional marketing authorization when the Committee for Medicinal Products for Human Use (CHMP) has found that the following requirements are met:

> the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive; it is likely that the applicant will be in a position to provide the comprehensive clinical data; unmet medical needs will be fulfilled; the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.[131]

Further, the EMA encourages sponsors to work with them throughout the process to ensure that clinical trials are designed in a way that will allow the EMA to approve an orphan drug if the data indicates safety and efficacy.[132] The CHMP is the committee within the EMA responsible for

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[128] U.S. FOOD & DRUG ADMIN, DRAFT GUIDANCE: RARE DISEASES: COMMON ISSUES IN DRUG DEVELOPMENT GUIDANCE FOR INDUSTRY 8–9 (Aug. 2015), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf.

[129] *Id.* at 9.

[130] *Id*.

[131] EUROPEAN MEDS. AGENCY, EUROPEAN MEDICINES AGENCY PRE-AUTHORISATION PROCEDURAL ADVICE FOR USERS OF THE CENTRALISED PROCEDURE 24 (2017), http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf.

[132] As an example:

making recommendations concerning new drug data.[133] The EMA bases their analyses on "a comprehensive scientific evaluation of data. They determine whether the medicine meets the necessary quality, safety and efficacy requirements and that it has a positive risk-benefit balance."[134] Additionally, CHMP publishes guidance documents (similar to the FDA's) about clinical efficacy and safety guidelines for a range of condition areas.[135]

The EMA's guidance documents explain what it is looking for at each clinical trial stage and provide specific guidance concerning special populations who pose unique risk/benefit considerations.[136] In Phase 1, the EMA looks at initial safety, tolerability, pharmacokinetics, pharmacodynamics, and early data concerning drug activity (e.g.

> For instance, the applicants may request CHMP scientific advice or protocol assistance, as applicable, on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in Article 2 and fulfils the requirement laid down in Article 4(1)(c) ("unmet medical needs will be fulfilled") of Regulation (EC) No 507/2006. It is recommended to discuss in advance the development plan and design of the intended studies (both the pre-authorisation studies and studies to be proposed as specific obligations for collection of remaining data after authorisation).

Id. at 25.

[133] COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP), EUROPEAN MEDS. AGENCY (2017), http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp&mid=WC0b01ac0580028c79.

[134] *Id.*

> The size of a trial is influenced by the disease to be investigated, the objective of the study and the study endpoints. Statistical assessments of sample size should be based on the expected magnitude of the treatment effect, the variability of the data, the specified (small) probability of error (see ICH E9) and the desire for information or subsets of the population or secondary endpoints. . . In some circumstances a larger database may be needed to establish the safety of a drug. ICH E1 and ICH E7 suggest a minimum experience to assess safety for a registration database for a new indication. These numbers should not be considered as absolute and may be insufficient in some cases (e.g. where long-term use in healthy individuals is expected).

EUROPEAN MEDS. AGENCY, ICH TOPIC E 8 GENERAL CONSIDERATIONS FOR CLINICAL TRIALS 12 (1998), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf.

[135] EUROPEAN MEDS. AGENCY, CLINICAL EFFICACY AND SAFETY GUIDELINES (2017), http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&mid=WC0b01ac0580027549.

[136] EUROPEAN MEDS. AGENCY, ICH TOPIC E 8 GENERAL CONSIDERATIONS FOR CLINICAL TRIALS, *supra* note 134, at 10.

potential therapeutic benefit).[137] Phase 2 is the primary step in therapeutic exploration and an important hurdle to pass. Here, the EMA guides sponsors that the "important goal for this phase is to determine the dose(s) and regimen for Phase [3] trials."[138] Next, the EMA looks for therapeutic benefit evidence in Phase 3 studies.[139] Finally, like the FDA, the EMA then considers evidence post-marketing approval in Phase 4.[140]

The main difference between the two frameworks is that the FDA provides a more hands-on approach to study design and appears to interact more frequently with sponsors of orphan drugs throughout the process. The EMA is not hands-off; instead, their system conveys a less shared approach to orphan drug approval. These differences are not trivial because different data requirements may impact the timing of a drug's marketing approval because longer studies cost more money. Moreover, higher research and development costs are likely to lead to a higher initial price once the orphan drug is granted market approval. In the EU, a drug company may profit earlier based on a conditional approval; however, in the US, a sponsor may end a trial sooner once it is clear the data are not sufficient to gain FDA approval.

In conclusion, the analysis of how each framework handles data does not clearly answer the question of why similarly situated drugs are priced differently across the frameworks. The differences between the systems are small enough that they likely do not produce outcomes varied enough to explain the price difference. Data requirement differences may certainly be a contributing factor, but it is necessary to look elsewhere for a more substantial explanation of the price differences.

2. Special Approval Pathways

The second topic analyzed is how the special approval pathways differ between the two frameworks. The FDA leads the EMA when it comes to accelerated pathways for drugs that fulfill an unmet medical need.[141] In the US, a drug can obtain "fast track designation," which

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[137] *Id.* at 8–9.

[138] *Id.* at 9.

[139] "Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population." *Id.*

[140] *Id.* at 9.

