ADDRESSING THE NEEDS OF PATIENTS WITH RARE DISEASES IN CANADA: AN EVALUATION OF ORPHAN DRUG INCENTIVES

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ABSTRACT

While it is currently uncertain whether or not a Canadian orphan drug policy will be given further consideration any time in the near future, this thesis seeks to consider the potential impact that three different orphan drug incentives could be expected to have in Canada. Specifically, market exclusivity, priority review vouchers, and a tax credit for orphan drug development are evaluated. This thesis is primarily informed by the literature about how orphan drug incentives operate in the United States. Admittedly, there is controversy about whether orphan drug policies in their current form are justifiable. This controversy is discussed, with this thesis proceeding on the basis that morality and a commitment to equality validate providing some form of orphan drug incentive(s) in Canada. That being said, it is unclear how exactly "orphan drug" should be defined and, accordingly, what criteria should govern the allocation of incentives. Market exclusivity appears to be effective at encouraging investment in orphan drugs and therefore it is recommended that the incentive be implemented in Canada in order to encourage foreign drug companies to obtain market authorisation from Health Canada for orphan drugs. Priority review voucher programs are still in their infancy and, therefore, it is difficult to make any strong assertions about the effect and impact of these programs. It is nevertheless not recommended that vouchers be introduced in Canada because it is unlikely that priority review here will be sufficiently valuable to have an impact. An orphan drug-specific tax credit offers a convenient means of subsidizing orphan drug development without being expected to be overly costly, given the narrow parameters within which the credit would operate. Therefore, a Canadian tax credit for orphan drug development is also recommended.

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CHAPTER 1: INTRODUCTION

A number of jurisdictions have developed policies that are designed to meet the needs of patients with orphan diseases. To date, policymakers in Canada have refrained from enacting an orphan drug policy. A Canadian orphan disease policy was proposed but ultimately rejected in 1997,[1] and in 2012 a draft framework for a Canadian orphan drug policy was under discussion.[2] Renewed interest in implementing an orphan drug framework was later expressed and, at least until recently,[3] Health Canada said it was considering how to amend the *Food and Drug Regulations* in order "to encourage the development of orphan drugs (i.e., drugs for rare diseases) and increase the availability of these products on the Canadian market."[4]

Rare disease and orphan disease are often used interchangeably, to indicate a disease that affects only a small number of people. The term "orphan" refers to the fact that these diseases have historically been neglected, or "orphaned", by the pharmaceutical industry, resulting in patients having few to no available treatment options.[5] There is no globally-agreed upon definition of rare disease, though the definitions used by legislators typically take account of the number of patients who are affected by a particular disease but may also include factors such as the severity of the disease and the existence of adequate treatments.[6] Canada's 2012 proposed orphan drug legislation would have defined a rare disease as "a life-threatening, seriously debilitating, or serious and chronic condition affecting a relatively small number of patients (less than 1 in 2, 000)."[7] An orphan drug is a drug that is intended to treat, prevent, or diagnose an orphan disease.

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[1] Pedro Franco, "Orphan Drugs: The Regulatory Environment" (2013) 18 Drug Discovery Today 163 at 165.
[2] Office of Legislative and Regulatory Modernization, *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework*, (13 December 2012).
[3] See e.g. Maura Forrest, "Health Canada gives 'kiss of death' to planned policy for rare-disease drugs" *National Post* (16 October 2017), online: National Post http://nationalpost.com.
[4] At the date of writing, it is unclear whether, or in what form, this initiative will be pursued.
[5] Franco, *supra* note 1 at 163.
[6] *Ibid*.
[7] Office of Legislative and Regulatory Modernization, *supra* note 2 at 4.

In countries with orphan drug policies, a pharmaceutical company can typically access significant incentives if it can obtain orphan drug designation for its drug. Some of these incentives have been in place for a number of years and have been the subject of considerable discussion. In 2007 an interesting and novel incentive for neglected tropical diseases was introduced in the United States: priority review vouchers ("PRVs").[8] PRVs are awarded for eligible drugs upon receiving approval from the Food and Drug Administration ("FDA") and can be redeemed in order to have a second, different drug subject to FDA's priority review process.[9] The use of vouchers as an incentive for drug development was subsequently expanded to encourage the development of treatments for rare pediatric diseases.[10] Vouchers are a unique incentive for drug development and have been the subject of much speculation about their efficacy.[11] Being such a recent addition to the existing orphan drug incentives, the impact of PRVs on behaviour has yet to be determined.

As a Canadian orphan drug policy, until recently, was the subject of renewed attention and apparent changes in policy direction, an assessment of potential incentives and the issues associated with them is timely and would be of value. This thesis considers three potential incentives for orphan drug development in Canada, and analyzes whether it would be reasonable to expect the incentives to have an impact in terms of increasing access to rare disease treatments in Canada. The ultimate goal of orphan drug policy is to improve the lives and well-being of patients with rare diseases;[12] this can be accomplished by encouraging the development of

[8] See e.g. Emily Waltz, "FDA Launches Priority Vouchers for Neglected-Disease Drugs" (2008) 26 Nature Biotechnology 1315.
[9] 21 USC § 360n (2010).
[10] 21 USC § 360ff (2012).
[11] See e.g. Cameron Graham Arnold & Thomas Pogge, "Improving the Incentives of the FDA Voucher Program for Neglected Tropical Diseases" (2015) 21 Brown J World Affairs 224; Aaron S Kesselheim, Lara R Maggs & Ameet Sarpatwari, "Experience With the Priority Review Voucher Program for Drug Development" (2015) 314 JAMA 1687; Andrew S Robertson et al, "The Impact of the US Priority Review Voucher on Private- Sector Investment in Global Health Research and Development" (2012) 6 PLoS Neglected Tropical Diseases e1750; Joel Lexchin, "One Step Forward, One Step Sideways? Expanding Research Capacity for Neglected Diseases" (2010) 10 BMC International Health & Human Rights 20 [Lexchin, "One Step Forward"].
[12] See e.g. CORD, *Our Work*, online: Canadian Organization for Rare Disorders www.raredisorders.ca.

appropriate treatments and promoting access to those drugs.[13] This thesis is based on the understanding that encouraging more investment in the development of orphan products should be a secondary goal, and that the primary objective of a Canadian orphan drug framework should be to facilitate access to approved treatments for patients with rare diseases. To elaborate, while it would likely be ideal from a public policy perspective if Canadian companies would invest in more research and development ("R&D") for orphan drugs,[14] increasing access to treatments is a matter of greater importance and urgency, regardless of where the treatments have been developed.

Specifically, the following three incentives are evaluated in this thesis: market exclusivity, PRVs, and a tax credit for orphan drug development. Market exclusivity is an incentive that is frequently provided in orphan drug policies, and was included in the 2012 Draft Discussion Document for a Canadian orphan drug framework.[15] PRVs, as mentioned above, are a relatively novel incentive initially introduced in the United States in 2007 for neglected tropical diseases and subsequently expanded to include rare pediatric diseases.[16] Tax expenditures, such as tax credits, are commonly used to promote valuable policy objectives,[17] and the United States has provided an orphan drug-specific income tax credit for qualified clinical trials costs of designated orphan drugs.[18] Market exclusivity and PRVs are both examples of "pull" (or "revenue-side") incentives, in the sense that they reward successful R&D activity, while tax credits for orphan drug development expenses subsidize the costs of doing R&D and are therefore considered a "push" (or "supply-side") type of incentive.[19]

The goal of this thesis is to assess how well these incentives for orphan drug development can be expected to function in Canada. Much of the thesis will focus on the literature about how orphan drug incentives operate in the United States, with some

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[13] *Orphan Drug Act*, Pub L No 97-414, § 1, 96 Stat 2049 at 2049 (1983) (codified as amended at 21 USC § 360aa (2010)).
[14] See below, at 31-32, for further discussion about the goals of orphan drug incentives in Canada.
[15] Office of Legislative and Regulatory Modernization, *supra* note 2 at 25.
[16] *Supra* notes 9, 10.
[17] See e.g. Department of Finance Canada, *2017 Report on Federal Tax Expenditures*, (Ottawa: FIN, 2017) online: FIN https://www.fin.gc.ca/fin-eng.asp at 6.
[18] 26 USC § 45C (2010).
[19] See e.g. David B Ridley, Henry G Grabowski & Jeffrey L Moe, "Developing Drugs for Developing Countries" (2006) 25 Health Affairs 313 at 316-17.

consideration given to how the European orphan drug framework differs. While other jurisdictions have also introduced their own orphan drug policies, the United States has historically led the way with respect to orphan drug policy and, accordingly, a large bulk of the literature focuses on the United States' *Orphan Drug Act* ("ODA")[20] and related orphan drug incentives.

This thesis is organized as follows: background information about the challenges particular to orphan disease drug development and how these have been addressed in various jurisdictions is provided in Chapter 2. Chapter 3 provides a succinct description of the competing arguments with respect to whether allocating resources to provide orphan drug incentives is justified. Without seeking to address all arguments on the subject, the Chapter concludes with the finding that providing some form of incentives to developers of orphan drugs is good public policy. Three incentives are then evaluated and assessed in Chapters 4-6. Market exclusivity is evaluated in Chapter 4, and this discussion leads to the conclusion that Canadian policymakers should offer exclusivity protection in order to encourage companies to market their orphan drugs here. Chapter 5 assesses the PRVs programs as they are currently being used in the United States and, while it is ostensibly too early to really understand the impact that vouchers may have, the incentive is likely to generate too great of a burden on Health Canada and in any event, the value of a priority review voucher in Canada is unlikely to be sufficiently valuable to have an impact. Finally, using the tax system to facilitate orphan drug development is considered in Chapter 6, leading to the conclusion that an orphan drug-specific tax credit should be used in conjunction with market exclusivity in order to lower the costs of developing drugs for rare diseases. A summary of the conclusions and recommendations is provided in Chapter 7.

[20] 21 USC § 360aa-360ee (2010).

CHAPTER 2: ADDRESSING THE NEEDS OF PATIENTS WITH ORPHAN DISEASES

2.1 Challenges with Orphan Drug Development

As a commercial enterprise, one can reasonably predict that pharmaceutical companies will prefer to invest in "R&D" activities that are likely to yield a generous profit. A significant disincentive to developing treatments for rare diseases already exists.[21] Rare diseases, by definition, provide only a small pool of potential buyers, making it unlikely that a rare disease treatment will be very profitable. As a result, rare diseases have been historically given less attention and were considered to be "orphaned" by the pharmaceutical industry.[22]

The perceived lack of profitability of orphan drug development is likely exacerbated by additional challenges that may be faced by orphan drug developers. Orphan drugs are held to the same standards of quality, safety, and efficacy as other drugs,[23] therefore drug developers must be able to produce the same level of clinical support for a rare disease treatment that would be required for the approval of any other treatment.[24] Further challenges particular to developing treatments for rare diseases include insufficient information about the natural course of many rare diseases, frequent late diagnosis of patients, and a lack of validated clinical end points by

[21] Franco, *supra* note 1 at 163.
[22] *Ibid*. See also *Orphan Drug Act*, *supra* note 13, § 1.
[23] See e.g. M Orfali et al, "Raising Orphans: How Clinical Development Programs of Drugs for Rare and Common Diseases Are Different" (2012) 92 Nature 262 at 262.
[24] That being said, there is a degree of flexibility that the regulatory authorities may permit in terms of the type of evidence used to support a marketing application. See e.g. Aaron S Kesselheim, Jessica A Myers & Jerry Avorn, "Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer" (2011) 305 JAMA 2320 at 2324 (pivotal trials for orphan cancer treatments are significantly less likely to be randomized or blinded, and significantly more likely to use a surrogate outcome to demonstrate a drug's efficacy than trials for non-orphan cancer treatments); Aaron S Kesselheim & Jerry Avorn, "Clinical Trials of Orphan Drugs for Cancer—Reply" (2011) 306 JAMA 1545 at 1546 (the flexibility granted for orphan drug clinical trials has resulted in a lower standard being applied to clinical trial design). Nevertheless, the same safety and efficacy standards apply to both orphan and non-orphan drugs. See e.g. Jun Mitsumoto et al, "Pivotal Studies of Orphan Drugs Approved for Neurological Diseases" (2009) 66 Ann Neurol 184 at 188.

which the efficacy of a treatment can be tested.[25] Assuming that sufficient information can be obtained so as to allow a potential treatment to be developed, drug developers may also have practical challenges to confront when conducting the necessary clinical trials for rare disease treatments. Rarity of a disease means that there are far less patients available to participate in clinical trials[26] and therefore orphan drug developers can find it difficult to recruit a sufficient number of participants.[27] Furthermore, within a given jurisdiction, the patients with a specific rare disease are likely to be fairly widely dispersed. Conducting clinical trials with participants who are geographically spread out creates additional difficulties.[28] As a result, it can be especially time consuming and expensive to conduct the tests required to support a marketing application for an orphan drug,[29] though it should be noted that not everyone agrees that orphan drug development is necessarily more expensive.[30] If orphan drugs are particularly unprofitable for pharmaceutical companies to invest in,[31] they may be unlikely to be developed without additional incentives. High R&D costs combined with a small market would result in what economists would classify as a market failure, where companies will not invest in orphan drugs at a rate that is sufficient from the point of view of society because it will not be sufficiently profitable to do so.[32] Government interventions are often validated by the need to address such

[25] Erik Tambuyzer, "Rare Diseases, Orphan Drugs and Their Regulation: Questions and Misconceptions" (2010) 9 Nature Reviews 921 at 923.
[26] Charles Oo & Lorraine M Rusch, "A Personal Perspective of Orphan Drug Development for Rare Diseases: A Golden Opportunity or An Unsustainable Future?" (2016) 56 J Clin Pharmacology 257 at 257.
[27] *Ibid*.
[28] *Ibid*.
[29] Roberta Joppi, Vittorio Bertele & Silvio Garattini, "Orphan Drug Development is Progressing Too Slowly" (2006) 61 Brit J of Clin Pharmacology 355 at 360.
[30] See e.g. Kiran N Meekings, Cory S M Williams & John E Arrowsmith, "Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D" (2012) 17 Drug Discov Today 660.
[31] Franco, *supra* note 1 at 165.
[32] See generally Kenneth Arrow, "Economic Welfare and the Allocation of Resources for Invention" in Universities-National Bureau, ed, *The Rate and Direction of Inventive Activity: Economic and Social Factors* (New Jersey: Princeton University Press, 1962) 609 for a discussion of how "classic market failure theory" supports the need for governments to provide incentives in order to encourage socially valuable innovation to occur at a sufficient rate.

market failures.[33] These are the concerns that motivated the implementation of orphan drug policies in other jurisdictions.

Some authors have suggested that without the incentives for orphan drugs many existing treatments for rare diseases would not have been developed.[34] On the other hand, concerns have been expressed about the extent of generosity of the incentives offered and the potential for abuse of orphan drug legislation.[35] These criticisms generally do not object to the existence of incentives, but, rather, their implementation, where it has been suggested that the costs of providing incentives may not be sufficiently justified by improvements in health outcomes.[36] Still, others do argue that there is no longer a need for orphan drug policies in their current form because being "rare" does not necessarily equate to being neglected by the pharmaceutical industry.[37] These criticisms will be discussed in greater detail below, in Chapter 3.

2.2 Orphan Drug Policy Landscape

Orphanet, an initiative devoted to providing high-quality information about rare diseases, defines "orphan drugs" as "drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need."[38] This definition is generally consistent with the spirit of orphan drug policies, however the specific criteria required to qualify as an orphan drug differ by jurisdiction. As discussed above, there are a number of difficulties associated with R&D of treatments for rare diseases. In recognition of these particular challenges the United States introduced legislation in 1983 that was intended to promote the development and market availability of rare disease treatments.[39] Australia, Singapore, Japan, the European

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[33] *Orphan Drug Act*, *supra* note 13, § 1.
[34] See e.g. Richard Y Cheung, Jillian C Cohen & Patricia Illingworth, "Orphan Drug Policies: Implications for the United States, Canada, and Developing Countries" (2004) 12 Health LJ 183 at 185-86.
[35] See e.g. David Loughnot, "Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?" (2005) 31 Am J L & Med 365 at 366.
[36] See e.g. Aaron S Kesselheim, "An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences" (2011) 89 Milbank Q 450 at 469 [Kesselheim, "An Empirical Review"].
[37] See e.g. Matthew Herder, "When Everyone is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada" (2013) 20 Accountability in Research 227at 243 [Herder, "When Everyone is an Orphan"].
[38] What is an Orphan Drug?, online: http://www.orpha.net.
[39] *Ibid*; *Orphan Drug Act*, *supra* note 13, § 1.

Union and Taiwan followed suit in 1989, 1991, 1993, 1999 and 2000, respectively.[40] In Canada, proposed orphan drug legislation was rejected as being unnecessary in 1997.[41] This section provides an overview of how each of these other jurisdictions has addressed the problems associated with orphan drug development as well as a discussion about the current status of orphan drug policy in Canada. The incentives available through orphan drug schemes will be briefly described here, with greater detail being provided in Chapters 4-6.