[141] *Id.* at 5.

allows for a rolling review and offers more meetings with the FDA.[142] Additionally, the FDA provides guidance on effective drug development for designated breakthrough therapies,[143] which includes a commitment "involving senior managers."[144] Finally, the FDA offers priority review designation, which, if granted, reduces the new drug application review time to six months from ten months.[145] The EMA's sister programs of the FDA's fast-track designation or breakthrough therapy designation program are the conditional approval program and the program for approval under exceptional circumstances.[146] Under this second program, the EMA may approve a drug even where there is incomplete data.[147] Additionally, under the EMA's accelerated assessment program, the review time is reduced to four months from seven months.[148]

When the two programs are compared, it appears that the US provides more access to periodic review. More access to agency review arguably allows the pre-market approval process to be more transparent which may entice companies to stop research earlier once it becomes clear that the data on safety and efficacy will not be sufficient for approval. On the corollary, more periodic review may also give the industry a better idea of what studies the FDA is looking for which can further reduce costs. The EU also has periodic review but it is less active than the US's model, at least on paper. For example, "[the EMA] has provided scientific advice for orphan designated products to ensure any proposed deviations from regular procedures are discussed and decided

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[142] *Id.* at 5.

[143] The following is an explanation of this special approval pathway:

> In 2012, FDA signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA) which created a new expedited drug development tool, known as the "breakthrough therapy" designation. This new designation allows FDA to assist drug developers to expedite the development and review of new drugs that have preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases.

Hall & Carlson, *supra* note 87, at 5.

[144] *Frequently Asked Questions: Breakthrough Therapies,* U.S. FOOD & DRUG ADMIN. (2017), https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/fdasia/ucm341027.htm.

[145] Hall & Carlson, *supra* note 87, at 5.

[146] *Id.* at 5.

[147] *Id.* (explaining further that "approval is conditional on providing additional post-approval data. After confirmation, authorization is converted to a normal approval.").

[148] *Id.* (stating that under accelerated assessment, review time for orphan drugs is reduced from 210 to 150 days).

on with EU regulators during the medicine's development."[149] Additionally,

> [s]ponsors [are encouraged to] submit annual development reports summarizing the status of the development of the medicine, including reviews of all ongoing clinical trials, preview of proposed investigations, and a list of anticipated or current problems in the process, difficulties in testing and potential changes that may have an impact on the medicine's orphan designation.[150]

The overarching difference between the systems is a hands-on, rolling approach, versus a periodic review or updating approach.

Additionally, there is arguably more room in the US system to classify orphan drugs as breakthrough therapies if they are intended to treat serious conditions.[151] This may expand approval options and allow sponsors to take advantage of the incentive structures. The EU does, however, provide consideration for the difficulty of obtaining data in the context of rare diseases.[152] By approving orphan drugs under exceptional circumstances, the EU can theoretically get more orphan drugs to the people who are placing their last hope in the new and novel treatment.[153] There are ethical questions that arise, but, like in oncology trials, a greater risk is generally more acceptable when the prognosis is fatal. The FDA has a program that produces roughly the same result, called expanded access (also referred to colloquially as compassionate use) which is available on a federal level through the FDA and on a state level through right-to-try laws.[154]

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[149] Ogbah, *supra* note 113.

[150] *Id.*

[151] *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (2017), https://www.fda.gov/forpatients/approvals/fast/ucm405397.htm.

[152] EUROPEAN MEDS. AGENCY, *supra* note 79.

[153] *See id.* (generally describing the exceptional circumstances provision available in the EU).

[154] U.S. FOOD & DRUG ADMIN., *supra* note 114, at 2.

> Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient rather than to obtain the kind of information about the drug that is generally derived from clinical trials. FDA has a long history of facilitating expanded access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives. FDA revised its IND regulations in 2009 by removing the existing regulations on treatment use and creating subpart I of part 312 to consolidate and expand the various provisions regarding expanded access to treatment use of investigational drugs.

Id. Expanded access is regulated by 21 C.F.R. Part 312.300 and will only be granted if the patient suffers from a serious disease or condition that is immediately life threatening. U.S. FOOD

The comparison of the two frameworks on this topic leads to the conclusion that US drugs should be cheaper because sponsors are helped more through the approval process by the FDA. However, we know that this is not the case and therefore, we are forced to look to other differences in an effort to assess whether the price differences are in fact due to the regulations or, in the alternative, how much the regulations factor into a drug's high starting market price.

3. Tax Incentives

The tax incentive has been particularly enticing for large pharmaceutical companies in the United States but is not a specific EU-wide incentive under the EMA's orphan drug legislation. Instead, Europe leaves the availability of tax incentives to individual member countries.[155] The cost of developing a new orphan drug is still incredibly high in the US despite the availability of a tax credit for up to half of the clinical trial expenses under current US regulations.[156] This is due in large part to basic economics: large drug companies are working to develop numerous drugs at once, on the premise that only a very small percentage of those drugs over a decade will gain marketing approval. Therefore, the companies need to recoup the cost of research that did not result in a new drug—but that may have contributed to the overall advancement of medicine.[157] The tax incentive of the Orphan Drug Act allows these

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& DRUG ADMIN., EXPANDED ACCESS: INFORMATION FOR PATIENTS, https://www.fda.gov/forpatients/other/expandedaccess/ucm20041768.htm (last visited Sept. 20, 2017); Carrie Feibel, *Patients Demand the 'Right to Try' Experimental Drugs, But Costs Can Be Steep*, NPR (Mar. 3, 2017, 2:17PM), http://www.npr.org/sections/health-shots/2017/03/03/517796956/patients-demand-the-right-to-try-experimental-drugs-but-costs-can-be-steep (mentioning that 33 U.S. states already have right-to-try laws).