2.2.1 United States

Orphan drug policy in the United States is primarily based in the *Orphan Drug Act* ("ODA"),[42] enacted in 1983 in response to concerns that pharmaceutical companies were unlikely to develop treatments for rare diseases in the absence of incentives,[43] though a number of other policy instruments supplement the ODA by also facilitating orphan drug development.[44] Under the ODA, a sponsor may apply for its drug to be granted orphan drug designation at any time throughout the drug development process.[45] Orphan drugs are defined under the ODA as drugs that are intended to treat a rare disease.[46] In the United States a "rare disease" is a disease or a condition that "affects less than 200,000 persons in United States" or one that affects more than 200,000 persons but for which "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States."[47] Orphan status confers a number of benefits for drug developers including guidance from the FDA about the clinical testing and regulatory review

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[40] Franco, *supra* note 1 at 165. Australia's legislation was revised in 1989 to include some incentive for orphan drug development, however, the full orphan drug framework was not implemented until 1997.
[41] *Ibid* at 165.
[42] *Supra* note 13.
[43] See e.g. Office of Inspector General, Department of Health and Human Services, *The Orphan Drug Act Implementation and Impact*, (OEI-09-00-00380) (May 2001) available online: http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf at 4.
[44] E.g. *Rare Diseases Act of 2002*, Pub L No 107-280, 116 Stat 1988 (codified at 42 USC § 281 (2010).
[45] 21 CFR § 316.23(b) (2011).
[46] 21 CFR § 316.3(b)(10) (2013).
[47] 21 USC § 360aa (2010). See also Loughnot, *supra* note 35 at 376 (the "prevalence-based" definition was not in the originally enactment of the ODA but was subsequently added in response to concerns expressed by the pharmaceutical industry about the difficulties associated with demonstrating "no reasonable expectation").

process.[48] Market authorisation (or regulatory approval), refers to the authorisation that is granted by the drug regulatory agency and is necessary in order to legally make a drug product available for public use. Clinical trial results demonstrating that product is a safe and effective treatment for its indicated use are needed in order to obtain regulatory approval. As in all jurisdictions discussed in this section, orphan drug designation does not exempt a treatment from needing to obtain regulatory approval prior to being marketed to the public.[49] Rather, orphan drug designation permits access to a number of incentives that are designed to facilitate the development and marketing of orphan drugs. In order to access the incentives associated with orphan status a company must have its product designated as an orphan drug prior to market approval being obtained.[50]

Under the ODA, a sponsor receives exclusive approval (i.e. market exclusivity) once its designated orphan drug has been approved for market.[51] Market exclusivity is granted for a drug only in relation to the specific indication (or use) for which orphan designation of the drug was granted and operates by preventing the FDA from approving another sponsor's marketing application for the same drug for the same indication for seven years.[52] Additional seven-year periods of exclusivity can be obtained if the drug is subsequently approved as a treatment for another orphan indication.[53] Market exclusivity can be "broken" in favour of a new orphan product that is essentially the same drug intended for the same indication but which demonstrates clinical superiority (i.e. is safer, more effective, or significantly more convenient to administer

[48] 21 CFR § 316.12(a) (2011) provides that "FDA will provide the sponsor with written recommendations concerning the nonclinical laboratory studies and clinical investigations necessary for approval of a marketing application if none of the reasons described in §316.14 for refusing to do so applies".
[49] That being said, the FDA has permitted flexibility with respect to how clinical trials for orphan drugs are designed, as noted above, at note 24.
[50] *Orphan Drug Regulations*, 21 CFR § 316.23 (2011).
[51] 21 CFR § 316.31(a) (2011).
[52] *Ibid*.
[53] 21 CFR § 316.31(b) (2011).

than the first orphan drug),[54] in circumstances where the original orphan product can no longer be supplied in sufficient quantities, or otherwise by consent of the market exclusivity holder. [55]

Market exclusivity is considered the primary incentive available for orphan drug development in the United States;[56] however a number of other incentives and means of regulatory assistance also exist to facilitate orphan disease R&D activity and to assist sponsors with navigating the approval process. For example, the application fee normally required when submitting a New Drug Application ("NDA") is waived for orphan products under the ODA.[57] The ODA also permits direct funding to be provided for orphan drug R&D, the recipients of which are determined according to a (competitive) applications process.[58] The Orphan Drug Tax Credit is a non-refundable credit that can be claimed for qualified clinical trials costs incurred in the development of designated orphan drugs and is equal to 50 percent of the costs incurred.[59]

Since the implementation of the ODA, other orphan drug incentives have been introduced that supplement the Act. As mentioned above, PRVs were introduced in 2012 under the *Food and Drug Administration Safety and Innovation Act* ("FDASIA") as an additional financial incentive to encourage the development of treatments for rare pediatric diseases.[60] Initially proposed as an incentive to promote the development of treatments for neglected tropical diseases,[61] under the FDASIA, PRVs may be awarded to a drug sponsor who obtains marketing approval for a rare pediatric disease drug.[62] A PRV entitles the holder to have a subsequent NDA

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[54] See generally 21 USC § 360aa-360dd (2010). See also 21 CFR § 316.3(b)(3) (2013); Carolyne Hathaway, John Manthei & Cassie Scherer, "Exclusivity Strategies in the United States and European Union", *Update* (May/June 2009) 34, online: Food and Drug Law Institute https://www.fdli.org/ at 36.
[55] 21 CRF § 316.31(a)(3)-(4) (2013).
[56] Office of Inspector General, *supra* note 43 at 8 ("market exclusivity...remains the most powerful incentive in the Orphan Drug Act"); Sinead M Murphy et al, "Unintended Effects of Orphan Product Designation for Rare Neurological Diseases" (2012) 72 Ann Neurol 481 at 482.
[57] FDA, *Designating an Orphan Product: Drugs and Biological Products*, online: US Food and Drug Administration http://www.fda.gov.
[58] 21 USC § 360ee (2010); Franco, *supra* note 1 at 167.
[59] Office of Inspector General, *supra* note 43 at 7.
[60] Alexander Gaffney, Michael Mezher & Zachary Brennan, "Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers" (2 October 2017), online: Regulatory Affairs Professionals Society < http://www.raps.org>.
[61] Ridley, Grabowski & Moe, *supra* note 19 at 313.
[62] Pub L No 112-144, § 908, 126 Stat 993at 1094 (2012) (codified as amended at 21 USC § 360ff (2015)) ["*FDASIA*"].

for a different drug product be subject to priority review.[63] Priority review can permit a pharmaceutical company to obtain market approval more quickly than if the drug had undergone standard review, thereby increasing a drug's profitability.[64] The value of a voucher is likely to be maximized when it can be redeemed for a potential "blockbuster drug" that would not be eligible for priority review on its own merits.[65] Vouchers can also be transferred indefinitely (i.e., sold) to another party.[66]

Overall, the ODA is considered to be a very successful piece of legislation.[67] Since the introduction of the ODA in the United States there have been significant increases in market approvals for rare disease treatments,[68] from 2 in 1983 to 49 in 2014,[69] up to a total of 637 approvals for orphan products as of September 2017.[70] According to the FDA "the Orphan Drug Act has unquestionably stimulated the development of drugs for rare diseases."[71] The ODA has been hailed as "one of the most successful health-care laws that has been passed in the late twentieth century" [72] because it has directly resulted in greater availability of approved treatments for patients with orphan diseases. This success has also been credited with encouraging the implementation of orphan drug policies in other jurisdictions.[73]

Nevertheless, while assessments of the ODA are generally positive, questions have been raised about whether the incentives being provided are more generous than necessary to promote

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[63] *Ibid.* Vouchers can be used for any drug, including non-orphan drugs.
[64] Gaffney, Mezher & Brennan, *supra* note 60.
[65] Ridley, Grabowski & Moe, *supra* note 19 at 314-15 ("blockbuster drugs" are drugs whose sales reach $1 billion within five years of being on the market).
[66] *FDASIA*, *supra* note 62, § 908(b)(2)(A).
[67] See e.g. Kurt R Karst, "The 2014 Numbers Are In: FDA's Orphan Drug Program Shatters Records" (15 February 2015, online: FDA LawBlog www.fdalawblog.net.
[68] See e.g. Cheung, Cohen & Illingworth, *supra* note 34 at 184.
[69] Karst, *supra* note 67. 49 is the current record for number of orphan drugs approved by the FDA in one year. As with drug approvals, requests for orphan drug designation has steadily risen over the years, with the FDA receiving 582 requests in 2016 (the agency granted 333 orphan designations that year).
[70] FDA, *Search Orphan Drug Designations and Approvals*, online: US Food & Drug Administration https://www.accessdata.fda.gov.
[71] Office of Inspector General, *supra* note 43 at 7.
[72] Marlene E Haffner, Janet Whitley & Marie Moses, "Two Decades of Orphan Product Development" (2002) 1 Nature 821 at 823.
[73] *Ibid.*

rare disease treatment development.[74] These questions are closely related to the high prices for many orphan drugs,[75] which prompt further inquiries about whether orphan drug legislation has been truly effective in terms of facilitating *access* to treatment.[76] It is also noted that roughly 95% of orphan diseases still do not have any approved treatments,[77] and many of the treatments that have been approved to date provide only symptomatic relief with no evidence that they slow the progression of the disease process.[78] Access and availability of treatments for rare diseases are, therefore, both perceived as problems that have not been fully addressed by orphan drug incentives. Furthermore, the effectiveness of PRVs, which require the FDA to allocate additional resources in order to perform a priority review, is generally considered to be uncertain.[79] These concerns form the basis for the following assessment, in Chapters 4-6, of orphan drug incentives.

2.2.2 European Union

European Union orphan disease legislation, introduced in 1995 following the apparent success of the ODA in the United States, was largely modelled on the ODA[80] but with a few key differences that were probably intended to address some of the problems perceived with that Act. One important difference is that the European Union Regulations take disease severity and the existence of previously approved treatments into consideration when determining orphan status. Orphan drug designation may be granted for medicinal products intended for the diagnosis, prevention or treatment of either a "life-threatening or chronically debilitating condition" that

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[74] See e.g. David C Babaian, "Adopting Pharmacogenomics and Parenting Repurposed Molecules under the Orphan Drug Act: A Cost Dilemma?" (2014) 13 J Marshall Rev IPL 667 at 668.
[75] See e.g. Cheung, Cohen & Illingworth, *supra* note 34 at 191, 197.
[76] See e.g. Ashish Kumar Kakkar & Neha Dahiya, "The Evolving Drug Development Landscape: From Blockbusters to Niche Busters in the Orphan Drug Space" (2014) 75 Drug Development Research 231 at 232. See also Office of Legislative and Regulatory Modernization, *supra* note 2 at 7 (where it has been pointed out that of the 2661 drugs granted orphan designation from 1983 to 2012 only 408 were approved for market).
[77] Christopher D Moen, "Helping "Orphans" Grow: Fostering Rare Disease Drug Development" (2015) 33 Delaware Lawyer 24 at 25.
[78] KA Burke et al, "The Impact of the Orphan Drug Act on the Development and Advancement of Neurological Products for Rare Diseases: A Descriptive Review" (2010) 88 Clinical Pharmacology & Therapeutics 449 at 452.
[79]Zachary Brennan, "Harvard Professor Questions Success of FDA's Priority Review Voucher Program" (30 September, 2015), online: Regulatory Affairs Professionals Society http://www.raps.org.
[80] Orphanet, *Orphan Drugs in Europe*, http://www.orpha.net.

affects fewer than five in ten thousand patients in the Community or for a "life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment".[81] There must also be no authorised satisfactory method of diagnosis, prevention or treatment of the condition or, where a product already exists, the medicinal product must offer a "significant benefit" to patients affected by the rare condition.[82]

As in the United States, market exclusivity is available once marketing authorisation is obtained.[83] This provision prevents marketing authorisation from being granted to a *similar* product for the same therapeutic indication for ten years, as opposed to the *same* product being protected for seven years under the ODA.[84] The Regulations also allow for the ten year period to be reduced to six years if the criteria for orphan designation are no longer being met, or under circumstances "where it is shown on the basis of available evidence that the product is sufficiently profitable" that providing market exclusivity can no longer be justified.[85] This provision has yet to be exercised and it is unclear how it would be applied (i.e. what would trigger a review of the "available evidence" or what threshold would be used to determine whether a drug has become "sufficiently profitable"). Sponsors of orphan-designated products will also be eligible for Community and Member State funded financial incentives, with additional financial assistance available for small- and medium-sized enterprises.[86]

Since the introduction of its orphan drug legislation, the European Union has granted orphan designation at a steadily increasing rate, suggesting that the incentives offered have successfully stimulated R&D of products for rare diseases.[87] At the same time, only a limited number of orphan products have actually received marketing authorisation.[88] Therefore, as in the

[81] EC, *Commission Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products*, [2000] OJ, L 18/1 at 3(1)(a).
[82] *Ibid* at 3(1)(b).
[83] *Ibid* at 8(1).
[84] *Ibid.*
[85] *Ibid* at 8(2).
[86] *Ibid* at 9(1).
[87] Eline Picavet, David Cassiman & Steven Simoens, "Evaluating and Improving Orphan Drug Regulations in Europe: A Delphi Policy Study" (2012) 108 Health Policy 1 at 1-2.
[88] Morgane Michel & Mondher Toumi, "Access to Orphan Drugs in Europe: Current and Future Issues" (2012) 12 Expert Review of Pharmacoeconomics & Outcomes Research 23 at 24.

United States, in spite of the general success of the orphan drug Regulations, many patients with rare diseases still do not have treatments approved for their conditions.

2.2.3 Other Jurisdictions

Australia, Singapore, and Taiwan also have orphan drug policies and, to varying degrees, incentives to encourage development and marketing of orphan drugs. These policies are significantly less elaborate than the United States and European Union schemes, and therefore are generally not considered throughout this thesis. The Australian criteria for orphan drug status are somewhat similar to that of the United States and the European Union, in that either disease prevalence or the commercial viability of a product will be considered. Orphan designation will only be granted for treatments of "life-threatening or seriously debilitating" conditions and that are "medically plausible".[89] The condition must be of low prevalence (affecting fewer than five in 10, 000 people in Australia) or "not likely to be financially viable for the sponsor to market the medicine in Australia" in the absence of the fee waiver incentive.[90] Finally, a drug must fill an unmet medical need, or be significantly safer or more efficacious than existing treatments in order to receive orphan designation.[91]

Financial incentives provided by the Australian orphan drug policy are limited to a waiver of the fees that would otherwise be required to apply for marketing authorisation, and the evaluation and registration as an orphan drug.[92] At the 2014/15 rates this amounts to $221,400 (AUD), or roughly $173,600 (USD).[93] As in other jurisdictions, the introduction of the orphan drug policy in Australia has been followed by an increasing number of applications for orphan

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[89] *Therapeutic Goods Regulations 1990* (Cth), r 16J(3). See also Therapeutic Goods Administration, *Orphan Drug Program Reforms* (26 June 2017), online: TGA https://www.tga.gov.au/ ([t]he requirement of "medical plausibility" means that generally only drugs treating distinct diseases/conditions will be granted "orphan" designation; "subgroups would only be considered appropriate where the product would be ineffective in the remaining population").

[90] *Ibid*, r 16J(3)(d).

[91] *Ibid*, r 16J(f).

[92] *Ibid*, r 45(12).

[93] Austl, Commonwealth, Therapeutic Goods Administration, *Orphan Drugs Program* (Discussion Paper) online: TGA https://www.tga.gov.au/sites/default/files/consultation-orphan-drugs-program.pdf at 5. By way of comparison, the 2018 FDA application fee for a New Drug Application has been set at $2,421,495 (FDA, *Prescription Drug User Fee Act (PDUFA)*, online: US Food & Drug Administration https://www.fda.gov).

drug designation as well as marketing authorisation applications for orphan drugs.[94] Increased submissions for orphan drug designation combined with concerns about the financial impact of the program prompted the Therapeutic Goods Administration (Australia's drug regulatory agency) to reconsider the orphan drug program,[95] and in July of 2017 amendments were made to the eligibility criteria in order to more closely align the definition of "orphan disease" with international criteria while continuing to promote the availability of treatments for rare diseases.[96]

Legislation in Singapore defines a rare disease as "a life-threatening and severely debilitating illness affecting less than 20,000 patients."[97] Orphan drugs are unapproved products that any doctor or dentist has identified as a necessary treatment for a rare disease for which there is no other effective alternative treatment available.[98] No incentives to facilitate research, development, and marketing of orphan drugs are provided by the legislation in Singapore. The orphan exemption policy is instead intended to enable doctors and dentists to more easily import orphan drugs for specific rare diseases.[99]As the Singapore orphan drug policy is not intended to promote orphan drug development, it is difficult, if not impossible, to assess the effectiveness of the policy in this light. With respect to patient access to treatment for rare diseases, it has been noted that obtaining orphan designation may be difficult because of lack of clarity with the orphan drug definition.[100]

In 1993, Japan amended its *Pharmaceutical Affairs Law* in order to promote the development of rare disease treatments.[101] A rare disease is defined as a disease affecting fewer than 50,000 patients in Japan, which is incurable, and for which there is no current treatment available or where the drug being applied for orphan status is "excellent in comparison with

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[94] *Ibid* at 11.
[95] *Ibid* at 7.
[96] Therapeutic Goods Administration, *Orphan Drug Program Reforms*, *supra* note 87 (the reforms increased the disease prevalence threshold and added the following criteria: that the condition be "seriously debilitating or life threatening" in nature; that there is either no approved product for the condition or that the product will provide a significant benefit over existing treatments; and that the condition be medically plausible).
[97] *Medicines (Orphan Drugs)(Exemption) Order*, (Cap 176, O 12, 2005 Rev Ed Sing), o 2.
[98] *Ibid.*
[99] Franco, *supra* note 1 at 165.
[100] Sharma et al, "Orphan Drug: Development Trends and Strategies" (2010) 2 J Pharma & Bioallied Sci 290 at 293.
[101] Franco, *supra* note 1 at 165.

other available drugs."[102] Additionally, orphan status will only be granted for drugs for which there is "a theoretical basis for the application of the product to the targeted disease and a feasible development plan for it."[103] Japan is the only jurisdiction considered here which has such a "feasibility" requirement for orphan designations.

In Japan orphan drugs can be granted a ten year re-examination period, which in practise functions as marketing exclusivity.[104] During the re-examination period, other applicants cannot apply for marketing approval for the same drug.[105] Under the Japanese legislation orphan products will automatically be subject to fast track (priority) review.[106] As in the United States, the Japanese government will provide funding to subsidize the costs of testing and research into orphan products.[107] Expenses incurred from orphan drug R&D activities are eligible for a tax deduction,[108] and drug sponsors can receive a 16% tax reduction for marketing approval application fees.[109]

Taiwan's orphan drug policy was initially implemented in 1998 and updated in 2010.[110] Orphan designation may be obtained for pharmaceuticals intended for the prevention, diagnosis, or treatment of a rare disease.[111] The *Rare Disease Control and Orphan Drug Act* defines a rare disease as one whose prevalence is "lower than that formulated and publicly announced by the central competent authority, and recognised by the orphan drug committee."[112] Market exclusivity may be granted for approved orphan drugs for up to ten years, during which time no marketing application for the same kind of pharmaceutical product will be accepted.[113]As in the United States, market exclusivity can be displaced in favour of a similar pharmaceutical that is

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[102] Orphanet, *Orphan Drugs in Japan*, http://www.orpha.net; Mamoru Narukawa, "Japanese Approach to Orphan Drugs" (2001) 3 Pharm Pol'y L 41 at 41-42.
[103] *Ibid* at 41.
[104] *Ibid* at 42.
[105] Franco, *supra* note 1 at 167.
[106] Narukawa, *supra* note 102 at 42. See also Franco, *supra* note 1 at 167 (fast track/priority review is available for orphan products in all the jurisdictions discussed in this thesis, however only Japan and Australia provided specifically for an accelerated review in the orphan drug legislation).
[107] *Ibid* at 41.
[108] *Ibid*.
[109] Franco, *supra* note 1 at 166.
[110] *Ibid* at 167.
[111] *Ibid.*
[112] *Ibid* at 164.
[113] *Ibid* at 167.

superior in terms of safety and efficacy.[114] Interestingly, the Taiwanese policy also permits market exclusivity to be broken if the central competent authority determines that the price of the original orphan drug is unreasonable.[115] The policy also requires central and municipal competent authorities to encourage orphan drug development through the provision of funds.[116]

2.2.4 Orphan Drug Policy in Canada

Canada has no specific policy to address the needs of rare disease patients. A Canadian orphan drug policy was rejected in 1997 on the basis that Canadian patients with rare diseases already have sufficient access to products approved in the United States and other jurisdictions via the Special Access Program ("SAP"), which is a program that grants patients access to treatments that are not approved in Canada.[117] It has also been suggested that a Canadian orphan drug policy would be unnecessary or otherwise unlikely to have a significant impact because of relatively low levels of innovative drug research in Canada, a reliance on the pharmaceutical industry in the United States, and a small population.[118] Tax credits for R&D, strong patent protection, and reduced new drug application fees have been also cited as reasons why specific orphan drug legislation is unnecessary in Canada.[119]

Nonetheless, in the past decade, interest in a Canadian orphan drug policy has been renewed and, at least until the middle of October 2017, Health Canada was said to be working toward amending the *Food and Drug Regulations*.[120] In 2012, a draft proposal for a Canadian orphan drug scheme was developed but never implemented.[121] Under the proposed framework, orphan drug status would be granted for drugs "intended for the diagnosis, treatment, mitigation or prevention of a life-threatening, seriously debilitating, or serious and chronic disease or condition affecting not more than five in 10 thousand persons in Canada" that will "provide a potentially substantial benefit for the patient distinguishable from the existing therapy."[122] Note that this definition, as with the definitions used by the European Union, Australia, and Singapore,

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[114] *Ibid.*
[115] *Ibid.*
[116] *Ibid* at 168.
[117] *Ibid* at 165.
[118] Cheung, Cohen & Illingworth, *supra* note 34 at 190.
[119] *Ibid.*
[120] See e.g. Forrest, *supra* note 3.
[121] Office of Legislative and Regulatory Modernization, *supra* note 2.
[122] *Ibid* at 10.

takes into account the severity or seriousness of the disease. This differs from how an orphan disease is defined in the United States under the ODA, where only prevalence or commercial (un)viability are considered.[123] Similar to policies of other countries, market exclusivity, for a period of up to eight years and six months, would be granted to orphan products that receive marketing authorisation from Health Canada.[124] While this proposal has not yet led to legislative changes, over the years, the Canadian Organization for Rare Disorders ("CORD"), a patient advocacy group, has persistently lobbied for an orphan drug framework.[125]

[123] 21 USC § 360aa (2010).

[124] Office of Legislative and Regulatory Modernization, *supra* note 2 at 25. The 2012 Discussion Draft states that market exclusivity for orphan drugs would be based upon the data protection provisions as they exist in the *Food and Drug Regulations*. Therefore, market exclusivity would typically be provided for a period of eight years, though an additional six months of exclusivity would be available for drugs that have undergone clinical testing with pediatric populations (*Food and Drug Regulations*, CRC, c 870, s C.08.004.1(3), (4)).

[125] See e.g. Ben Spurr & Allan Woods, "Canadian Families Pushing for a Rare Diseases National Strategy" *The Star* (20 January 2016), online: The Star www.thestar.com; CORD, *CORD Statement in the House of Commons on March 10, 2016*, online: online: Canadian Organization for Rare Disorders www.raredisorders.ca. See also CORD, *Our Work*, *supra* note 12 for a description of Rare Disease Day. See also Mark Gary Embrett, "Examining Why the Canadian Federal Government Placed an Orphan Drug Strategy on Their Decision Agenda Now", online: (2014) 2:1 Health Reform Observer 3 <https://escarpmentpress.org/hro-ors/article/view/1186> for details on the strategy that CORD has taken over the years that led to the 2012 discussion paper for a Canadian orphan drug policy, which was "primarily accomplished through the collective action of CORD by reiterating their message through extensive media coverage".

CHAPTER 3: JUSTIFYING INCENTIVES FOR ORPHAN DRUG DEVELOPMENT

While this thesis seeks to evaluate the impact that incentives for orphan drug development could be expected to have in Canada, it must be noted that there is controversy over whether it is appropriate for governments to provide incentives for orphan drugs at all. This Chapter first describes how market failure theory provides the underlying justification for orphan drug policies and then addresses two overarching complaints about orphan drug incentives. The first line of argument against orphan drug incentives is that they are not necessary. The "unnecessary" argument has been applied to orphan drug policy in Canada specifically as well to orphan drug incentives in general. The second argument is that, even if some form of government incentives for orphan drug development are still necessary, "rarity" alone is insufficient to justify the provision of incentives. The Chapter concludes by summarizing the arguments in favour of providing orphan drug incentives in Canada and providing recommendations about how orphan drug policy could be introduced so as to address the complaints about orphan drug frameworks.

3.1 Controversy Regarding the Need for Orphan Drug Incentives

Government subsidization of private, commercial innovation is widespread and generally accepted as justifiable.[126] It is believed that government-provided financial incentives for innovation do in fact "pay off" in the long-run.[127] Market failure theory is frequently cited as providing a strong economic rationale for governments to provide some form of R&D subsidy, either directly via a cash-based transfer or indirectly through the tax system.[128] The market for innovation is considered to be incomplete because "there is abundant empirical evidence that an

[126] See e.g. Tommy H Clausen, "Do Subsidies Have Positive Impacts on R&D and Innovation Activities at the Firm Level?" (2009) 20 Structural Change and Economic Dynamics 239 at 240.
[127] David L Burn, "Observations on a Presentation Given on the Comparative Tax Aspects of Technological Change in Canada and the United States" (1999) 25 Can-USLJ 225 at 226; JW Fedderke & BG Teubes, "Fiscal Incentives for Research and Development" (2011) 43 Applied Economics 1787 at 1799.
[128] See e.g. Isabel Busom, Beatriz Corchuelo & Ester Martinez-Ros, "Tax Incentives… Or Subsidies for Business R&D?" (2014) 43 Small Bus Econ 571 at 572.

individual firm cannot capture all the benefit of its investment in R&D."[129] Rather, R&D activities can produce "spillovers", where some knowledge and technological advancements resulting from privately funded R&D activities are likely to be picked up and used free-of-charge by others, thereby providing a benefit that extends beyond the company that undertook the R&D project.[130] In other words, R&D activity is generally expected to result in benefits that will be enjoyed by those other than the party engaging in the R&D.[131] Therefore, because companies cannot expect to fully recoup the costs of doing R&D it is unlikely that they will invest in innovation at a satisfactory rate in the absence of subsidization.[132] It is therefore generally expected that one's government will bear at least some of the costs of private R&D activity.

Orphan drug policies were implemented as a response to concerns that, in the absence of incentives, the pharmaceutical industry would neglect to develop treatments for diseases that were rare or otherwise unlikely to be profitable. In other words, a market failure was perceived to exist with respect to diseases of low prevalence and therefore it was considered good public policy for governments to provide incentives that would address this market failure by encouraging drug developers to develop and market treatments for diseases that were otherwise being neglected.[133]

In spite of the market failure perceived with respect to orphan drug development, it has been argued that incentives for orphan drug development are not necessary. To begin with, as

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[129] Expert Panel Report - Review of Federal Support to Research and Development, *Innovation Canada: A Call to Action* (Ottawa: Public Works and Government Services Canada, 2011) at 3-1.

[130] *Ibid* (the extent to which spillover occurs does depend on the extent to which knowledge is made available, though the literature indicates that spillovers do in fact occur at least to such an extent that private firms are not expected to engage in R&D at a sufficient rate in the absence of government provided incentives).

[131] Tim Edgar, Arthur Cockfield & Martha O'Brien, *Materials on Canadian Income Tax*, 15th ed (Toronto: Carswell, 2015) at 55.

[132] See e.g. Clausen, *supra* note 126 at 240. For a discussion about classic market failure theory in the context of innovative activity see Arrow, *supra* note 32. See also Department of Finance Canada & Revenue Canada, *The Federal System of Income Tax Incentives for Scientific Research and Experimental Development: Evaluation Report*, (Ottawa: FIN, 1997) at 48 ("since the benefits of research and development spill over, or extend beyond the performers themselves, to other firms and sectors of the economy and the value of these benefits is not fully captured by the performed then, in the absence of government support, firms would perform less research and development than is desirable from the economy's point of view").

[133] *Orphan Drug Act*, *supra* note 13 § 1.

discussed above, two primary reasons that have been cited as rendering a Canadian orphan drug unnecessary are: one, that incentives are unlikely to be successful because of relatively low levels of innovative drug research taking place in Canada,[134] and two, that Canadian patients already have sufficient access to treatments coming from the United States, including the ability to access unapproved drugs via the SAP.[135]

In response to the first reason, a potentially low level of pharmaceutical innovation in Canada provides a relatively weak argument against providing *any* orphan drug incentives. There is evidence that Canada does lag behind other countries with respect to the amount of money being invested in pharmaceutical R&D, as compared to the amount being spent via pharmaceutical sales.[136] To put this into perspective, R&D spending by PhRMA member companies in the United States was 50.7 billion in 2010,[137] while Canada's *total* pharmaceutical business R&D spending was 1.18 billion in that year.[138] In 2011, pharmaceutical industry spending on R&D was 0.30% and 0.03% of gross domestic product in the United States and Canada, respectively.[139] Nevertheless, Canada's pharmaceutical industry is second only to the IT industry in terms of innovative levels.[140] At the very least, it is not obvious that there is insufficient potential within Canada's pharmaceutical industry for orphan drug incentives to have an impact and, in any event, incentives that are not "used" will not be very costly (aside from the costs of setting up the administration of an orphan drug program – i.e. design costs). We should consider the possibility that there is in fact significant (or, at least, sufficient) potential in Canada for innovative pharmaceutical activity and that what is actually lacking are incentives to innovate. As will be discussed in greater detail below, industry incentives for innovation can supplement patent law as a means of addressing market failures. As Canadian patent law has

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[134] Cheung, Cohen & Illingworth, *supra* note 34 at 190.
[135] Franco, *supra* note 1 at 165.
[136] Patented Medicine Prices Review Board, *Annual Report 2015*, (Ottawa: PMPRB, 2016) at 52.
[137] Statista, *Research and development expenditure of total U.S. pharmaceutical industry from 1995 to 2015 (in billion U.S. dollars)*, online: Statista https://www.statista.com, this source does not provide a figure of the R&D expenditures by the total (PhRMA members and non- PhRMA member companies) pharmaceutical industry.
[138] Innovation, Science and Economic Development Canada, *Canadian Pharmaceutical Industry Profile*, online: ISED http://npaf.ca/wp-content/uploads/2015/11/Pharmaceutical-industry-profile-Canadian-Life-Science-Industries.pdf, at 4.
[139] OECD, *Health at a Glance 2015: OECD Indicators*, Health at a Glance Series (Paris: OECD, 2015) at 189.
[140] Innovation, Science and Economic Development Canada, *supra* note 138 at 4.

been cited as being especially restrictive and stringent,[141] it may be particularly important that additional encouragement for orphan drug development be provided.

Furthermore, the assertion that Canadian patients can adequately obtain access to rare disease treatments that are developed in other jurisdictions is certainly open for debate. There is evidence indicating that patients with rare diseases in Canada are not receiving appropriate treatment at a satisfactory rate. One study has confirmed that there is a "significant disparity" between the number of orphan drugs available in Canada and the number of orphan drugs available in the United States.[142] CORD asserts that currently "only 60% of treatments for rare disorders make it into Canada and most get approved up to six years later than in the United States and Europe,"[143] though at least one investigation indicates that roughly 75% of orphan drugs approved in the United States are in fact also available on the market in Canada.[144] Nevertheless, there does appear to be some delay between when companies apply for market approval in the United States or the European Union and when they apply for approval in Canada, with smaller companies being more likely than larger companies to delay marketing their drug in Canada.[145]

In circumstances where an orphan drug has not been approved as a treatment for a particular rare disease, very often the only available treatments for rare disease patients in Canada will be found in off-label drug use, a practice that is associated with higher risks than taking the same drug for its approved indication(s) because the off-label use has not been subject

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[141] Se e.g. David J Kappos, "Canada: A Penalty Box for Pharma Innovation" *Fortune* (2 July 2014) online: Fortune http://fortune.com.

[142] Victoria Divino et al, "Pharmaceutical Expenditure on Drugs for Rare Diseases in Canada: A Historical (2007-13) and Prospective (2014-18) MIDAS Sales Data Analysis" (2016) 11 Orphanet J Rare Diseases 68 at 5 (between the years 2007 and 2013 147 orphan drugs (identified according to orphan designation granted in the US) were available in Canada while 316 were available in the US).

[143] CORD, *Our Work*, *supra* note 12.

[144] Matthew Herder & Timothy Mark Krahn, "Some Numbers behind Canada's Decision to Adopt an Orphan Drug Policy: US Orphan Drug Approvals in Canada, 1997–2012" (2016) 11 Health Pol'y 70 at 75 (specifically, 74% of orphan drugs approved by the FDA between 1997 and 2012 were also given at least one market approval in Canada).

[145] Ali Shajarizadeh & Aidan Hollis, "Delays in the Submission of New Drugs in Canada" (2015) 187 CMAJ E47 at E59 (the authors suggest that this is because smaller companies have less resources to navigate the approval process and therefore, quite reasonably, choose to prioritize marketing their product in a larger market).

to regulatory review.[146] In the alternative, rare disease patients who wish to obtain drugs that are not approved in Canada can apply to the SAP; however, drugs that are accessed through this program are usually not covered by either public or private health care plans, thereby putting patients who must use the SAP in order to gain access to appropriate treatments at a disadvantage relative to other patients because of the significant financial costs. [147]

It is not uncommon for pharmaceutical companies to refrain from marketing their products in Canada and this is not necessarily a cause for concern,[148] but, for patients with rare diseases that have no alternative treatment options, this is a problem. "Access" to approved orphan treatments via the SAP comes at a cost that patients with common diseases are not generally required to bear. If appropriate treatments were available without the costs and delays associated with using the SAP, there could be improved health outcomes as well as a reduction in the public healthcare costs of caring for patients in the advanced stages of a disease, some of which could be avoided by earlier or more effective treatment.[149]

It is also argued that orphan drug policies in general have outlived their usefulness and are no longer necessary in light of scientific advances and changes in the pharmaceutical industry that have made the orphan drug market more attractive to drug developers. In other words, some

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[146] Natalie de Paulson, "The Regulatory Gap: Off-Label Drug Use in Canada" (2005) 63 UT Fac L Rev 183 at 186-87. "Off-label use" refers to the practice of prescribing a medication to treat a condition where the drug has not been specifically approved for that condition; in other words, rare disease patients must frequently be treated with drugs that have not been approved as a treatment for their disease.

[147] Carly Weeks, "Without Rare-Disease Policy, Patients in Canada Face Steep Costs for Drugs", *The Globe and Mail* (24 Feburary 2017) online: The Globe and Mail http://www.theglobeandmail.com. This problem is exacerbated by the generally high costs of orphan drugs relative to drugs for more common disorders.

[148] See e.g. Joel Lexchin, "A Comparison of New Drug Availability in Canada and the United States and Potential Therapeutic Implications of Differences" (2006) 79 Health Policy 214 at 216 for a discussion of how the majority of new drug products available in the United States but not in Canada "offer little to no therapeutic advantage" over products available on the Canadian market [Lexchin, "A Comparison"]. Furthermore, delays in access to new drugs may have some advantages for patients. See e.g. Herder & Krahn, *supra* note 144, for comments about how Canadian patients may in fact benefit from the additional information about safety and efficacy of a drug that may only become available after it has been sold in foreign markets for a period of time, at 79.