[155] Segundo Mariz et al., *Worldwide collaboration for orphan drug designation*,15 NATURE REVS. DRUG DISCOVERY 440, 441 (2016).

[156] *See supra* Section I.A.

[157] Alden F. Abbott, *FDA Reform: A Prescription for More and Better Drugs and Medical Devices*, HERITAGE FOUNDATION (June 20, 2016), http://www.heritage.org/government-regulation/report/fda-reform-prescription-more-and-better-drugs-and-medical-devices (explaining that

> the cost of developing a new FDA-approved drug is astronomical: '[i]n part because so many drugs fail, large pharmaceutical companies that are working on dozens of drug projects at once spend [around] $5 billion per new medicine.' When they do bring forth pharmaceutical treatments, drug companies must recoup the hundreds of billions of dollars in costs that they have absorbed in pursing unfruitful as well as successful R&D.).

companies to recoup fifty percent of the costs associated with clinical trials which can equate to over $200 million per new drug.[158] As a result of these tax incentives and the fact that orphan drugs are designed to treat rare populations, drug companies can run clinical trials sufficient for FDA marketing approval at a much lower over-head cost.[159] A 2015 study found that the average Phase 3 trial size in orphan drugs was 538 people compared to 1,558 people in non-orphan drugs.[160] The same study compared the differences in Phase 3 trial costs and concluded that non-orphan drug sponsors can expect to spend $16.2 billion more than orphan drug sponsors in this clinical phase alone.[161] Despite the significantly lower cost of clinical trials, due in part to the tax incentive, the average cost per patient of an orphan drug in 2014 was $111,820 compared to $23,331 for a non-orphan drug.[162] These prices continue to rise with an average growth rate of over 4% annually.[163] Along this line, "[t]he profitability of these medications is fueled by orphan drugs receiving approvals for other more prevalent non-orphan indications or capturing significant off-label use for other non-orphan diseases."[164]

While the tax incentive may not be responsible for a difference in drug pricing, it is an important incentive. Researchers have predicted that the tax incentive alone is responsible for nearly one-third of the drugs that have begun development since 1983.[165] In this report, the authors conclude that one of the most important roles the tax credit plays is in attracting sufficient investors because it reduces the amount needed by over $100 million in many cases.[166] Additionally, other researchers have found that the tax credits will total more than $1.75 billion in 2016.[167] This research is further supported by Kathleen Miller who has

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[158] BIOTECHNOLOGY INDUS. ORG. & NORD, IMPACT OF THE ORPHAN DRUG TAX CREDIT ON TREATMENTS FOR RARE DISEASES 7 (2015), https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf.

[159] AHIP, ORPHAN DRUG UTILIZATION AND PRICING PATTERNS (2012-2014) 3 (2016), https://www.ahip.org/wp-content/uploads/2016/10/OrphanDrug_DataBrief_10.21.16.pdf.

[160] *Id.* at 17.

[161] *Id.* at 19.

[162] HADJIVASILIOU, *supra* note 1, at 9.

[163] *Id.* at 10.

[164] AHIP, *supra* note 159, at 3.

[165] BIO & NORD, *supra* note 158, at 19.

[166] *Id.* at 16–20.

[167] NICHOLAS BAGLEY, THE BENEFITS AND COSTS OF PROMOTING THE DEVELOPMENT OF NEW ORPHAN DRUGS 4 (2017), http://theincidentaleconomist.com/wordpress/wp-content/uploads/2017/02/2.12-orphan-drug.pdf.

connected the announcement of orphan designation with increased stock prices.[168]

Changing the tax incentive structure in the US under the Orphan Drug Act is predicted to have deleterious effects on the development of future orphan drugs. One study suggests that "in the absence of the [orphan drug tax credit,] 67 orphan drugs, or 33%, would likely not have been developed over the past 30 years."[169] Taking a prospective approach, the same study concludes that, "going forward, if the [orphan drug tax credit] were repealed, it is estimated that 57, or 33% fewer, new orphan drugs would be approved over the next 10 years."[170]

In conclusion, the available research shows it is likely that the US tax credit incentive has been successful at contributing to the rise in orphan drug research in the United States. It is not determinable, however, whether this incentive has either decreased or increased the cost of orphan drugs because there is no equivalent centralized tax incentive available through the EMA.

4. Market Exclusivity

Market exclusivity is the area where the frameworks differ significantly and therefore offers the best insight into whether and to what extent the legal systems in the US and EU impact price points for orphan drugs. To review, market exclusivity in the US is seven years, with the potential to add six months if the drug is approved for a pediatric indication.[171] In the EU, the base market exclusivity is ten years, while pediatric drugs can receive 12 years.[172] That period of ten years may be reduced to six years if the drug is shown to be profitable.[173]

Market exclusivity seems to be the most important incentive offered by each framework impacting the price of an orphan drug

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[168] Kathleen L. Miller, *Do investors value the FDA orphan drug designation?*, 12 ORPHANET J. RARE DISEASES 114, 5 (June 2017) (concluding that "investors place positive, statistically significant, value on the orphan drug designation. These results were especially pronounced for oncology drugs and the smallest companies.").

[169] EY, *Impact of the Orphan Drug Tax Credit on treatments for rare diseases: prepared for the Biotechnology Industry Organization and the National Organization for Rare Disorders* i (June 2015), https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf.