[149] Eline Picavet et al, "Orphan Drugs for Rare Diseases: Grounds for Special Status" (2012) 73 Drug Development Research 115at 116 [Picavet et al, "Special Status"].

authors contend that a market failure no longer exists with respect to rare diseases.[150] Within the pharmaceutical industry, developing and marketing rare disease drugs has become a fairly attractive investment, thereby reducing the likelihood that such diseases will be "orphaned" by the pharmaceutical industry as they historically have been.[151] The orphan drug market is now actually seen by some pharmaceutical companies as profitable niche to invest in,[152] and the additional risk and costs associated with orphan drug development may no longer exist in light of factors that increase the potential profitability of orphan drugs and lower development costs.[153] That being said, interest in orphan drug development could simply be a reflection that the industry is using orphan drug incentives as they were always intended: to enable companies to profit from developing and marketing orphan drugs.[154] Increasing the profitability of orphan drugs, and therefore removing the disincentive to invest in orphan drugs, was *the* point of the ODA.[155] This argument has been countered by pointing out that increasing use of disease stratification coupled with the disproportionate development of cancer-treating orphan drugs does not allow for such a simple explanation,[156] thereby calling into question the original justifications for orphan drug policies.[157] Nevertheless, this issue is not settled and the pharmaceutical industry contends that the incentives for orphan drugs are still necessary to ensure continued investment in what is still a financially risky endeavour.[158] In further support of the ongoing utility of orphan drug incentives are observations that orphan drug schemes can incite a domino effect whereby further interest and development in the orphan drug field appears

[150] See e.g Steven Simoens, "Pricing and Reimbursement of Orphan drugs: The Need for More Transparency" (2011) 6 Orphanet J Rare Diseases 42 at 2. See also Kakkar & Dahiya, *supra* note 76 at 233 ("with the loss of patents on blockbuster NMEs, a drought in product pipelines, and mounting clinical trial costs, the blockbuster model may have seen its day"); Herder, "When Everyone is an Orphan", *supra* note 37 at 243.
[151] Herder, "When Everyone is an Orphan", *supra* note 37 at 242-43
[152] *Ibid* at 243.
[153] Meekings, Williams & Arrowsmith. *supra* note 30 at 663.
[154] *Orphan Drug Act*, *supra* note 13 § 1.
[155] See e.g. Franco, *supra* note 1 at 165.
[156] Herder, "When Everyone is an Orphan", *supra* note 37 at 243.
[157] R, Rodriguez-Monguio, T Spargo & E Seoane-Vazquez, "Ethical Imperatives of Timely Access to Orphan Drugs: Is Possible to Reconcile Economic Incentives and Patients' Health Needs?" (2017) 12 Orphanet J Rare Diseases 1 at 4.
[158] See e.g. Tambuyzer, *supra* note 25 at 928.

to be stimulated when other jurisdictions implement orphan drug policies.[159] For example, since the European Union introduced its own orphan drug legislation, the number of orphan drug designations in the United States has sharply increased (by roughly 475%).[160]

3.2 Questions about the Allocation and Impact of Incentives

Another set of questions surrounds the ways in which incentives allocate resources to particular types of rare diseases or to rare diseases as a group as compared to other diseases or conditions. As discussed above, orphan drug policies are generally regarded as having been successful at encouraging the development of rare disease treatments.[161] The original justification for providing incentives probably were correct, and many authors do agree that some rare disease treatments currently available would not exist had it not been for the incentives.[162] However, it is undeniable that obtaining market exclusivity and other orphan drug incentives is not currently dependent on developers demonstrating that they incurred any additional risk or cost associated with developing an orphan drug. Orphan drug policies in both the United States and European Union allow it to be assumed that drugs intended to treat a disease suffered by fewer than 200,000 patients (in the United States)[163] or not more than five in ten thousand persons (in the European Union) will not be commercially viable.[164] It was originally intended that orphan status would only be granted for diseases for which there was "no reasonable expectation" that the R&D costs for a treating drug could be recovered from sales of the drug in the United States.[165] Drug developers would therefore have been required to provide information about their anticipated costs of bringing a drug to market. The regulations were amended to include a prevalence-based definition of rare disease, which allows financial risk to be assumed for diseases that are suffered by less than 200,000 people.[166] In at least some cases this assumption is likely to be false.[167]

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[159] EM Bachman, J Kumar & Q Zaidi, "The US Orphan Drug Landscape: Before and After EU Orphan Drug Legislation of 2000" (2012) 15 Value in Health A30.
[160] *Ibid.*
[161] See e.g. Cheung, Cohen & Illingworth, *supra* note 34 at 185-86.
[162] *Ibid.*
[163] 21 USC § 360ee(a)(2) (2011).
[164] Regulation EC No 141/2000, *supra* note 81 at 3(1)(a).
[165] *Orphan Drug Act of 1983*, Pub L No 97-414, § 526(a)(2), 96 Stat 2049 (Jan. 4, 1983).
[166] 21 USC § 360ee(a)(2).
[167] See e.g. Simoens, *supra* note 150 at 2.

In spite of the success of the ODA in creating "an environment in which orphan drug development is realistic and attainable", 95% of orphan diseases still do not have any approved treatments.[168] One possibility is that orphan drug incentives do not work at all, but it is more likely that the incentives do not direct investment in a manner that is sufficiently equitable or effective. Several authors have expressed the concern that orphan drug incentives such as market exclusivity "promote the concentration of marketing activities in a few profitable therapeutic areas at the expense of others that are equally, if not more, important."[169] As will be discussed in greater detail below, there is evidence that factors including disease type and the amount of publically available knowledge about a disease can determine whether companies choose to develop a treatment for a given disease.[170] The type of rare disease that a patient suffers from does in fact seem to be a significant factor in determining the likelihood that a treatment will be developed and approved.[171] Cancer-treating drugs in particular dominate the orphan drug market, likely because drug companies can expect to make greater profits from cancer treatments (especially when one considers that off-label use of drug products is particularly common in oncology) than from other orphan drugs.[172] It is therefore reasonable to argue that incentives for orphan drug development are still justified, but what does need to be amended is how "orphan drug" is defined. In other words, the eligibility criterion that governs the allocation of orphan drug incentives should be refined to ensure that incentives direct the pharmaceutical industry toward diseases that are in fact at risk of being orphaned.

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[168] Moen, *supra* note 77 at 25.

[169] See e.g. Andre Cote & Bernard Keating, "What is Wrong with Orphan Drug Policies?" (2012) 15 Value in Health 1185 at 1190.

[170] See Section 4.3.1, below, for further discussion about the factors that drive investment decisions.

[171] See e.g. Aaron S Kesselheim, Carolyn L Treasure & Steven Joffe, "Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage" (2017) 14 PLoS Medicine e1002190 at 4.

[172] Matthew Herder, "Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the USA and Canada" (2016) 3 JL & Biosci 158 at 160 [Herder, "Orphan Drug Incentives"]. See also Olivier Wellman-Labadie & Youwen Zhou, "The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?" (2010) 95 Health Pol'y 216 at 218, 220, 225 (oncology products accounted for 32% of orphan designations and 27% of approved orphan drugs between 1983 and May of 2009, while "[n]o other therapeutic class was found to account for more than 10% of orphan designations").

From a broader perspective, it has been suggested that "funding policies that take resources from elsewhere in health economy budgets to fund these [rare disease] treatments are not in the public interest"[173] because they may result in research into more common diseases being neglected in favour of pursuing the incentives offered for rare diseases. Orphan drug incentives may have the undesirable effect of directing industry focus and resources away from other, equally deserving areas.[174] It is not obvious that diseases should be given priority based solely on prevalence, and one could legitimately question whether public resources should focus on diseases that are rare and therefore less likely to create a significant burden on society,[175] particularly when one considers the competing claims to a government's finite resources. "Rarity" in and of itself may not justify the allocation of government resources,[176] and how Canadian policymakers can address this issue will be discussed in greater detail at the conclusion of this Chapter.

With respect to rare diseases, allocating a disproportionate amount of resources in order to promote the development of appropriate treatments can be justified on the basis of morality and a commitment to equality. Embedded within the arguments against orphan drug incentives in Canada is an assumption of judicious government spending; incentives should not be pursued where they reap insufficient positive results. Nevertheless, public health policies are not always determined solely by strict considerations about cost and impact, and a moral imperative to respond to people in need may justify incentives even where the cost of doing so is disproportionate to the result. The rule of rescue, whereby "standard" cost-effectiveness considerations may give way to a moral imperative to "rescue" identifiable individuals (or a group of individuals so small that its members are in effect "identifiable"), is one basis for saying

[173] M Palmer & DA Hughes, "Orphan Drug Legislation: Heyday or Had Their Day?" (2013) 16 Value in Health A491.
[174] Matthew Herder, "What is the Purpose of the Orphan Drug Act?" (2017) 14 PLoS Med e1002191 at 2 [Herder, "What is the Purpose"].
[175] See e.g. Michael Drummond & Adrian Towse, "Orphan Drugs Policies: A Suitable Case for Treatment" (2014) 15 Eur J Health Econ 335 at 339.
[176] See e.g. Herder, "When Everyone Is an Orphan", *supra* note 37 at 244. But see Hanna I Hyry et al, "The Legal Imperative for Treating Rare Disorders" (2013) 8 Orphanet J Rare Diseases 135 at 4 where the authors argue that rarity is in fact given value in terms of a factor for determining allocation of resources.

there is a moral obligation to allocate resources to encourage orphan drug development.[177] The rule of rescue can be engaged under circumstances that threaten the lives, or well-being, of identifiable individuals and there is an opportunity to avoid or neutralize that threat.[178] When the rule of rescue is in operation, an otherwise disproportionate allocation of resources is considered not only justifiable but morally required.[179] The moral imperative for directing resources toward orphan drug development may be strengthened by the fact that many orphan diseases are serious in nature,[180] and frequently suffered by children.[181] Arguments for a Canadian orphan disease framework frequently employ such reasoning,[182] suggesting that the moral imperative to rescue is one basis for justifying orphan drug incentives.

Furthermore, it is actually relatively common to have a rare disease and therefore the economic impact of rare diseases all together is likely not insignificant. While, by definition, the number of patients that suffer from a single rare disease is very small, roughly 6,000 to 8,000 rare diseases have been identified worldwide,[183] and therefore the total number of patients suffering from a rare disease is substantial. It is estimated that over 30 million Europeans, or

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[177] See e.g. John McKie & Jeff Richardson, "The Rule of Rescue" (2003) 56 Soc Sci & Med 2407 at 2408 for an explanation of the elements that will trigger the RR, and how "[d]ecisions influenced by the RR show a strong tendency to disregard cost-effectiveness when the life of an identifiable individual is in danger." See also David C Hadorn, "Setting Health Care Priorities in Oregon: Cost-Effectiveness Meets the Rule of Rescue" (1991) 265 JAMA 2218 at 2219: "any plan to distribute health care services must take human nature into account if the plan is to be acceptable to society. In this regard there is a fact about the human psyche that will inevitably trump the utilitarian rationality that is implicit in cost-effectiveness analysis: people cannot stand idly by when an identified person's life is visibly threatened if rescue measures are available" (as cited by McKie & Richardson at 2408).

[178] See e.g. *ibid* at 2411.

[179] See e.g. *ibid*.

[180] Picavet et al, "Special Status", *supra* note 149 at 116. See also Office of Legislative and Regulatory Modernization, *supra* note 2 at 4 (while the definition of "rare disease" used in a given jurisdiction may or may not include reference to its severity, more than half of rare diseases are life-threatening).

[181] CORD, *Our Work*, *supra* note 12.

[182] See e.g. Kelly Grant, "Why drugs like these for 'orphan' diseases are a booming business with colossal costs for patients", *The Globe and Mail* (7 April 2017) online: Globe and Mail https://www.theglobeandmail.com ("[a]n orphan-disease framework in Canada could establish new protocols for judging the cost-effectiveness of rare-disease breakthroughs, rather than evaluating them as though they're the latest hypertension pill to join a crowded market").

[183] Office of Legislative and Regulatory Modernization, *supra* note 2 at 4.

roughly 6 to 8% of the EU population are living with an identified rare disease[184] and similar statistics have been suggested for the United States, where approximately 1 in 10 people are affected by a rare disease.[185] CORD estimates that 1 in 12 Canadians, roughly 3 million, suffer from a rare disease.[186] Therefore, it is incorrect to state that rare diseases do not generate a large impact on society, particularly when one also takes into account the family of a patient with a rare disease (and, given that many rare diseases affect children, it is likely that many parents have to withdraw from the workforce to act as caregivers).

Concerns about equality also favour the implementation of a Canadian orphan drug policy and support the argument that governments may have an obligation to encourage pharmaceutical innovation if no treatments are available in the absence of incentives.[187] Proponents of orphan drug incentives argue that patients with rare diseases should not suffer from a lack of treatment on account of the fact that their disease is rare.[188] CORD suggests that the challenges faced by patients and their families, such as misdiagnosis, unnecessary surgeries, social isolation, financial hardship, lack of treatment options and early death, affect those with rare diseases to a greater degree.[189] Patients with rare diseases may also face additional challenges specifically because they have a rare disease as opposed to a more common one; for example, very often the doctor who first examines a patient with a rare disease has never seen that disease before, thereby making timely diagnoses difficult,[190] which can lead to negative clinical outcomes and untimely death.[191] The additional risks (such as delayed diagnosis) and costs (of drugs accessed through the SAP that are not typically covered by health care plans) that individual rare disease patients often incur *because their disease is rare* strengthen the argument that, for the sake of equality, incentives for orphan drugs are warranted. Therefore, providing orphan drug incentives is, at least in principle (aside from potential implementation and design costs), good public policy.

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[184] EURORDIS, *What is a rare disease?*, online: Rare Diseases Europe www.eurodis.org.
[185] Babaian, *supra* note 74 at 677.
[186] CORD, *Our Work*, *supra* note 12.
[187] See e.g. Franco, *supra* note 1 at 165, 171.
[188] Picavet et al, "Special Status", *supra* note 149 at 116.
[189] CORD, *Our Work*, *supra* note 12 (a lot of this additional hardship may be attributed to the fact that "because each specific rare disease affects only a small number of individuals, scientific understanding and clinical expertise may be limited and fragmented across the country").
[190] Moen, *supra* note 77 at 26.
[191] Picavet et al, "Special Status", *supra* note 149 at 116.

In addition to morality and equality-based arguments in favour of orphan drug incentives, there has been some suggestion that governments have a legal obligation to fund rare disease treatments; [192] this argument could reasonably be expanded to suggest that governments, at the very least, are obligated to provide incentives that are designed to promote development and marketing of rare disease treatments. Potential routes for establishing a legal obligation have been identified in disability legislation, national and health systems constitutions, judicial review, tort law, and human rights legislation.[193] In 2010 Canada ratified the 2007 United Nations Convention on the Rights of Persons with Disabilities.[194] The definition of "persons with disabilities" is not fixed and arguably can include patients with rare diseases.[195] Ratifying the Convention may impose an obligation on Canadian policymakers with respect to certain rare disease patients; relevant provisions include the obligation to:

> adopt legislation and administrative measures to promote the human rights of persons with disabilities; protect and promote the rights of persons with disabilities in all policies and programmes; undertake research and development of accessible goods, services and technology for persons with disabilities *and encourage others to undertake such research*; and to consult with and involve persons with disabilities in developing and implementing legislation and policies and in decision-making processes that concern them.[196]

Failing to introduce incentives for orphan drug development, or to at least meaningfully re-consider enacting an orphan drug policy, could reasonably be considered a failure to implement Canada's commitments under this Convention.

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[192] See e.g. Hyry et al, *supra* note 176.
[193] *Ibid* at 2.
[194] See e.g. Canada, *Reports on United Nations Human Rights Treaties*, online: Government of Canada https://www.canada.ca/en.html.
[195] See e.g. Division for Social Policy and Development of the United Nations, *Frequently Asked Questions regarding the Convention on the Rights of Persons with Disabilities*, online: United Nations https://www.un.org/development/desa/disabilities/ (the Convention does not define "disability" but recognizes that "disability results from the interaction between persons with impairments and attitudinal and environmental barriers that hinders their full and effective participation in society on an equal basis with others"). See also Hyry et al, *supra* note 176 at 3, where the authors point out that rare diseases are "understood to fall within the definition of disability under the United States Social Security Act."
[196] *Convention on the Rights of Persons with Disabilities*, 30 March 2007, 2515 UNTS 3 at 74, emphasis added.

The *International Covenant on Economic, Social, and Cultural Rights*, to which Canada is a signatory, provides another possible basis for finding that Canada has a legal obligation to provide incentives for orphan drug development.[197] Article 12 affirms the "right of everyone to the enjoyment of the highest attainable standard of physical and mental health" and Article 15 confirms the right of everyone "to enjoy the benefits of scientific progress and its applications".[198] If the pharmaceutical industry neglects certain types of diseases because they are not sufficiently profitable, then patients who suffer from those neglected diseases are unable to enjoy "the highest attainable standard" of health and are being denied "the benefits of scientific progress and its applications." It is known that companies significantly delay bringing their orphan drugs to the Canadian market.[199] Providing incentives to encourage sponsors to apply for market authorisation in a timely manner could serve as one way for Canada to honour its international commitments.

As the ODA appears to have been successful at encouraging the pharmaceutical industry to invest in orphan drugs (with limitations on that success, as noted above), at the very least Canada should introduce incentives that are aimed at encouraging companies to market these drugs in Canada (i.e. to apply for regulatory approval). This will serve to reduce the financial burden of patients with rare diseases whose only option is to access treatments via the SAP. As there continues to be many rare diseases for which no treatments have been developed, encouraging innovative drug development to address these unmet medical needs remains a suitable secondary goal of a Canadian orphan drug policy. The following Chapters proceed on

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[197] 19 December 1966, 993 UNTS 3 (accession by Canada 19 May 1976).

[198] *Ibid.* These rights, while broadly stated, do not require State Parties to spend limitless resources in order to provide the highest attainable standards of health. Rather, Article 2 specifies that State Parties are to "take steps, individually and through international assistance and co-operation, especially economic and technical, to the maximum of its *available* resources, with a view to achieving progressively the full realization of the rights recognized in the present Covenant by all appropriate means, including particularly the adoption of legislative measures" [emphasis added]. The word "available" seems to denote an understanding that government spending will indeed be limited by budgetary constraints, and the phrase "particularly the adoption of legislative measures" suggests orphan drug incentives as they have been provided for in orphan drug policies are one means by which State Parties can uphold their obligations under the Covenant.