[170] *Id.* at i–ii.

[171] See *supra* Section I.A.

[172] *Id.*

[173] *Id.*

because of its promise of profit for sponsors. In the US, an extra six months of market exclusivity can easily reach $1 billion in additional revenue.[174] Thus, a baseline difference of three years is a significant timeframe when analyzing the initial market price of an orphan drug. This is therefore one incentive where the EU offers sponsors of orphan drugs an opportunity to price their drug lower as compared to the US. For a "blockbuster" orphan drug like Rituximab, this metric may swing the other way. Rituximab had $6.9 billion in sales in 2014,[175] which would likely result in the EMA reducing its market exclusivity period to six years. However, for biologics in particular, it is difficult to develop a generic drug (a biosimilar), and thus, even though a drug's market exclusivity period for a biologic orphan drug may expire, it has not been the case that there is a biosimilar waiting in the approval process to consume a portion of the market.[176]

Compared with other incentives, market exclusivity exceeds the financial benefits of all other incentives combined. Therefore, this may be the most influential factor from the legal perspective when addressing the question of whether and how the legal frameworks impact the price of a new orphan drug. Changing market exclusivity periods is a delicate game though, and finding the balance between incentivizing new drug development and promoting lower costs is a moving target due to changes in biosimilar regulations and the rise of specialized medicine for targeted therapies.

In conclusion, it is not clear that the legal frameworks are principally responsible for the high cost of orphan drugs. This conclusion is, however, not entirely surprising given the multiple fields that impact health care expenditure. Therefore, the easiest answer is the most likely: it depends on a number of different factors, including regulations. Recent developments in both the US and EU address some of these different

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[174] For example, in 2015 Merck reported $1,794 million in annual sales of its brand name drug Remicade. Form 10-K, United States Securities and Exchange Commission, Merck & Co., Inc., 1 (2016), http://www.merck.com/investors/financials/2015%20Form%2010-K_FINAL%20(r879).pdf.

[175] *Id.*

[176] As of September 14, 2017, there were seven FDA approved biologics with an FDA approved biosimilar. U.S. FOOD & DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, LIST OF LICENSED BIOLOGICAL PRODUCTS 1–4 (Sept. 14, 2017), https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf

factors, such as the impact of court decisions on current and future regulations and regulatory practice.

B. RECENT DEVELOPMENTS IN THE UNITED STATES

The actions of the FDA have been the subject of numerous lawsuits over the past decade. Despite legal challenges, the power of the FDA to regulate both the approval process and the advertising of orphan drugs remains in place. For example, the FDA has been the subject of lawsuits related to generic drug approvals, first-amendment issues, and the timeliness of application responses. These court cases are instructive because they signal what future challenges will arise in this area and may foreshadow future regulatory developments in response to the outcomes.

In 2015, the Southern District Court of Maryland affirmed the FDA's power to approve generic versions of prescription drugs.[177] The 1984 Hatch-Waxman Amendments (part of the Drug Price Competition and Patent Term Restoration Act of 1984) "permits a drug manufacturer to submit an abbreviated new drug application (ANDA) requesting approval of a generic version of an already approved drug product."[178] To be approved by the FDA, the "ANDA must include data showing that the generic drug product is bioequivalent to the innovator product."[179] The product at issue in *Ostuka Pharm* was Abilify, a blockbuster drug that was approved for orphan drug designation to treat Tourette's Disorder in 2006.[180]

> Ostuka [contended] that by receiving . . . pediatric approval, which is protected by orphan drug exclusivity, it is entitled to a seven-year period of total market exclusivity. . . . During that time, Ostuka argues that the law precludes FDA from approving any generic version of Abilify for any of its FDA-approved indications.[181]

This case provides an example of how the orphan drug incentives are being used by companies to increase profits of drugs used principally for non-orphan indications. It is easier for a company like Ostuka to sell Abilify at a lower price because it is widely used outside of an orphan

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[177] Otsuka Pharm. Co., Ltd. v. Burwell, 2015 U.S. Dist. LEXIS 68230, at *32 (D. Md. May 27, 2015).

[178] *Id.* at *5.

[179] *Id*.

[180] *Id.* at *11.

[181] *Id.* at *12.

disease population. This is one example of how the cost of an orphan drug can be lowered. Therefore, in the context of targeted therapies where biologics are developed for a very specific gene sequence, a company has little ability to sell a drug outside its target market.

The court in *Ostuka Pharm* analyzed the FDA's decision to approve a generic drug for the non-orphan indications under *Chevron*.[182] Deference to the FDA was given because

> the complexity of the statutory regime at issue, FDA's expertise in regards to this complex scheme, and the fact that FDA's decision on the scope of Otsuka's exclusivity under the FDCA was based on its longstanding understanding of its general carve-out authority . . . and its precedent addressing the specific question of whether to approve ANDAs that carve out pediatric information protected by orphan drug exclusivity.[183]

The FDA's authority was further affirmed in *Baker Norton Pharms* where the US District Court for the District of Columbia upheld the FDA's decision that a determination based only on the active ingredient in the orphan drug context was permissible.[184] The issue in this case was that two sponsors were given orphan drug approval for the same condition which created "a race for orphan drug approval since both Taxol and Paxene had been granted orphan drug designation; whichever drug was approved first would receive the seven-year period of market exclusivity."[185] The court held that the FDA's interpretation of "drug" in the orphan drug act exclusivity regulation was permissible.[186] In determining that the drugs were the same based only on active ingredients, the FDA furthered legislative intent because "the financial incentive for companies to develop such drugs is provided by the period of market exclusivity, which would be undermined if other companies could develop drugs with the same active moiety but minor differences in active ingredients."[187]