[199] See e.g. CORD, *Our Work*, *supra* note 12. See also Weeks, *supra* note 147 for a discussion regarding a drug to treat Duchenne muscular dystrophy: "[i]n an e-mail, a spokesperson for [the drug's sponsor] said there are no plans to seek approval in Canada as 'the U.S. is our main market.'"

the basis that orphan drug incentives are justifiable in principle and, from that basis, assess the potential for three different incentives to promote the policy objectives of both increasing access to approved treatments and facilitating the development of new treatments for orphan diseases.

At this point it should be noted that it is unclear how exactly orphan drug incentives should be allocated, as there is certainly room to question whether it is appropriate to allocate government resources based solely on disease prevalence (or lack thereof).[200] Existing orphan drug policies are relatively blunt instruments. The ODA definition of "orphan disease" does not specify disease features beyond prevalence, though the EU policy does require that the disease also be life-threatening or chronically debilitating in order to be granted orphan status.[201] Arguably, disease severity should be a consideration. As discussed above, incentives for orphan drug development were introduced to address concerns that rare diseases were being neglected by the pharmaceutical industry because they are not seen as profitable.[202] In 1983, when the ODA was introduced, being "rare" in and of itself likely warranted the provision of incentives because rare diseases, in general, were being neglected. With rare diseases now representing a potentially profitable business opportunity,[203] in order to avoid overburdening public resources, being "rare" may no longer be sufficient to justify incentives. Furthermore, in light of scientific advances that allow relatively prevalent diseases to be divided into distinct groups, some of which may then be classified as "rare", identifying diseases that are legitimate targets for incentives on the basis of prevalence is no longer such a straightforward matter.[204] It might be more appropriate to grant orphan disease status only to rare diseases that are also life-threatening or chronically debilitating. Alternatively, it has been suggested that the definition of "orphan disease" should direct companies toward diseases that are truly in danger of being neglected, for

[200] Admittedly, disease prevalence is not the only basis on which orphan disease designation may be granted; a lack of potential "commercial viability" provides an alternative way to obtain orphan status. However, this definition is rarely if ever used by companies as the basis for claiming orphan status (see e.g. Herder, "When Everyone is an Orphan", *supra* note 37 at 233). It is therefore safe to conclude that orphan drug incentives are provided primarily, if not exclusively, on the basis of disease prevalence.
[201] Regulation EC No 141/2000, *supra* note 81 at 3(1)(a).
[202] *Orphan Drug Act*, *supra* note 13 § 1.
[203] Shannon Gibson, Hamid R Raziee & Trudo Lemmens, "Why the Shift? Taking a Closer Look at the Growing Interest in Niche Markets and Personalized Medicine" (2015) 7 World Medical & Health Pol'y 1 at 5.
[204] See e.g. Herder, "When Everyone is an Orphan", *supra* note 37 at 244.

whatever reason, regardless of prevalence or severity.[205] With no orphan drug policy at the moment, Canada is well-positioned to confront these questions. Starting from the ground up affords policy makers the opportunity to give careful consideration to the definition of "orphan".

Furthermore, in order to address the concerns that orphan drug policies have become unnecessary it has been suggested that incentives need to be more closely tied to public health outcomes,[206] though it is unclear how exactly this could be achieved. One solution is to impose stricter criteria for what qualifies to receive incentives, such as by refining the definition of "orphan drug" to better align with the spirit of the regulations, which is to prevent diseases from being neglected by the pharmaceutical industry.[207] In the United States, unlike in the European Union and Australia, applicants do not need to show that there is a lack of alternative treatments, or that their drug offers a significant benefit over existing treatments, in order to access orphan drug incentives.[208] Including this requirement would have the benefit of tying incentives to a demonstration of an actual problem and is one opportunity to avoid granting an incentive where it would be unnecessary to do so, and instead direct incentives to where there is the greatest need for them.

[205] Herder, "What is the Purpose" *supra* note 174 at 5.
[206] Kesselheim, "An Empirical Review", *supra* note 36 at 492.
[207] Tambuyzer, *supra* note 25 at 928.
[208] Genevieve Michaux, "EU Orphan Regulation - Ten Years of Application" (2010) 65 Food Drug LJ 639 at 641.

CHAPTER 4: INCENTIVE OPTION 1 – MARKET EXCLUSIVITY

4.1 Introduction

Market exclusivity is provided by orphan drug policies in both the United States and the European Union to pharmaceutical companies that successfully apply for marketing authorisation for a designated orphan drug.[209] The incentive is available in addition to patent protection, and may offer a number of advantages over patent law in terms of being an effective incentive, as will be discussed in greater detail below. Widely considered to be the primary incentive available to orphan drug developers,[210] market exclusivity for an orphan drug operates only in relation to the specific orphan disease for which the drug is an approved treatment.[211] To elaborate, when exclusivity is in effect the regulatory agency (e.g. in the United States, the FDA) will not approve a subsequent marketing authorisation application for the same drug to treat that orphan disease for a specified period of time.[212] In the United States, market exclusivity protection lasts for seven years.[213] Under the European Union Regulations exclusivity is maintained for 10 years, though the protection period may be shortened to six years if it is shown that the drug is "sufficiently profitable" to make market protection no longer necessary.[214] Multiple periods of exclusivity can be obtained for single orphan drug, one for each indication for which the drug is approved as a treatment.[215] As will be discussed in greater detail below, there is controversy over the practice of obtaining multiple periods of protection for a single drug.[216]

As a "pull", (or "revenue-side") incentive, market exclusivity functions by maximizing the ability of a developer to profit from marketing an orphan drug for a pre-determined period of

[209] 21 CFR § 316.31(a) (2011).
[210] See e.g. Office of Inspector General, *supra* note 43 at 8.
[211] 21 CFR § 316.25(a)(3) (2013).
[212] *Ibid.* In the EU, market exclusivity prevents a "similar" drug being approved to treat the disease in question (Regulation EC No 141/2000, *supra* note 81 at 8(1).
[213] 21 CFR §316.31(a)(2011).
[214] Regulation EC No 141/2000, *supra* note 81 at 8(2).
[215] 21 CFR § 316.23(b)(2014) (sponsors can obtain additional orphan drug designations for the same drug).
[216] See e.g. Simoens, *supra* note 150 ("the small number of patients treated with an orphan drug and the limited economic viability of orphan drugs can be questioned in a number of cases" at 6).

time, and thereby addresses a presumed disincentive to developing orphan drugs. The 2012 draft discussion document for a proposed Canadian orphan drug framework did include market exclusivity as an incentive,[217] and it is reasonable to assume that any future Canadian orphan drug policy could also use market exclusivity to encourage the development and marketing of orphan drugs. Therefore, an evaluation of the issues with market exclusivity and how it could be expected to function in Canada is warranted.

This Chapter is informed by the market exclusivity provisions as they have been implemented in the United States and by the European Union and the evaluation of their effectiveness.[218] The following discussion leads to the conclusion that market exclusivity is an effective incentive for orphan drug development and should be implemented in Canada, albeit with some modifications to the United States and European Union models. This Chapter is organized as follows: Section 4.2 describes how market exclusivity functions as an incentive for pharmaceutical innovation relative to patent law. Market exclusivity addresses some public policy concerns about patent law and has features that likely make it an attractive and useful incentive for pharmaceutical companies. In Section 4.3, the overall impact market exclusivity has had on public health outcomes is analyzed. This discussion leads to the conclusion that the effectiveness of market exclusivity is somewhat tempered by the ongoing problems relating to affordable access to approved treatments. It follows from this conclusion that, while market exclusivity should be introduced as a Canadian orphan drug incentive, exclusivity periods should be terminated for drugs that have become "sufficiently profitable" and that the profits made for a drug as a treatment for related orphan disease subsets should be added up when the profitability of a drug is being assessed. These provisions will hopefully dissuade companies from setting excessively high prices and, at the very least, will help to quell concerns about pharmaceutical companies exploiting orphan drug policies for profit. Section 4.4 concludes with a summary of the conclusions and findings arrived at in this Chapter and the suggestions described therein.

This thesis primarily considers the relatively broader issues and aspects of market exclusivity: in particular, its effectiveness, the overall impact market exclusivity has had on the availability of and access to treatment, and the main public policy issues surrounding use of the

[217] Office of Legislative and Regulatory Modernization, *supra* note 2 at 25.
[218] Other jurisdictions (e.g. Japan and Taiwan) also use market exclusivity as an incentive for orphan drug development. Nevertheless, this thesis will consider only the regulations in the US and EU.

incentive. Other important concerns regarding market exclusivity exist, such as the interpretation that regulatory authorities give to "same drug" or disease in determining whether or not exclusivity protection applies,[219] but these concerns are beyond the scope of this thesis and will therefore not be discussed in detail.

4.2 The Role of Exclusivity in Innovation Policy

Market exclusivity gives drug developers protection from potential competitors in a manner that is similar to the protection available via a patent, but may also offer a number of advantages in terms of addressing public policy concerns regarding patent law, specifically with respect to the scope of protection. This section describes these advantages. Additionally, the criteria for obtaining a patent and market exclusivity, as well as the length and strength of the protection conferred by each, are considered from the perspective of drug developers. The theory underlying patent protection is that it is necessary to provide some sort of incentive for innovation, and patents are considered to be particularly necessary with respect to ensuring that pharmaceutical innovation occurs at a satisfactory rate.[220] As the two incentives function in a relatively similar manner it is appropriate to compare how they both operate with respect to encouraging investment in orphan drugs. The following discussion leads to the conclusion that market exclusivity likely acts as a more powerful motivator for pharmaceutical companies than patent law, while involving a lesser sacrifice on the part of the public.

4.2.1 Market Exclusivity May Satisfy Some Public Policy Concerns about Patent Law

As the public temporarily gives up certain rights in exchange for valuable innovation, both patent protection and market exclusivity can be seen as forming a sort of a "give-and-take" relationship between the inventor/drug developer and all other members of the public. Market exclusivity functions similar to a patent in that it reduces competition for a certain length of time

[219] See e.g. Herder, "When Everyone is an Orphan", *supra* note 37 at 235-37.
[220] Though there is some debate over whether it is actually necessary to provide incentives for innovation or whether people would continue to be inventive regardless of a lack of incentives, this discussion is quite beyond the scope of this paper. But see Shamnad Basheer, "Alternative Incentives for Pharmaceutical Innovation" (2014) 27 IPJ 13 at 17 ("[a]n assessment of empirical evidence on this count suggests that there is, as yet, no persuasive data to conclude that patents definitely enhance the rate of innovation. However, the pharmaceutical industry appears an exception, with scholars arguing that the high costs endemic to the industry warrants the institution of a patent regime to protect such drugs from free riders") [Basheer, "Alternative Incentives"].

during which pharmaceutical companies are expected to be able to profit from their investment in developing and marketing an orphan drug.[221] Where market exclusivity or a patent is in effect, potential competitors are prevented from marketing the protected product and the general public is denied the ability to purchase the product from another company that makes it available at a lower cost. However, the protection (i.e. the rights given up by the public) provided via market exclusivity is arguably narrower in scope than a patent.[222] Patentees are granted very broad rights over their patented invention and can exclude all others from making, using, and selling the invention.[223] As such, granting patent protection requires a significant degree of "give" on the part of society for the duration of the patent term.

The total exclusivity over an invention that inventors are granted is a common criticism of patent law, with some considering the scope of protection to be overly-generous.[224] Market exclusivity, on the other hand, is far narrower in scope.[225] Under the European Union Regulations, when exclusivity is in effect no "similar medicinal products" will be approved as treatments for the same orphan disease,[226] and in the United States, market exclusivity prevents market authorisation being granted for a subsequent drug that is the "same" as the first drug to treat the same orphan disease.[227] Therefore, the protection that a drug developer gets via market exclusivity is limited to the specific orphan indication for which market approval was granted;

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[221] See e.g. Cynthia Luchetti, "Market Exclusivity Strategies for Pharmaceuticals (2009) 23 Pharm Med 77 at 79.
[222] Aaron S Kesselheim, "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation" (2010) 363 N Engl J Med 1855 at 1857 [Kesselheim, "Using Market-Exclusivity"].
[223] *Patent Act*, RSC 1985, c P-4, s 42.
[224] See e.g. Benjamin J Kormos, "Giving Frankenstein a Soul: Imposing Patentee Obligations" (2009) 21 IPJ 309 at 330.
[225] Kesselheim, "Using Market-Exclusivity", *supra* note 222 at 1857. There is some debate regarding relative breadth of protection See e.g. Peter S Arno, Karen Bonuck & Michael Davis, "Rare Diseases, Drug Development, and AIDS: The Impact of the Orphan Drug Act" (1995) 73 Milbank Quarterly 231 at 235 for the argument that market exclusivity provides a broader scope of protection because in order to avoid infringing market exclusivity a subsequent drug must be sufficiently not the "same" (i.e. it must have "'major' differences) while patents protect only against a competitor that is "literally either the same as the patent claim or substantially so". See also Herder, "When Everyone is an Orphan", *supra* note 37 at 239 for further elaboration on the two sides of this debate. That being said, in this context, which is in regard to the scope of rights over the use of the protected product that are temporarily forfeited by the public, market exclusivity is narrower than patent protection.
[226] Regulation EC No 141/2000, *supra* note 81 at 8(1).
[227] 21 CFR § 316.31(a) (2012).

other drug developers are free to get market approval for the protected drug for a different disease (barring any applicable patent protection), or to market a different drug as a treatment for that orphan disease. The narrower scope of market exclusivity means that society is not "giving up" as much as it does when patent protection is in effect.

Furthermore, both the ODA and the European Regulations allow for exclusivity to be "broken" in favour of a subsequent application that is for the same drug to treat the same indication if the second drug is essentially the same (or, in the EU, similar) but otherwise "clinically superior" to the protected drug.[228] "Clinical superiority" may be established with respect to either greater effectiveness or greater safety.[229] The ability to "break" exclusivity protection is significant because it is intended to "ensure that orphan drug exclusivity approval does not preclude significant improvements in treating rare diseases."[230] This provision ties the ongoing application of exclusivity to concerns about the well-being of patients, in a way that patent protection does not. From a public policy perspective this aspect of how market exclusivity operates represents a potentially meaningful advantage over patent law.

Market exclusivity can address a related policy concern about patent law regarding public access to protected products. Obtaining patent protection does require that inventors "disclose" their inventions;[231] it does not, however, require that they develop, use, sell or otherwise make their invention available for public consumption so that the public may benefit from it. This has been a criticism of patent protection, which in theory represents a quid pro quo arrangement between the inventor and society, but in reality seems to initially require relatively little from an

[228] 21 CFR § 316.25(a)(3) (2010); Regulation EC No 141/2000, *supra* note 81 at 8(3)(c).
[229] 21 CFR § 316.3(3) (2013) ("clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways: (i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or
(ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary").
[230] FDA, *Designating an Orphan Product: Drug and Biological Products Frequently Asked Questions (FAQ)*, online: US Food & Drug Administration http://www.fda.gov.
[231] *Patent Act*, *supra* note 223, s 2.

inventor.[232] Market exclusivity, on the other hand, can be terminated if a drug company cannot or will not make its protected drug available in a sufficient quantity "to meet the needs of persons with the disease or condition for which the drug was designated".[233] The wording and inclusion of this provision serves to explicitly tie the application of exclusivity protection to ensuring that public health needs are being met, at least to some extent. This aspect of market exclusivity requires the commercialisation of orphan drugs, and therefore supports the underlying goal of orphan drug incentives of getting appropriate treatments to patients with rare diseases (because the incentive is not available until the drug is actually brought to market and may be rescinded if a drug developer does not make the drug sufficiently available). From the point of view of society, the ability to terminate market exclusivity may represent an improvement over patent protection, which is not necessarily dependent on an inventor making the patented subject matter available for public use. That being said, Canada's *Patent Act* does allow for compulsory licensing of patent-protected items under circumstances where exclusivity rights associated with a patent are being abused, including where demand for a patented article is not being adequately met.[234] Furthermore, making a product available on the market does not equate to providing affordable access and neither regime really addresses affordability issues. Concerns about the prices of orphan drugs are discussed in greater detail below, in Section 4.3.2.

4.2.2 Market Exclusivity Could Provide a More Effective Incentive than Patent Law

As described in the above section market exclusivity can address some of the public policy concerns surrounding patent law. At the same time, the incentive can also provide additional advantages for drug developers. From the perspective of the pharmaceutical industry, the ability of patent protection to generate innovation is probably limited because of the strict requirements of patent law and the associated uncertainty.[235] Marketing exclusivity operates in a manner that may make it a more effective incentive for orphan drug development.[236] Specifically, obtaining exclusivity can be easier in some respects than satisfying the strict

[232] See e.g. Edwin C Hettinger, "Justifying Intellectual Property" (1989) 18 Philosophy & Public Affairs 31 at 48.
[233] 21 USC § 360cc; Regulation EC No 141/2000, *supra* note 81 at 8(3)(b).
[234] *Supra* note 218, s 65(2)(c).
[235] See generally Shamnad Basheer, "The Invention of an Investment Incentive for Pharmaceutical Innovation" (2012) 15 J World IP 305 [Basheer, "An Investment Incentive"].
[236] Luchetti, *supra* note 221 at 83.

requirements of patent law, exclusivity regimes offer greater predictability than the patent application process, exclusivity protection may last longer than the effective patent life of a drug product, and marketing exclusivity provides an arguably stronger degree of protection than a patent because it is enforced by the drug regulatory agency. Each of these features are discussed in the following paragraphs and lead to the conclusion that market exclusivity is probably more likely to have an impact with respect to orphan drugs than patent law.