In another case, the FDA's power to approve a drug with one less side effect and thus nullify another orphan drug's market exclusivity

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[182] *Id.* at *20.
[183] *Id.* at *20–21.
[184] Baker Norton Pharms., Inc. v. U.S. Food and Drug Admin., 132 F. Supp. 2d 30, 37 (D.D.C. 2001).
[185] *Id.* at 6.
[186] *Id.* at 37.
[187] *Id.* at 38.

was upheld because it was a permissible interpretation of the language, "clinically superior."[188] This holding, as well as the previous holdings show that the courts are willing to give the FDA broad deference in furthering the mission of the orphan drug act. By having strict definitions of "clinically superior" and "drug," the FDA promotes constant development and improvement of existing orphan drugs because companies are at risk of losing their market share if their drug becomes inferior.

The topic of orphan drug regulations and the price of prescription drugs is widely discussed. In fact, it is one of the current "hot topics" in the United States and across the world. Patients in the United States spent nearly $424 billion in 2015 on prescription drugs, including orphan drugs.[189] Health care costs and coverage in the United States is a hotly debated topic with no easy answers concerning cost containment. For example, insurance companies criticize pharmaceutical companies for high prices which they have to pass along to the consumer, and pharmaceutical companies criticize insurance companies for not including drugs for rare diseases or off-label drugs in their formularies of coverage.[190] This debate is at the center of many recent regulations and congressional committees. For example, Senators Susan Collins, R-Maine, and Claire McCaskill, D-Montana, have recently

> launched a large-scale investigation into sudden and aggressive price increases by four drug makers, including Turing and Valeant, requesting that the companies turn over documentation to justify the hikes. And earlier this year, Rep. Cummings held a similar congressional hearing, releasing reams of internal memos to the public that detailed the profit goals that companies like Turing were trying to reach by setting the price hikes.[191]

Even though this inquiry is not directly concerned with orphan drugs, it signals congressional awareness of the problem of high drug prices.

Congress has acted numerous times over the last ten years to fight rising costs, mostly through acts designed to ease the process for

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[188] Berlex Lab v. FDA, 942 F. Supp. 19, 27 (D.D.C.1996).

[189] IS THERE A CURE FOR HIGH DRUG PRICES?, CONSUMER REPORTS 1 (2016) http://www.consumerreports.org/drugs/cure-for-high-drug-prices (finding that "America spends a tremendous amount of money for prescription drugs - $424 billion last year alone before discounts, according to a new report by IMS Institute for Healthcare Informatics, a firm that tracks the pharmaceutical industry.").

[190] *Id.*

[191] *Id.*

generic approval. In 2012, Congress approved the Food and Drug Administration Safety and Innovation Act (FDASIA) which allows the FDA to collect user fees, increases access to new products, increases stakeholder involvement in the new drug approval process, and improves the safety of the drug supply chain.[192] The result of this legislation has been a steep decline in drug shortages which helps avoid premium prices.[193] More recently, the US has also enacted legislation encouraging generic competition for biologic drugs. This is an area where the US has lagged behind Europe: the FDA has approved four biosimilar (biologic generics) compared to Europe's twenty-two approved biosimilars.[194] The approval of biosimilars is governed by the Biologics Price Competition and Innovation Act (BPCIA), which creates a pathway for the FDA to approve generic biologic drugs.[195] Under BPCIA, a biologic is "biosimilar" and will be approved as a generic if data shows that "the product is 'highly similar' to an already-approved biological product."[196]

Academics and policy-makers in the US have begun discussions about what some see as the "gaming" of the Orphan Drug Act. In the last decade, sponsors have been able to get orphan status for drugs that arguably do not "adhere to the original intent of the law."[197] Critics of this "gaming" argue that "the exploitation of these imperfections in the Orphan Drug Act contribute to the high price of biologic drugs as over 60% of Orphan Drugs are biologics."[198] Having orphan status has implications on the cost of the drug beyond the benefits seen by the sponsor. For example, in 1992, Congress approved the 340B drug program, under which drug manufacturers are required to discount drugs sold to hospitals and clinics serving poor communities.[199] The sponsors

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[192] Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-144, 126 Stat. 993 (2012).

[193] LISELORE VAN EKDOM, PRICE SETTING ORPHAN DRUGS 32 (2006).

[194] FIONA SCOTT MORTON & LYSLE T. BOLLER, ENABLING COMPETITION IN PHARMACEUTICAL MARKETS 10 (Ctr. for Health Policy at Brookings, Working Paper No. 30, 2017), https://www.brookings.edu/wp-content/uploads/2017/05/wp30_scottmorton_competitioninpharma1.pdf.

[195] INFORMATION ON BIOSIMILARS, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm (last updated May 10, 2016).

[196] *Id.*

[197] MORTON & BOLLER, *supra* note 194, at 15.

[198] *Id.*

[199] MORTON & BOLLER, *supra* note 194, at 15.

benefit under the program because they are then included in Medicaid formularies, which arguably increase the product's demand.[200] It is estimated that 40% of hospitals meet the criteria of serving poor communities and are thus eligible to participate in the 340B program."[201] The catch is that orphan drugs are excluded from this program which means that sponsors are not required to sell their drugs at a discounted rate to these hospitals.[202] Most interesting given the legislative impetus to reduce health care spending is that since October, 2015, "a drug that has gained orphan status for treatment of one condition gains exclusion from the 340B program for all its sales" and indications.[203]

Additionally, the FDA released its orphan drug modernization plan on June 29, 2017.[204] The plan addresses the ability of new technology to target rare diseases, including genetic diseases.[205] Because of this new technology, the FDA has ended up with a backlog of orphan drug designation requests, which this modernization plan seeks to remedy.[206] The FDA intends to accomplish this goal by implementing a new template for designation and seeks to have more intra-agency coordination between CDER and CBER (Center for Biologics Evaluation and Research).[207] In the longer-term, the FDA's goal is that this modernization plan will streamline the orphan drug pathway so that new and novel drugs to treat rare diseases get to the market as fast as reasonably possible.[208]

The United States has progressed forward with regulations aimed at increasing competition and lowering the cost of orphan drugs and biologics. There are still ways, however, that orphan drugs can legally differentiate themselves from non-orphan drugs including the above 340B program, and previously discussed incentives and market-approval pathways.

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[200] *Id.*

[201] *Id.* at 14.

[202] *Id.* at 15.

[203] *Id.*

[204] ORPHAN DRUG MODERNIZATION PLAN, U.S. FOOD & DRUG ADMIN. (2017), https://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/UCM565068.pdf.

[205] *Id.* at 1.

[206] *Id.*

[207] *Id.* at 3.

[208] *Id.*

C. RECENT DEVELOPMENTS IN THE EUROPEAN UNION

Price controls are a common approach to harnessing orphan drug costs in the European Union.[209] This approach has been critiqued in many countries and is not used in the United States. The EU utilizes three main forms of price control: mutual agreement, indirect price control, and reference pricing. Under the procedure of mutual agreement, "the member state, in which the drug already has a marketing authorization, will function as a reference member state by giving the reports to the requesting member state."[210] Indirect price controls, on the other hand, are "in or through company profit controls (e.g. UK)."[211] Finally,

> [t]he main goal of reference pricing is to control the third-party (e.g. insurers/buyers) expenditures on prescription drugs, not the limitation of overall pharmaceutical expenditure. Reference pricing aims to reduce the price of referenced products through a demand-side approach or a supply-side approach. Reference pricing implies a reimbursement limit, not a final market price; it is thus strictly speaking not a pricing system. Although pricing and reimbursement decisions are conceptually linked, whether the drug should be reimbursed or the extent to which it is reimbursed (i.e. purchased by government or other third-party payer,) is dependent on the price of the drug.[212]

How to pay for the expensive drugs is one of the major political concerns in both frameworks. "The equity principle states that everyone should have the opportunity to attain his or her full potential for health. However, limits are currently assessed by NICE and RVZ."[213] NICE states that the maximum is £20.000 - £ 30.000 (2005)."[214] "The limit set by the RVZ is €80.000 per [Quality Adjusted Life] year as a maximum for the costs of a medical intervention (2006). Some Orphan Drugs prices are much higher, which may lead to exclusion of Orphan Drugs from

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[209] "Each country in the European Union (EU) currently employs a safe form of direct price controls or permutations of direct price controls, depending on the national pricing and reimbursement systems. Four types of pricing policies and regulations are recognized: [Product price control, Reference pricing, Profit control, No control. Often mixtures of these policies are used]." VAN EKDOM, *supra* note 193, at 30.

[210] *Id.* at 22.

[211] *Id.* at 31.

[212] *Id.* (internal citations omitted).

[213] *Id.* at 69. NICE is the abbreviation for the National Institute for Health and Clinical Excellence in the UK and RVZ is a Dutch Acronym for the Council for Public Health and Health Care. *Id.*

[214] *Id.* at 7.

public funding, although this is against the equity principle."[215] Price controls in Europe have been criticized by the Biotechnology Organization which argues that "price controls weaken the intellectual property rights" which will result in less drug development because "price control[s] remove the innovators' ability to establish their own price for their product."[216]

Another approach taken in Europe is to set price based on specific drug characteristics.[217] The most important consideration in this price setting scheme is the relationship between the drug's value and the drug's indications. "From an economic point of view, the aim of pricing rules is to promote efficiency of the health care system and surplus of the pharmaceutical industry."[218] Under this program, "price should be set in relation to the additional value created by the product."[219] A problem that arises under this scheme is that a drug's value over time varies from one indication to another due to the introduction of generics or non-generic competitor drugs.[220]

The EMA has also faced challenges from major pharmaceutical companies in court. In 2016, the Sixth Chamber court dismissed Teva Pharmaceutical's action against the EMA where they moved for an annulment of the EMA's decision rejecting its application for a generic orphan drug to treat chronic myeloid leukemia.[221] The case concerned periods of market exclusivity and whether this period changes based on the marketing authorization of a similar medicinal product.[222]

In another case, the sponsor sued the EMA when the EMA required the sponsor to obtain pediatric clinical trial data. The court held that the sponsor's plea could not succeed because an abuse or misuse of power is only possible where the power taken is not circumscribed.[223]

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[215] VAN EKDOM, *supra* note 193, at 7.

[216] *Id.* at 32.

[217] *Id.* at 33.