To begin with, it may be considered easier to obtain market exclusivity than it is to secure a patent because of the strict requirements of patent law. Both novelty and inventiveness are requirements of patent law[237] and therefore, patent regimes may insufficiently protect investments in pharmaceutical development.[238] Some valuable drug developments will involve finding how an existing drug can be used to treat an orphan disease; patent protection does not encourage such developments and may therefore be insufficient to protect the investments made to get marketing approval for an orphan disease. Many important medical advances and developments do not necessarily result in a patentable product because they are not sufficiently novel.[239] The goal of orphan drug policies is to increase access to safe and effective treatments for diseases would otherwise be neglected; whether or not such treatments are "novel" is immaterial from the perspective of patients. Market exclusivity may be a more effective incentive for orphan drug development than patent protection because it will be available regardless of whether or not a drug will be expected to satisfy the "novelty" requirement.

Similarly, aside from the risks inherent in the drug development process,[240] market exclusivity provisions can offer pharmaceutical companies greater predictability than patent regimes. To qualify for market exclusivity, one must "only" demonstrate that a drug is a safe and effective treatment for a designated orphan disease, the same standard that must be met for

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[237] *Patent Act*, *supra* note 223, s 2.

[238] Basheer, "Alternative Incentives", *supra* note 220 at 18 ("[t]he novelty and non-obviousness requirements make no concession for the development costs of inventions and thus cause patents to be withheld from drugs that are unlikely to reach the public without that protection. This gap in the patent system for drugs has created a pervasive problem in the pharmaceutical industry, causing firms to regularly screen their drugs during the research-and-development process and discard ones with weak patent protection").

[239] See e.g. Kakkar & Dahiya, *supra* note 76 at 232.

[240] See e.g. Ismail Kola & John Landis, "Can the Pharmaceutical Industry Reduce Attrition Rates?" (2004) 3 Nature Reviews 711 at 711-12 ("in aggregate only one in nine compounds makes it through development and gets approved").

market authorisation.[241] A company will know in advance whether their drug has orphan designation and can therefore rely on receiving exclusivity protection upon demonstrating the safety and efficacy of its product. Pharmaceutical companies looking to secure the investments needed to complete the development process can more confidently predict whether or not they will be granted exclusivity protection. Applying for a patent is less predictable because it involves interpretation of the legislation and is a far more subjective process.[242] Inventors seeking a patent risk being denied protection after they have already invested in R&D because they may be unable to demonstrate that their invention satisfies the applicable criteria (i.e. novelty and inventiveness). As such, patent law suffers from indeterminacy that may impair the effectiveness of patents as an incentive.[243] The predictability associated with market exclusivity permits pharmaceutical companies to plan their R&D strategy at less risk to their investment and with greater confidence that they will receive market exclusivity (provided the drug does receive market authorisation), making market exclusivity a more effective incentive.

Market exclusivity also arguably lasts longer than patent protection, at least during the period when a company can profit from its efforts, because it does not become effective until market authorisation is granted (i.e. from the moment a drug may be sold).[244] Patent protection, on the other hand, must typically be secured well before the drug development process can be completed and may, therefore, have expired or be close to its expiration by the time the drug is approved for the market.[245] Even if there is the opportunity for companies to have their patent extended, this is neither guaranteed nor free of charge.[246] Market exclusivity, unlike a patent extension, is granted automatically and without the additional legal fees of a patent application.[247] Therefore, in addition to being easier and more certain to obtain, market exclusivity can provide drug developers with protection from competition longer than a patent.

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[241] See e.g. Kakkar & Dahiya, *supra* note 76 at 232; Orfali et al, *supra* note 23 at 262.
[242] Basheer, "Alternative Incentives", *supra* note 220 at 20.
[243] *Ibid.* Basheer goes on to describe how the indeterminacy of patent regimes is heightened with respect to drug products "where the element of uncertainty is higher than other technological domains."
[244] Haffner, Whitley & Moses, *supra* note 72 at 821.
[245] Se e.g. Maxwell R Morgan, ""Regulation of Innovation under Follow-on Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism" (2010) 11 Colum Sci & Tech L Rev 93 at 105.
[246] *Ibid* at 106.
[247] Luchetti, *supra* note 221 at 83.

As such, market exclusivity protection may be of greater value to pharmaceutical companies and therefore more likely to encourage orphan drug development than patent law.

Finally, market exclusivity can be seen as offering a stronger, albeit narrower, degree of protection than patent law. Patent infringement is relatively common, and enforcing a patent is a time-consuming, expensive, and uncertain process.[248] Enforcing market exclusivity, on the other hand, is taken care of by the regulators of medicinal products. In the United States, for example, the FDA protects a product's exclusivity by not granting market approval for the same drug to treat the same orphan disease.[249] Pharmaceutical companies can therefore rely more confidently on exclusivity protection because sales of unauthorized medical treatments are rare, and will be quickly dealt with by the FDA in the unlikely event that a competitor does attempt to market an unauthorized drug.[250] Patent holders may also have to contend with challenges to their patent and the ensuing legal costs associated with defending their patent, and always face the possibility that their patent protection may be narrowed or found to be altogether invalid.[251] Market exclusivity more or less safeguards companies from this uncertainty,[252] apart from disputes with the FDA over whether another product is the "same" as the protected product or is clinically superior.

In summary, market exclusivity addresses some of the major public policy concerns about patent protection. Additionally, exclusivity functions in a manner that likely makes it a more attractive and useful incentive for pharmaceutical companies. It is suggested that patents, compared with market exclusivity, actually "play a very limited role in fostering innovation" because of such relative weakness and uncertainty.[253] Therefore, at least in theory, market exclusivity offers a number of advantages over patent protection. With respect to promoting orphan drug development market exclusivity appears to provide an effective supplement to patent law.

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[248] See e.g. Dov Greenbaum, "Incentivizing Pharmacogenomic Drug Development: How the FDA can Overcome Early Missteps in Regulating Personalized Medicine" (2008) 40 Rutgers LJ 97 at 124-25.
[249] *Ibid.*
[250] *Ibid.*
[251] *Ibid.*
[252] *Ibid.*
[253] Basheer, "An Investment Incentive", *supra* note 235 at 315.

4.3 Effect and Impact of Market Exclusivity

Orphan drug policies in general are considered to have been successful at encouraging pharmaceutical companies to invest in and develop treatments for rare diseases, with market exclusivity being the most important or "cornerstone" incentive in these policies, and many authors also consider that market exclusivity has, in fact, been effective at promoting the development of orphan drugs.[254] Nevertheless, there is some debate over the extent to which market exclusivity has been a factor in the increased development of orphan drugs. There certainly are other factors that have promoted interest in orphan drugs development (such as scientific advances and over-crowding of the "blockbuster drug" markets).[255] It has been suggested that simply looking at whether orphan drug development has increased since the introduction of the incentive is too simplistic and therefore market exclusivity regimes should require independent expert review in order to get a better understanding of the incentive's effectiveness.[256] At the same time, it is difficult to ignore the dramatic improvement in orphan drug availability since the introduction of orphan drug incentives. While it is not possible to identify the exact degree of effectiveness of any single incentive, and other factors have certainly played a part in promoting orphan drug development, it can reasonably be concluded that market exclusivity has had some positive impact on the number of orphan drugs being developed and brought to market.

That being said, it remains to be considered how well market exclusivity functions in terms of addressing the underlying goals of the incentive. Critics argue that orphan drug policies do not promote the development and marketing of drugs for neglected diseases to a satisfactory degree.[257] Two problems in particular have been identified in the literature: availability of approved treatments and access to approved treatments. Many identified orphan diseases still do not have any drugs approved for use, and, therefore, patients with those diseases do not have

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[254] See e.g. Franco, *supra* note 1 at 171; Haffner, Whitley & Moses, *supra* note 72 at at 821, 824; Office of Inspector General, *supra* note 43 at 8 ("market exclusivity...remains the most powerful incentive in the Orphan Drug Act").

[255] Kesselheim, "Using Market-Exclusivity", *supra* note 222 at 1859

[256] *Ibid*, i.e. correlation does not equate to causation.

[257] See e.g Moen, *supra* note 77 at 25 (there are still no treatments developed for the majority of rare diseases); Cheung, Cohen & Illingworth, *supra* note 34 at 191, 193 (the ODA does not limit what companies can charge for an orphan drug and this may be unethical because patients with rare diseases often do not have alternative treatment options).

appropriate treatment options available to them.[258] This first problem can largely be attributed to the definition of "orphan drug" that is used to determine the allocation of incentives. As discussed above, changes should be made to the eligibility criteria for "orphan drug" designation in order to direct investment in R&D toward diseases that are still without any available treatments. The second problem is that even where approved treatments exist, high prices for many orphan drugs can act as an insurmountable barrier to actually accessing these products.[259] Market exclusivity has been specifically cited in relation to both of these issues, with one vocal critic of orphan drug policies having observed that "unless a rare disease patient has a rare form of cancer and/or belongs to a high socioeconomic class, the US approach to orphan drugs seems unlikely to improve the patient's lot."[260] At best, it has been suggested that market exclusivity does not sufficiently direct pharmaceutical investments to rare diseases in an equitable manner with the result that many diseases are ignored in favour of the rare diseases that show the greatest potential to be profitable.[261] At worst, allegations have been made that market exclusivity actually impedes access to the very drugs it was meant to incentivize because pharmaceutical companies can charge very high prices without facing competition from another company marketing the same product.[262] The following section considers these issues, and arrives at the conclusion that while modifying market exclusivity schemes is not sufficient to address availability concerns, longer periods of exclusivity combined with the ability to terminate the protection in circumstances where it is no longer warranted could make some headway toward promoting affordable access to orphan drugs.

4.3.1 Impact of Market Exclusivity on Orphan Drug Development

As discussed in Chapter 3, for many patients a lack of available approved treatment is still very much an issue. Notwithstanding the observed successes of orphan drug policies, many rare diseases are still without any approved treatments[263] and, therefore, many patients with rare

[258] See e.g. Burke et al, *supra* note 78 at 452.
[259] See e.g. JE Davies, S Neidle & DG Taylor, "Developing and Paying for Medications for Orphan Indications in Oncology: Utilitarian Regulation vs Equitable Care?" (2012) 106 Brit J Cancer 14 at 15.
[260] Herder, "Orphan Drug Incentives", *supra* note 172 at 166.
[261] Herder, "When Everyone is an Orphan", *supra* note 37 at 253.
[262] See e.g. Cote & Keating, *supra* note 169 at 1186.
[263] See e.g. Rodriguez-Monguio, Spargo & Seoane-Vazquez, *supra* note 157 at 7 where the authors suggest there are over 6,500 diseases without approved treatments.

diseases still do not have approved treatments available to them.[264] Market exclusivity has been criticized on the basis that it does not sufficiently dictate the direction that pharmaceutical companies must take with respect to orphan drug development or, in other words, that exclusivity still permits market forces to direct R&D investment.[265] Recall that orphan drug incentives were introduced in order to address market failures for rare diseases. Obviously a number of factors will influence pharmaceutical investment, but there is evidence that disease prevalence[266] and the amount of publically available research about a disease do predict investment as between rare diseases.[267] Rare diseases that show the most potential for profit (such as rare cancers and cancer-related diseases) are the ones for which drugs are developed. Further, pharmaceutical companies are more likely to develop treatments for more prevalent rare diseases, in part because there is more publically available knowledge about these diseases due to their relative prevalence.[268] Unsurprisingly, research about a given disease will foster and promote the development of treatments for that disease.[269] As such, market exclusivity is not as precise or as targeted as would be desirable if the justification for providing incentives is that everyone deserves medical treatment regardless of how prevalent (or not) their disease is. On the other hand, it is unlikely that exclusivity periods actually *contribute* to diseases being neglected. Rather, market exclusivity merely does not sufficiently address the market forces that favour drug development for certain diseases. It is notable that this is only a failure if, as discussed above in Chapter 3, one concludes that there should be equitable access to treatment regardless of prevalence.

The concerns regarding diseases that remain orphaned by the pharmaceutical industry have been discussed at length in Chapter 3 and, without attempting to conclusively state how orphan drug incentives should be allocated, disease prevalence arguably should not be the sole

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[264] See e.g. Burke et al, *supra* note 78 at 452.
[265] See e.g. Herder, "When Everyone is an Orphan", *supra* note 37 at 253.
[266] Kesselheim, Treasure & Joffe, *supra* note 171 at 4.
[267] Cote & Keating, *supra* note 169 at 1190.
[268] Michelle Putzeist et al, "Drug Development for Exceptionally Rare Metabolic Diseases: Challenging but Not Impossible" (2013) 8 Orphanet J Rare Diseases 179 at 6.
[269] Publically available knowledge about disease history aids drug development by providing a greater understanding about the natural progression of a disease and the identification of clinically relevant endpoints by which the efficacy of a potential treatment can be measured. See generally Michael Silber, "Driving Drug Discovery: The Fundamental Role of Academic Labs" (2010) 2 Sci Translational Med 30cm16.

factor in designating "orphan" status. Concerns about which diseases drug companies choose to invest in, and the lack of availability of approved treatments for those with other diseases, does not necessarily lead to the conclusion that market exclusivity should not be implemented. Rather, the terms dictating the availability of market exclusivity should be carefully crafted to target drug development where most desirable from a policy perspective. This involves answering broad policy questions regarding what should qualify as justifying incentives and for what diseases incentives are warranted. In large part, this has been discussed in Chapter 3, where it was concluded that orphan drug incentives should strive to promote investment in diseases that are serious and/or likely to be neglected.

Furthermore, which diseases attract pharmaceutical investment may actually be of lesser concern in the Canadian context. Recall that it was originally determined that the potential for pharmaceutical innovation in Canada is too low to justify having an orphan drug policy.[270] If the development of new drugs for ultra rare or otherwise less profitable diseases is unlikely to happen in Canada regardless of any incentives being offered, then the issue of availability is less of a concern for Canadian policymakers. Market exclusivity in Canada could still encourage foreign drug developers of orphan drugs to apply for regulatory approval in Canada, which would be of benefit to Canadian patients because there does appear to be a time lag between approval in the United States or European Union and in Canada.[271] Ideally, from the perspective of patients with no available treatment, jurisdictions with greater innovative potential will address this shortcoming of orphan drug policies and see fit to direct R&D investments by some other means. As market exclusivity appears to be an effective incentive, it should be included in a Canadian orphan drug policy. The definition of "orphan" will determine eligibility for exclusivity and careful wording therefore should assist in directing pharmaceutical investments in a manner that will best address the availability problem.

4.3.2 Impact of Market Exclusivity on Access to Orphan Drugs

While the implementation of the ODA has been followed by dramatic increases in the development of rare disease treatments, it is not uncommon for patients with rare diseases to

[270] Cheung, Cohen & Illingworth, *supra* note 34 at 190.
[271] CORD, *Our Work*, *supra* note 12.

have trouble accessing these treatments because of their extremely high prices.[272] The biggest complaint about orphan drug policies is that they promote high drug prices,[273] and in general orphan drugs are expensive relative to treatments for common disorders.[274] Evidence shows that access to treatment for rare diseases is in fact hindered in both Canada and the United States by the substantial co-payments that are required for orphan drugs.[275] Market exclusivity in particular is frequently associated in the literature with high prices for orphan drugs.[276] This is problematic as the ultimate goal of orphan drug policies is to address the unmet medical needs of patients with rare diseases, a goal that cannot be accomplished if patients are unable to afford the drugs they need. There is therefore a strong imperative to "balance incentives for investment in research and development with assurance that the products will be available at a reasonable cost to patients."[277] This section explores the connection between market exclusivity and the high prices that are typical of orphan drugs.

It is alleged that market exclusivity encourages excessively high prices because the incentive in effect creates a monopoly within which a company may charge whatever it likes during the period of protection,[278] but it is uncertain whether or not market exclusivity actually operates in this manner. To begin with, even where exclusivity protection applies, other drug developers are free to market a different drug. "Non-similar" (in the European Union) or "non-same" (in the United States) treatments are not excluded by the market exclusivity regulations,

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[272] J Russell Teagarden, Thomas F Unger & Gigi Hirsch, "Access and Availability of Orphan Drugs in the United States: Advances or Cruel Hoaxes?" (2014) 2 Expert Opinion on Orphan Drugs 1147 at 1148.
[273] Cheung, Cohen & Illingworth, *supra* note 34 at 197.
[274] See e.g. Basheer, "An Investment Incentive", *supra* note 235 at 324.
[275] See e.g. Carl Rudolf Blankart, Tom Stargard & Jonas Schreyogg, "Availability of and Access to Orphan Drugs: An International Comparison of Pharmaceutical Treatments for Pulmonary Arterial Hypertension, Fabry Disease, Hereditary Angioedema and Chronic Myeloid Leukaemia" (2011) 29 Pharmaeconomics 63 at 80 (rare disease drugs that are not approved in Canada can be accessed via the Special Access Program but drugs accessed in this manner are not covered). See also Eve A Roberts, Matthew Herder & Aiden Hollis, "Fair Pricing of "Old" Orphan Drugs: Considerations for Canada's Orphan Drug Policy" (2015) 187 CMAJ 422 at 422-23 (describing one example of prices for an orphan drug being significantly raised, thereby impairing the ability of patients to access a necessary treatment).
[276] See e.g. Cote & Keating, *supra* note 169 at 1190. But see Babaian, *supra* note 74 at 712.
[277] Kesselheim, "Using Market-Exclusivity", *supra* note 222 at 1856.
[278] See e.g. Basheer, "An Investment Incentive", *supra* note 235 at 324.

and even similar/same treatments can be approved for sale if they are clinically superior.[279] At least one study indicates that orphan drugs protected by market exclusivity do not dissuade alternative treatments from being developed and marketed.[280] As discussed above,[281] a number of factors increase the likelihood of additional drugs entering the market for a specific orphan disease, with the greatest predicator being the amount of scientific output for that disease (whereby more scientific publications about a disease increases the chances that another orphan drug will be developed as a treatment for that disease).[282] In addition, certain types of rare diseases are the subject of more R&D investment regardless of whether there are exclusivity-protected drugs already on the market, with rare oncological disorders having a greater chance of having subsequent orphan drug products developed.[283] Furthermore, rare diseases for which a previously approved orphan product has been shown to be highly profitable are more likely to invite competition, and the more prevalent rare diseases are more likely to have subsequent treatments developed and marketed.[284]

Additionally, even for diseases for which there is only a single approved treatment, it is not necessarily accurate to say that market exclusivity has created a monopoly for that disease. Rare disorders can lead to the appearance of a monopoly regardless of any exclusivity rights being granted, simply because small markets are less likely to attract competitors.[285] At least one member of the pharmaceutical industry argues that what appears to be a monopoly may in fact be merely a reflection of either a market that is too small to draw additional drug developers, or that insufficient time has passed to allow for a competitor to successfully develop a different drug and enter the market.[286] Therefore, while high prices for orphan drugs are indeed a problem, it is not necessarily true that market exclusivity causes the high prices. Even the recent Kaiser Health News report, which is highly critical of market exclusivity and the high prices of orphan drugs, acknowledges that it "is difficult to say exactly how *or if* orphan exclusivity affects the price of

[279] Tambuyzer, *supra* note 25 at 924.
[280] Anne EM Brabers et al, "Does Market Exclusivity Hinder the Development of Follow-on Orphan Medicinal Products in Europe?" (2011) 6 Orphanet J Rare Diseases 59 at 9.
[281] At 45.
[282] Brabers et al, *supra* note 280 at 7.
[283] *Ibid.*
[284] *Ibid.*
[285] Babaian, *supra* note 74 at 712.
[286] Tambuyzer, *supra* note 25 at 924.