[218] *Id.*

[219] *Id.*

[220] *Id.*

[221] Case C-138/15 P, Teva Pharma BV v. EMA, http://curia.europa.eu/juris/document/document.jsf?text=&docid=174762&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=104821 (unpublished op.)

[222] *Id.* ¶¶ 26–33.

[223] Nycomed Danmark ApS v. EMA (Third Chamber) Dec. 14, 2011, Case T-52/09 http://curia.europa.eu/juris/document/document.jsf?text=&docid=116583&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=110691, ¶¶ 101–05.

Here, the court said the EMA was within its power to require the sponsor to file a pediatric investigation plan so that its product could be used to diagnose all forms of myocardial perfusion defects.[224]

Additionally, the EMA is in the process of litigating a case against Bristol-Myers Squibb Pharmaceuticals. In this case, Bristol-Myers is arguing that the EMA was wrong to remove its drug, "elotuzumab" from the orphan drug list.[225] There is no outcome yet since the action was brought in June 2016. Additionally, in 2016, the court held that a supplementary protection certificate is available for a former orphan drug "that was previously designated and authorized as an orphan medicinal product, but was subsequently (voluntarily) removed from the EU's community register of orphan medicinal products."[226] The court reasoned that this understanding of the regulations was in keeping with the main objective of the EU pediatric regulations and the orphan drug act.[227] The allowance of a six-month pediatric extension rewards the sponsor for conducting pediatric research on a former non-pediatric orphan drug.[228] Thus, like the FDA, the EMA constantly faces challenges from pharmaceutical companies who are looking to maintain their exclusivity or push through new orphan products or generics of orphan drugs.

III. POSSIBLE ALTERNATIVES

The issue addressed by this article is not new, and therefore, there are a number of theories proposed by academics and policy makers about how to reduce the cost of orphan drugs. Some of these theories are examined in this section in order to understand the breadth of possible alternatives.

One article, co-written by numerous academics from around the world, addresses the problem of how orphan drugs are priced after

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[224] *Id.* ¶ 101.

[225] Case T-52/09, Nycomed Danmark ApS v. EMA, http://curia.europa.eu/juris/document/document.jsf?text=&docid=116583&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=110691, ¶¶ 101–05.

[226] *The Hague Court confirms paediatric extension of SPC for former EU orphan drug imatinib*, HOGAN LOVELLS (Apr. 6 2016), http://ehoganlovells.com/rv/ff0026906d346456ea3685f4fc44bb17e6ebfe93.

[227] *Id.*

[228] *Id.*

reimbursement.[229] The authors categorize current strategies relating to orphan drug reimbursement into the following groups: "(1) comprehensive value assessment, (2) early dialogues among relevant stakeholders. . ., (3) innovative reimbursement approaches to allow timely access. . ., and (4) societal participation in producing [orphan drugs]."[230] The category of comprehensive value assessment includes ideas such as value-bearing pharmaceuticals where certain factors are analyzed to determine cost.[231] These factors include "disease and patient characteristics," non-health outcomes, health outcomes, and the value of innovation.[232] The principles guiding the weighing of these factors may be the utilitarian approach and the rule of rescue.[233] Additionally, some countries have been exploring innovative reimbursement approaches such as "cost capping, utilization capping, and free and/or discounted initiation."[234] These approaches aim to reduce healthcare expenditures for costly drugs "without collecting real-life health data from patients."[235] Finally, the authors also suggest that different stakeholders—such as physicians, patients, and advocacy groups—may have a role in decreasing marketing costs and therefore allowing for a reduction in price.[236]

In general, the EU differs from the United States in that more countries in the EU have nationally established price controls which force drug manufacturers to negotiate price and volume on a country-by-country basis.[237] The cost of orphan drugs varies between member states,[238] which may be due to different regulations concerning price controls and health coverage. For example, 43% of orphan drugs are

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[229] Pierpaolo Mincarone et al., *Reimbursed Price of Orphan Drugs: Current Strategies and Potential Improvements*, 20 PUB. HEALTH GENOMICS 1 (2017).

[230] *Id.* at 2.

[231] *Id.* at 3.

[232] *Id.* at 3.

[233] *Id.* at 3 (explaining that "[t]wo main and contrasting principles can be distinguished: the utilitarian approach (i.e., healthcare resources are distributed so as to achieve maximum 'benefit' in terms of population health), and the rule of rescue (i.e., resources are only assigned to satisfy the needs of identifiable groups in serious danger).").

[234] *Id.* at 5.

[235] *Id.*

[236] *Id.*

[237] VAN EKDOM, *supra* note 193, at 30.

[238] Katherine Eve Young et al., *A comparative study of orphan drug prices in Europe*, J. MKT. ACCESS & HEALTH POL., 2017, at 1, 6, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405561/pdf/zjma-5-1297886.pdf.

cheaper in France compared to the UK, while in Germany, only 29% of orphan drugs are less expensive than the UK.[239]

In Belgium, the National Institute for Health and Disability Insurance has responded to the proposed question with a policy that "restricts reimbursement of some orphan drugs to prescribers belonging to specialized centers, but no policy or research incentives exist."[240] This approach attacks the cost question at the provider level rather than at the patient level. This is important because it provides an example of a system entirely different than the consumer-based framework employed in the United States and across much of the EU.