Humira [an orphan drug]..."[287] This point is important because it would be unwise to not implement what has been shown to be an effective incentive if exclusivity is not actually contributing to the problem of high prices.

A number of factors likely work in conjunction to inform drug pricing decisions, thereby making it difficult to identify unreasonable drug prices.[288] While not necessarily the case for all orphan drugs, it can be incredibly expensive to successfully develop and produce safe and effective treatments for a very limited patient population.[289] A number of features specific to rare diseases can make the development and testing of treatments particularly challenging and, therefore, costly to pharmaceutical companies.[290] From the perspective of the pharmaceutical industry, the high prices of orphan drugs are necessary because of the additional risks and challenges associated with developing, testing, and marketing orphan drugs.[291] A small market, such as that for an orphan disease, naturally creates the need to charge a higher price in order to profit from one's investment because costs cannot be spread among a large group of buyers.[292] Without the protection provided by an exclusivity period, developers would be even less likely to recover their R&D investment and make a profit from orphan drugs.

On the other hand, other authors suggest that the prices of orphan drugs are artificially high,[293] that developing and bringing orphan drugs to market is no longer the financially risky endeavour it was once thought to be, and that orphan drugs can actually be highly profitable.[294] Orphan drugs may in fact be more profitable than non-orphan drugs because of a number of factors that both increase potential revenue (e.g. higher price points, larger market shares,

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[287] Sarah Jane Tribble & Sydney Lupkin, "The Orphan Drug Machine: Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies" *Kaiser Health News* (17 January 2017), online: KHN < http://khn.org> [emphasis added].
[288] Eline Picavet et al, "Shining a Light in the Black Box of Orphan Drug Pricing" (2014) 9 Orphanet J Rare Diseases 62 at 3 [Picavet et al, "Shining a Light"].
[289] See e.g. Oo & Rusch, *supra* note 26 at 257.
[290] Tambuyzer, *supra* note 25 at 923 (a lack of information about natural course of the disease, late diagnosis, lack of validated clinical end points as well as considerable practical challenges in running clinical trials (getting a sufficient number of research participants, transporting them and providing accommodation and – sometimes – language translation) are cited as reasons why developing orphan drugs is particularly challenging and expensive).
[291] *Ibid* at 922-24.
[292] Babaian, *supra* note 74 at 712.
[293] Murphy et al, *supra* note 56 at 483.
[294] Rodriguez-Monguio, Spargo & Seoane-Vazquez, *supra* note 157 at 4.

exclusivity protection, and faster uptake) and decrease development costs (e.g. shorter and smaller clinical trials, fee waivers, and subsidies).[295] These factors call into question the claims from the pharmaceutical industry that orphan drug development remains a risky and costly investment. Furthermore, some orphan drugs are effective treatments for multiple indications, including some common diseases, and therefore have a relatively large pool of potential buyers.[296] Just because a drug treats one extremely rare disease does not necessarily mean that the drug will yield a low return on investment overall when one considers all the other indications for which the drug may be approved. In other words, "the small number of patients treated with an orphan drug and the limited economic viability of orphan drugs can be questioned in a number of cases."[297]

The preceding discussion shows that orphan drugs are not a homogenous group; some orphan drugs represent highly lucrative investments while others will be barely profitable at all. While there is some evidence that companies will set lower prices when there are multiple competing treatments available,[298] this does not lead directly to the conclusion that the drug prices were unjustifiably high to begin with. Arguments that orphan drugs are overly expensive, based on the fact that companies reduce their prices when they face competition in the market,[299] over-simplify the issue and are not accurate with respect to all orphan drugs.

It is not necessarily accurate to say that market exclusivity gives a developer a monopoly over a disease. It is more likely that the costs of orphan drug development combined with a smaller market also "encourages" high prices, not entirely the market exclusivity period itself. This point is important because it speaks to how to most effectively address the problem of patient access. As market exclusivity allows high prices then it would be more useful to seek to lower the costs of orphan drug development. Interfering with exclusivities is unlikely to significantly improve patient access if the costs of orphan drug development are not also decreased. Subsidizing orphan drug development will be addressed in further detail below, in Chapter 6. Furthermore, it is at least possible that this will be less of an issue in Canada because,

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[295] Meekings, Williams & Arrowsmith. *supra* note 30 at 663. This is likely contributed to by the fact that once labeled an "orphan", drug prices are substantially increased (see e.g. Roberts, Herder & Hollis, *supra* note 275 at 422, 23).
[296] Simoens, *supra* note 150 at 3.
[297] *Ibid* at 6.
[298] Picavet et al, "Shining a light", *supra* note 288 at 13.
[299] *Ibid*.

unlike the United States, Canada does have a price control mechanism that is intended to prevent companies from charging excessively high prices for pharmaceuticals.[300]

4.3.3 Concerns about Exploitation of Market Exclusivity

The high prices of many orphan drugs invite close scrutiny and there has been renewed criticism about orphan drug policy in general, and market exclusivity in particular.[301] Market exclusivity has been criticized as encouraging exploitation by pharmaceutical companies. This line of criticism stems largely from two core concerns about how the exclusivity provisions function: one, multiple exclusivity periods can be obtained for the same orphan drug and two, obtaining market exclusivity is not related to any additional costs or risks being incurred to develop and market an orphan drug. Some authors argue that pharmaceutical companies exploit orphan drug policy by obtaining multiple periods of exclusivity for the same drug, a practice that is permitted when the drug is approved to treat another orphan indication.[302] This concern has become particularly pressing in the wake of scientific advances that allow for more precise identification of distinct orphan indications.[303] The second concern relates to the original justification for having orphan drug incentives, with some authors considering that the incentives are no longer necessary because the development of orphan drugs no longer incurs the same degree of risk and additional cost.[304] This second argument has already been addressed above, in Chapter 3.[305] The following paragraphs consider the issue of granting multiple exclusivity periods for the same orphan drug.

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[300] *Patent Act*, *supra* note 223, ss 79-103 (these sections allow the Patented Medicine Prices Review Board ("PMPRB") to take action against patentees that charge an "excessive price" for a patented drug). On the other hand, it is fairly unlikely that this measure will suffice to ensure affordable access given that Canada actually pays a lot for drug products relative to other countries. See generally Health Canada, *Consulting on Proposed Amendments to the Patented Medicines Regulations*, online: Government of Canada https://www.canada.ca (the agency recently solicited comments on proposed amendments to the Regulations governing the operation of the PMPRB, citing concerns that, because the regulations are outdated, Canadians are not being adequately protected from excessive prices for patented drugs). As there is reason to question the effectiveness of the PMPRB in its current form, the PMPRB is likely to also be ineffective with respect to orphan drug price control.

[301] See e.g. Tribble & Lupkin, *supra* note 287.

[302] See e.g. Loughnot, *supra* note 35 at 366.

[303] *Ibid* at 374-75.

[304] See e.g. Simoens, *supra* note 150 at 2.

[305] At 23-24.

Both the ODA and the European Union Regulations permit a company to obtain multiple exclusivity periods for the same drug (provided it can be shown to be a safe and effective treatment for multiple orphan conditions).[306] Permitting multiple exclusivities for the same drug is not necessarily problematic in and of itself because it requires a company to undertake additional clinical trials and incur the costs associated with obtaining approval for other uses and may, therefore, be an appropriate application of the incentive.[307] However, advances in the field of pharmacogenomics since orphan drug policies were first implemented have compounded this concern.[308] Pharmacogenomics can be used to sub-divide a disease population in order to create distinct groups of patients with less than 200, 000 people (i.e. "creating" an orphan disease that did not previously exist).[309] The opportunity to obtain multiple exclusivity periods for each designated orphan disease is sometimes seen as encouraging this practice of "salami slicing",[310] and some authors argue that these scientific advancements need to be accounted for by making amendments to the current orphan drug regulations.[311] However, it is debateable whether this is a problem or an advantage of orphan disease policy.

On the one hand, patients may benefit from the increased attention on their specific rare disease subset. Recall that more scientific knowledge about a disease increases the likelihood that a drug will be developed to treat that specific disease.[312] This supports the assertion that the use of pharmacogenomics to increasingly identify narrower disease targets should be regarded as "an achievement [of orphan drug policies] rather than a handicap or nuisance."[313] Increasing interest, and therefore investment, in rare diseases was *the* point of enacting an orphan drug policy; doing so ensured that these diseases are no longer being "orphaned" by the pharmaceutical industry.

On the other hand, the practice of splitting a disease into subcategories may in essence be artificially creating an orphan disease, something pharmaceutical companies may be inclined to

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[306] See e.g. Loughnot, *supra* note 35 at 366.
[307] Tambuyzer, *supra* note 25 at 924
[308] See e.g. Loughnot, *supra* note 35 at 366.
[309] See e.g. Alain Denis et al, "Issues Surrounding Orphan Disease and Orphan Drug Policies in Europe" (2010) 8 Appl Health Econ Health Pol'y 343 at 344.
[310] *Ibid.*
[311] Cheung, Cohen & Illingworth, *supra* note 34 at 193-94.
[312] Putzeist et al, *supra* note 268 at 12.
[313] Panos Kanavos & Elena Nicod, "What Is Wrong with Orphan Drug Policies? Suggestions for Ways Forward" (2012) 15 Value in Health 1182 at 1183.

do specifically in order to access the related incentives. This can be considered to be misaligned with the spirit of orphan disease policy.[314] Increased stratification of diseases is alleged to be overburdening the rare disease regime, with the result that common diseases are being "artificially" classified as rare and exclusivity protection is being granted where it is not truly warranted (i.e. for diseases that would not otherwise be neglected in the absence of incentives).[315] There is some evidence indicating that drugs for biomarker-defined disease subsets require less time and money to develop, fueling concerns that companies are taking advantage of the prevalence-based definition of "orphan" in order to access incentives.[316] Exploitation of the rules for profit does in fact appear to be an unintended consequence of orphan drug incentives.[317] For example, the European Regulations permit products that have been used for many years to be subsequently authorized as orphan products with relatively little developmental work (but with great cost to individual patients and/or their health care payers) and for schemes that are meant to reward socially valuable innovation this potential exploitation is troublesome.[318]

4.4 Recommendations for Implementing Market Exclusivity in Canada

4.4.1 Addressing the Affordability Issue

Modifying the rules that govern exclusivity protection may address the issue of high prices for orphan drugs, but only to the extent that the prices are actually related to exclusivity periods. One suggestion to promote affordable access to orphan drugs is to provide shorter periods of market exclusivity.[319] This suggestion is made under the, fairly reasonable, expectation that companies will have to lower their prices when the period of exclusivity ends in order to avoid losing all of the market sales to a competitor who sells the same drug at a reduced price.[320] To the extent that drug companies could not rely on price increases to recoup costs,

[314] Denis et al, *supra* note 309 at 344.
[315] Palmer & Hughes, *supra* note 173.
[316] Kesselheim, Treasure & Joffe, *supra* note 171 at 7.
[317] See generally Robin E Ferner & Dyfrig A Hughes, "The Problem of Orphan Drugs: Incentives to Make Orphan Drugs Should be Proportionate to their Benefits" (2010) 341 British Med J 1059.
[318] I Hudson & A Breckenridge, "The Challenges of Orphan Drugs and Orphan Diseases: Real and Imagined (2012) 92 Clinical Pharmacology & Therapeutics 151 at 155.
[319] See e.g. Loughnot, *supra* note 35 at 368.
[320] *Ibid*.

significantly shorter exclusivity terms could impair the effectiveness of the incentive altogether, by once again making orphan drug development unprofitable and causing the pharmaceutical industry to lose interest in the orphan drug market.

A better solution, at least in theory, would be to grant longer periods of exclusivity. This is likely to be an unpopular recommendation, one that relates back to the question of whether or not market exclusivity encourages high prices. Market exclusivity at least *allows* companies to charge as much as they think they can get, for as long as the exclusivity period lasts. In theory, lengthening the period of exclusivity could encourage companies to set lower prices because they would have a longer period of time during which they would not have to share the market with a competitor selling the same drug to the same group of patients.

Longer periods of exclusivity are a reasonable policy solution provided that the claims of those in the industry, that market protection is necessary to off-set the additional risks and costs of orphan drug development and that orphan drug prices are an honest reflection of what companies need to charge in order to make orphan drug development profitable,[321] are correct. As discussed above, in all likelihood orphan drug prices are probably justified in some cases and not in others. Accordingly, providing a longer period of exclusivity should be done in conjunction with the possibility of extinguishing market protection once a drug becomes "sufficiently profitable" because this should discourage companies from pricing their drugs overly high.[322] This is provided for by the European Union Regulations, though some clarification of the term "sufficiently profitable" is necessary.[323] For example, it would need to be determined whether "sufficiently profitable" means that a company has recovered its R&D costs, or that they have recovered their costs and made a specified amount of profit. It has been suggested that the threat of reducing the length of exclusivity might impair the effectiveness of the incentive.[324] However, the effectiveness of market exclusivity would likely be weakened only if the provision were to be vague and companies uncertain about how and when it would be applied.

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[321] See e.g. Tambuyzer, *supra* note 25 at 926.
[322] *Ibid*.
[323] Picavet, Cassiman & Simoens, *supra* note 87 at 7. While EU policy provides for termination of exclusivity upon a drug becoming "sufficiently profitable", this has never been used.
[324] Michaux, *supra* note 208 at 668.

A significant limitation of this recommendation is the lack of transparency surrounding the pricing of orphan drugs,[325] and this limitation would need to be addressed in order for the potential termination of exclusivity to have an impact on orphan drug pricing. The information and knowledge imbalance as between drug developers and the regulatory authority would likely result in some orphan products remaining unnecessarily protected by market exclusivity. There would also be the possibility that companies that are more forthcoming about their R&D costs would be "punished" by having their market exclusivity terminated while competitors who intentionally withhold information keep their protection intact. It is unclear whether or not this possibility could be addressed through legislation, for example by putting the onus of justifying continued protection on the company (e.g. by requiring an accounting of costs and profits halfway through the exclusivity period), though such a requirement is unlikely to be popular with the pharmaceutical industry and could impair the effectiveness of market exclusivity as an incentive for orphan drugs.

Additionally, any positive impact of terminating market exclusivity for sufficiently profitable orphan drugs hinges on Health Canada's ability to collect financial information from companies post-approval and to enforce post-approval requirements. Assessments of Health Canada's administration of its Notice of Compliance with Conditions ("NOC/c") policy may provide helpful insight regarding how well the agency can be expected to determine whether an orphan drug has become sufficiently profitable and terminate market exclusivity accordingly. The NOC/c program is intended to accelerate the approval of treatments for rare and serious conditions where patients may benefit from earlier access even though clinical trials have not yet demonstrated that the product has a clinical benefit.[326] Under the NOC/c program, drugs can be approved for market based on clinical trials showing efficacy on a surrogate outcome, as opposed to a demonstration that the drug has a clinical benefit, subject to certain post-marketing

[325] Pricing mechanisms for orphan drugs have been referred to as a "black box" as there is so little concrete knowledge about how orphan drug prices are set. See generally Jonathan C P Roos, Hanna I Hyry & Timothy M Cox, "Orphan Drug Pricing May Warrant a Competition Law Investigation" (2010) 341 BMJ 1084; Picavet et al, "Shining a Light", *supra* note 288.
[326] Health Canada, *Guidance Document: Notice of Compliance with conditions (NOC/c)*, (Ottawa: Public Works and Government Services Canada, 2016) online: Government of Canada https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/compli-conform/noccg_accd-eng.pdf at 1-2.

conditions (a common condition being that the drug company supply evidence that the drug actually does provide a clinical benefit).[327] Lexchin and Law both found that it is not unusual for conditions to remain unfulfilled for many years, seemingly without any action taken to enforce the conditions.[328] That being said, under the NOC/c policy conditions are enforced by withdrawing market approval for the drug in question, which Law notes is a drastic, "all-or-nothing" measure that Health Canada may be hesitant to take.[329] Terminating market exclusivity would be a less drastic means of applying the provision, and the onus of providing information could be placed on the drug company (by automatically terminating market exclusivity at a specific time unless the company provides evidence that the drug is not sufficiently profitable).

4.4.2 Addressing Concerns about Exploitation of Orphan Drug Policies

The potential for exploitation, particularly to the extent that it has been compounded by scientific advances, indicates that orphan drug policies in their current form are somewhat outdated. As originally enacted, the ODA does not appear to have contemplated potential exploitation in this manner. While greater attention to specific disease subsets may be beneficial to patients, Canada should take advantage of hindsight by introducing a more nuanced incentive scheme that will account for the scientific advances that have generated concerns about abuse of orphan drug incentives by pharmaceutical companies.