In France, the French National Plan for Rare Diseases has established an authorization system where a committee "negotiates the price of an orphan drug with the pharmaceutical company, taking into account the improvement in clinical added value of the drug, with prices based on those that serve the same therapeutic purpose in other European countries."[241] This approach mirrors the approach of the United States where insurance companies agree to plans with providers for subsidized treatment and service costs. What is interesting about the French approach is that part of the negotiation correctly highlights the benefit of more data to drug developers. This helps patients by creating a built-in negotiating tool: If a sponsor is willing to price a drug a little lower, then more patients can theoretically afford the drug, and in return, the sponsor gets access to more data that it can use to either expand the drug's approved indications or improve the treatment.

In the Netherlands, the maximum price is "set based on therapeutically equivalent drugs."[242] The process also incorporates most orphan drugs in a list that is part of the drug reimbursement system; however, this maximum price setting element seems ill-suited to address new drugs that have been approved to treat rare diseases for which there exists no previous treatment. The Dutch also benefit from a

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[239] *Id.* at 6.

[240] Robert Handfield & Josh Feldstein, *Insurance Companies' Perspectives on the Orphan Drug Pipeline*, 6:9 AM. HEALTH DRUG BENEFITS 589, 591 tbl. 1 (2013).

[241] *Id.*

[242] *Id*.

reimbursement program under which hospitals are reimbursed 100% for prescribing approved orphan drugs.[243]

The Italian National Health Service Plan relies on data and the price setting of other countries to set the price of an orphan drug. Conversely, Sweden takes a very particularized approach: Reimbursement is "conducted by public social insurance. If the total cost exceeds 4300 SEK the patient will receive the medicines free of charge."[244] Sweden also considers the orphan drug's cost-effectiveness and the drug's human value.[245]

Finally, in the United Kingdom, the reimbursement policy directly involves pharmaceutical companies. Explicitly,

> [p]rices are set by the pharmaceutical company but need to meet profit control criteria, as stated in the Pharmaceutical Price Regulation Scheme; reimbursement considers budget impact and cost-effectiveness; the UK's NICE has stated that many orphan drugs had incremental cost-effectiveness ratios at the high end of what the appraisal committee deemed to be cost-effective.[246]

The policy has "defined a category of "ultra-orphan disease" for conditions affecting <1000 patients" which takes into account 'harder' cases.[247]

The presence or absence of price setting regulations is the biggest difference between the two frameworks. In the EU, countries have more latitude to negotiate with sponsors in an effort to make drugs more accessible to their citizens. In the United States, there are no such regulations, and thus pharmaceutical companies are able to price their products to account for the cost of development, and future costs of improving the product and developing other drugs. This distinction is not particular to the pre-market regulation of orphan drugs which does not discount its importance, but does lead to a much broader topic about price setting economics.

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[243] Todd Gammine et al., *Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations, and Policies in 35 Countries*, PLOS ONE (2015), at 11, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140002.

[244] *Id.*

[245] *Id.*

[246] Handfield & Feldstein, *supra* note 240, at 591, tbl. 1.

[247] *Id.*

IV. CONCLUSION

When I started thinking about this topic over a year ago, I was initially drawn to research how orphan drugs are paid for in the US and in the EU. Based on articles I read in preparation for an article on my initial interest area, I gradually became more interested in learning how the regulatory frameworks impact the price of orphan drugs for patients. What I have learned throughout this process is that in the United States the Orphan Drug Act effectively promotes research on orphan diseases in part because the incentive structure makes orphan drugs financially worthwhile to sponsors. Similarly, the EU uses legal incentives to promote research into orphan diseases. For example, eight different orphan drugs reported sales of over $1 billion in 2014.[248] The most profitable orphan drug—Rituximab—had $6.9 billion in sales in 2014 alone.[249]

The main difference between the two legal frameworks is how orphan drugs are treated by each system's regulations post-marketing approval. In the EU, orphan drugs benefit from a longer exclusivity period which varies according to the drug's indications. In the United States, an orphan drug is eligible for only a single finite market exclusivity period. Therefore, based on current developments and practices, the most reasonable and feasible idea is to complete a cost-benefit analysis on the impact of these different exclusivity periods to find the length of time that incentivizes research and minimizes starting orphan drug costs. Finally, other differences between the frameworks may contribute to the high price of orphan drugs, and to the differences in price between the frameworks. These include the availability of research grants and whether the agency reconsiders or requires renewal of orphan designation.[250] Additional steps come with higher costs to sponsors and agencies alike.

This article explored how the legal frameworks governing the pre-market approval of orphan drugs in the US and EU differed. The main questions asked were whether and to what extent the legal frameworks are responsible for the high cost of orphan drugs, and

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[248] BAGLEY, *supra* note 167, at 3.

[249] *Id.*

[250] Olga Bruyaka et al., *Strategic Corporate Social Responsibility and Orphan Drug Development: Insights from the US and EU Biopharmaceutical Industry*, 117 J. BUS. ETHICS 1, 49 (2013).

whether the legal frameworks are the cause or a primary factor of pricing differences. While concrete answers may not have been found to these complex questions, it is evident that incentive structures—particularly market exclusivity periods—have a definable impact on how orphan drugs are priced both worldwide and between the US and EU. This article exposed a range of contributing factors that together with the legal frameworks, make up a cursory overview of orphan drug economics.

Finally, because the high cost of healthcare is one of the most hotly debated topics, this article sought to introduce ways other countries are combatting high orphan drug prices. Therefore, the thoughts explored in this article provide a comprehensive overview of the regulatory pre-market frameworks concerning orphan drugs and the likely impact that these frameworks have on the cost to consumers.