It was concluded above that market exclusivity regulation in Canada should include the possibility of terminating the period of exclusivity once a drug becomes "sufficiently profitable". Building on this recommendation, determinations of "sufficiently profitable" should take into account profitability from multiple indications for which a drug is approved.[330] Typically, the prevalence of these combined indications are not "added up" when determining how profitable a drug is, and it has been convincingly argued that doing so would better align with the spirit of the legislation.[331] Not "adding up" profitability from multiple indications when assessing the profitability of an orphan drug assumes that a developer is incurring roughly equivalent

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[327] *Ibid* at 2-3.
[328] Joel Lexchin, "Notice of Compliance with Conditions: A Policy in Limbo" (2007) 2Health Pol'y 114 at 119; Michael R Law, "The Characteristics and Fulfillment of Conditional Prescription Drug Approvals in Canada" (2014) 116 Health Pol'y 154 at 160)
[329] *Ibid* at 160.
[330] Kanavos & Nicod, *supra* note 313 at 1183.
[331] Denis et al, *supra* note 309 at 344.

additional costs and risks for each subsequent orphan indication, an assumption that was probably reasonable when these policies were originally enacted. If this assumption is correct, then considering each use of an orphan drug as separate is reasonable; it would make sense to assess whether Drug X as a treatment for Disease A is sufficiently profitable by only considering the profits made by selling Drug X as a treatment for Disease A.

It is not necessarily appropriate to assess profitability by considering all indications for which a drug is approved, particularly when the indications relate to very different diseases and would have involved significant additional costs to test. However, "adding up" profits is appropriate where the approvals have been essentially "built off" the first approval and the associated clinical testing such that the subsequent approvals required relatively less risk and cost to obtain. Conducting clinical trials for a drug to treat bio-marker defined disease subsets does in fact appear to be quicker and cheaper.[332] Where Drug X is approved to treat Diseases A(1), A(2), and so on, with each distinct orphan disease being a bio-marker defined subset of Disease A, it would be logical to add up the associated costs and profits for the purpose of determining whether Drug X is "sufficiently profitable" that termination of the exclusivity period is warranted. In these circumstances, the identification of each disease subset and the associated drug development would have built off each other, and the associated risks and costs would be highly related. A Canadian market exclusivity regime should, therefore, clearly state that the assessment of a drug's profitability will take into consideration all of the bio-marker defined disease subsets for which a drug is approved.[333]

As with the issue of availability, it will be difficult to significantly deter misuse of orphan drug policy by making amendments at the individual incentive level. To meaningfully deter exploitation, changes need to be made at the orphan drug designation stage, for example by restricting what type of drugs will be given orphan status.[334] In the alternative, it is possible that the potential for exploitation is simply a price that has to be paid in order for market exclusivity to be a sufficiently effective incentive. While it may go against the spirit of the legislation, given

[332] Kesselheim, Treasure & Joffe, *supra* note 171 at 7.
[333] This recommendation is made while also acknowledging the difficulties that exist with respect to obtaining a full and accurate understanding of the costs and profits associated with orphan drug products, as discussed above (at 55-56).
[334] See e.g. Kesselheim, Treasure & Joffe, *supra* note 171 at 7.

the increased development of treatments for patients with rare diseases, whether or not this is actually detrimental to public health outcomes is open to debate.

4.5 Summary

Market exclusivity appears to be an effective incentive to promote investment in rare disease treatments. As Canadian patients still face a significant time lag between when orphan drugs are approved in other jurisdictions and when they become available on the Canadian market,[335] market exclusivity should be introduced in Canada as an orphan drug incentive. This will hopefully encourage drug developers to at least market their orphan drug products in Canada.

As affordable access to approved treatments remains a problem, measures should be taken to address the exceptionally high prices of orphan drugs. This could include lengthening periods of exclusivity, which although it seems counterintuitive, could ultimately result in lower prices by allowing a longer period in which the drug's sponsor can recoup its investment. In order to alleviate some public policy concerns, and attempt to discourage over-pricing, the period of exclusivity should be terminated once a drug becomes "sufficiently profitable," with this assessment taking into account profits from all related disease subsets. The potential to exploit orphan drug policy by "salami-slicing" diseases, while ostensibly misaligned with the spirit of orphan drug policy, may actually improve patient health outcomes in the long run by generating greater attention to disease subsets.

The above recommendations, to lengthen the exclusivity period and provide the possibility that it will be terminated, are unlikely to cause orphan drug prices to drop dramatically; any modifications to market exclusivity provisions can only be expected to temper some unreasonably high prices. While market exclusivity would likely have some positive impact in Canada, its implementation should not be done in isolation. It should be implemented with complementary measures that also more widely disperse the costs of the incentive. To elaborate, market exclusivity is "paid for" by consumers of orphan drugs (and any third party paying for those orphan drugs), to the extent that it contributes to higher prices. The moral imperative and commitment to equality that justify having orphan drug incentives in the first place also justify spreading the cost of incentives beyond the very patients that are intended as

[335] During which time patients must apply to the SAP, and pay for the drugs themselves in order to access drugs that are not approved in Canada.

the primary beneficiaries of orphan drug policies. Both PRVs and tax credits for orphan drug development more widely distribute the burden of paying for the incentives. These complementary measures are discussed in the following two Chapters.

CHAPTER 5: INCENTIVE OPTION 2 – PRIORITY REVIEW VOUCHERS

5.1 Introduction

Compared to market exclusivity, PRVs are relatively novel incentives that are used in the United States to encourage pharmaceutical innovation in circumstances where market failures have otherwise led to medical needs being neglected. As with market exclusivity, PRVs supplement patent law as an incentive for drug development. PRVs operate as a "pull strategy" to encourage drug development because they reward research output (i.e. by increasing financial returns), as opposed to a "push strategy" (one that would subsidize research input).[336] A PRV entitles a drug sponsor to have a new drug application ("NDA") subject to priority review by the FDA, as opposed to standard review.[337] Priority review is typically reserved for drugs that are expected to provide a significant benefit over existing treatments,[338] and a voucher allows a drug developer to circumvent this criterion. The FDA's goal is to complete a priority review of a NDA within 6 months.[339] As the FDA typically takes about 10 months to complete a standard review,[340] priority review of a NDA can allow a sponsor to market, and profit from, their product within an accelerated timeframe (provided that they are successful in obtaining market authorisation). Priority review can also allow a company to beat a competitor to the market. There are currently three programs under which PRVs are available: neglected tropical diseases, rare pediatric diseases, and, most recently, for medical countermeasures.[341]

This Chapter will proceed as follows: Section 5.2 describes how the voucher programs came to be implemented and the vouchers that have been awarded and sold thus far; Sections 5.3 and 5.4 provide a critical analysis of the voucher program, first from the perspective of public policy concerns, then by considering the impact and effect of the programs; Section 5.5 considers

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[336] Ridley, Grabowski & Moe, *supra* note 19 at 316.
[337] 21 USC §360ff(a)(2) (2012).
[338] FDA, *Priority Review*, online: US Food & Drug Administration https://www.fda.gov.
[339] *Prescription Drug User Fee Act of 1992*, Pub L 102-571, § 103(1)(b), 106 Stat 4491 at 4491 (codified as amended at 21 USC 379g (2010) ["*PDUFA*"].
[340] FDA, *Priority Review*, *supra* note 338.
[341] *21st Century Cures Act*, Pub L No 114-255, § 3086, 130 Stat 1033 at 1144 (2016) (to be codified at 21 USC § 360bbb-4a) ["*21st CC Act*"].

how PRVs would function as an orphan drug incentive in Canada; finally, Section 5.6 summarizes the issues and conclusions reached in this Chapter.

5.2 The Development and Adoption of Priority Review Vouchers

The idea for PRVs as an incentive for pharmaceutical development was originally proposed by David B Ridley, Henry G Grabowski and Jeffrey L Moe, a trio of academics based out of Duke University, in a 2006 article published in *Health Affairs.*[342] In this article they describe how market failures have resulted in tropical diseases being neglected by the pharmaceutical industry.[343] Infectious and parasitic diseases are typically suffered by people living in low-income countries and, therefore, there is little financial incentive for companies to invest in developing treatments for these diseases.[344] As with rare diseases, tropical diseases are unlikely to be a profitable investment and therefore have been neglected by pharmaceutical companies.[345] In order to address this problem Ridley, Grabowski, and Moe proposed that a voucher for FDA priority review be awarded to drug sponsors who develop and register with the FDA treatments for tropical diseases.[346] In order to be eligible for a voucher, the proposed voucher program would have required that companies forgo patent rights, and have at least one manufacturer for the product.[347] These particular eligibility requirements ultimately were not included in the enacted legislation. Following this proposal, the Tropical Disease Priority Review Voucher program was formally introduced in 2007.[348] In order to be eligible, a drug must be intended for the treatment or prevention of a designated tropical disease.[349] There is a list of targeted diseases from which drug eligibility will be determined, though additional diseases can be, and have been, added to this list by order of the Secretary.[350] Drugs must also be eligible for priority review, in other words, be expected to provide a significant benefit over existing

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[342] *Supra* note 19.
[343] *Ibid* at 313.
[344] *Ibid*.
[345] *Ibid*.
[346] *Ibid.*
[347] *Ibid* at 314.
[348] *Food and Drug Administration Amendments Act of 2007*, Pub L No 110-85, § 1102, 121 Stat 823 (codified as amended at 21 USC 360n (2011)) ["*FDAAA 2007*"].
[349] 21 USC 360n(b) (2012).
[350] 21 USC § 360n(a)(3) (2012) i.e. Ebola, Zika Virus Disease have been added since the program was implemented.

(previously approved) treatments in terms of safety or effectiveness,[351] in order to qualify for a voucher.[352]

Pediatric populations have also historically been neglected by companies when conducting clinical trials and, therefore, safety and efficacy information about the use of drugs that are approved for use by adults in pediatric populations is lacking.[353] Furthermore, there is also a dearth of drug development for diseases, rare or otherwise, that specifically occur in pediatric populations.[354] A voucher program for rare pediatric diseases ("RPDs") was, therefore, subsequently introduced in 2012 via the *Food and Drug Administration Safety and Innovation Act* ("*FDASIA*").[355] An RPD is defined as a rare disease that is serious or life-threatening "in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents."[356] This is not the first FDA incentive directed at improving the treatment options for pediatric populations. "Pediatric exclusivity" provides an additional six months of exclusivity to companies who conduct studies of new and previously approved drugs with pediatric populations.[357] As with the tropical disease program, RPD treatments must qualify for priority review in order to be eligible for a voucher.[358] A formal assessment of the effectiveness of the

[351] *PDUFA*, *supra* note 339, § 103(1)(b).
[352] 21 USC § 360n(4)(A)(ii) (2012).
[353] See e.g. Charles C Cote et al, "Is the "Therapeutic Orphan" About to be Adopted?" (1996) 98 Pediatrics 118 at 118.
[354] See e.g. Edward Connor & Pablo Cure, "'Creating Hope' and Other Incentives for Drug Development for Children" (2011) 3 Science Translational Medicine 66cm1 at 1.
[355] *FDASIA*, *supra* note 62, § 360ff.
[356] *Advancing Hope Act of 2016*, Pub L No 114-229, § 2(a)(1)(A), 130 Stat 943 at 943 (to be codified at 21 USC 360ff) recently revised definition of "rare pediatric disease" in a manner that arguably broadens the eligibility criteria. The previous definition stated ""The disease primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents." See also Alexander J Varond, "Senate Votes to Extend Pediatric Voucher Program and Expand Eligibility" (26 September 2016), online: FDA Law Blog www.fdalawblog.net (describing how the *Advancing Hope Act* "would likely expand eligibility for pediatric vouchers. For example, diseases with varying degrees of severity (i.e., diseases with very serious forms with very short life expectancy and less serious forms with much longer life expectancy) would be eligible. In addition, diseases that are extremely severe in childhood but tend to be less severe in adulthood may qualify").
[357] Initially provided for by the *Food and Drug Administration Modernization Act of 1997*, Pub L No 105-115, § 111, 111 Stat 2296 at 2305(codified as amended at 21 USC 351a (2012)).
[358] 21 USC 360ff(a)(4)(C) (2012).

RPD program was mandated and completed by the Government Accountability Office ("GAO") in 2016.[359] The RPD voucher program included a sunset clause that would have terminated the program in 2015,[360] but the *21st Century Cures Act*, enacted in 2016, extended the program until September 30, 2020.[361] That Act also introduced a third PRV program, one for material threat medical countermeasures,[362] and requires that a more detailed evaluation of all three voucher programs be completed by the GAO and submitted by January 31, 2020.[363]

There are conditions on the use of vouchers under all three programs; presumably these were included in the legislation in order to mitigate the additional workload that vouchers are expected to impose on the FDA. In order to redeem a PRV, a sponsor must pay an additional priority review user fee, the amount of which is to be based on the difference between the average cost incurred by the FDA in the previous year of reviewing a New Drug Application according to its standard review process and the average cost to perform a priority review.[364] The FDA is in charge of setting this price each fiscal year, and amounts have ranged from $2,325,000 in 2014 to $5,280,000 in 2012.[365] The RPD priority review fee for 2017 was $2,706,000.[366] Sponsors also have to give the FDA 90 days notice of their intention to redeem a PRV, in order

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[359] The original PRV program for tropical diseases never had any requirement for a formal assessment of its efficacy.

[360] *FDASIA*, *supra* note 62, § 908(b)(5). More specifically, the sunset clause would have ended the program "after the last day of the 1-year period that begins on the date that the Secretary awards the third rare pediatric disease priority voucher under this section".

[361] *Supra* note 341, § 3013. The RPD PRV program is now set to terminate in 2020 but drugs that have been given RPD designation prior to September 30, 2020 and are approved by the FDA no later than September 30, 2022 will still be eligible for a voucher.

[362] *Ibid*, § 3086(a)(4). Eligible products are those that are "intended for use to prevent or treat harm from a biological, chemical, radiological, or nuclear agent (or harm caused by an MCM used against such agent) determined by the Department of Homeland Security to be a material threat" and have not been previously approved by the FDA.

[363] *Ibid*, § 3014.

[364] 21 USC § 360ff(c) (2012). See also US, Department of Health and Human Services, *Tropical Disease Priority Review Vouchers: Guidance for Industry*, (Silver Spring, MD: Office of Communications, Division of Drug Information, 2016) online: US Food & Drug Administration https://www.fda.gov/downloads/Drugs/Guidances/UCM080599.pdf at 9 (the FDA has indicated that the user fee will be the same for vouchers awarded for NTDs) [Department of Health and Human Services, *Tropical Disease PRVs*].

[365] See e.g. Gaffney, Mezher & Brennan, *supra* note 60.

[366] *Fee for Using a Rare Pediatric Disease Priority Review Voucher in Fiscal Year 2017*, 18 Fed Reg 67360 (2016).
This fee is in addition to the *PDUFA* user fee that is typically required for NDAs.

to give the agency sufficient time to organize its resources and plan its review strategy.[367] The tropical disease voucher program originally required advance notice of 365 days but subsequent amendments have reduced this to 90 days.[368] Drug sponsors who have been awarded a voucher may either use the voucher themselves or transfer it to another company.[369] The tropical disease voucher program, as originally enacted, stated that vouchers could only be transferred once,[370] though this has since been amended and the FDA has specified that all PRVS may be the subject of an unlimited number of transfers.[371] Allowing transfers, unlimited or otherwise, is important because companies that develop eligible drugs may not necessarily have a potential "blockbuster" drug in its portfolio (or any other drug for that matter) and therefore a sale would be the only way for it to benefit from being awarded a voucher.

As of November 2017, 16 priority vouchers have been awarded, 11 for rare pediatric diseases and five for tropical diseases.[372] Novartis was the first company to redeem a voucher, for its gouty arthritis medication, but the company did not ultimately obtain market approval any faster; instead, the FDA requested that more data be submitted in support of the company's NDA.[373] This caused some further concern about the utility of the voucher program.[374] Since

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[367] 21 USC § 360ff(b)(4) (2012); Lesley Hamming, "The Promise of Priority Review Vouchers as a Legislative Tool to Encourage Drugs for Neglected Diseases" (2013) 11 Duke L & Tech Rev 390 at 408.

[368] 21 USC § 360ff(b)(4)(a) (2012). Unsurprisingly, given the uncertainties associated with the drug development process, the requirement to give 1 year notice was considered too onerous by the pharmaceutical industry. See e.g. Hamming, *supra* note 367 at 408.

[369] 21 USC § 360ff(b)(2)(a) (2012) specifically states that [t]here is no limit on the number of times a priority review voucher may be transferred before such voucher is used."

[370] *FDAAA 2007*, *supra* note 348, § 1102(b)(2).

[371] Department of Health and Human Services, *Tropical Disease PRVs*, *supra* note 364 at 8 (specifies that tropical disease vouchers can be transferred an unlimited number of times). Not explicitly stating that vouchers could be transferred multiple times was thought to impair the impact that vouchers programs would have on drug development because potential buyers would be hesitant to purchase a voucher that they could not rely on being able to subsequently sell. Drug development is a highly uncertain process and a project can "fail" (i.e. a drug can show unfavourable results) at any point throughout the testing phases. If vouchers could be sold only once, drug developers would only be willing to purchase a voucher at the very end of the testing phase, when certainty about whether a drug would receive marketing approval would be at its highest. This was thought to decrease the price that a seller could get for their voucher, and therefore reduce the value of vouchers and thus the effectiveness of the incentive. See e.g. Hamming, *supra* note 367 at 408.

[372] See e.g. Gaffney, Mezher & Brennan, *supra* note 60.

[373] Bethan Hughes, "Priority Voucher Flops" (2011) 29 Nature Biotechnology 958 at 958.

then, a number of companies have held on to their vouchers, though at least five vouchers have been sold, at prices ranging from $67 million up to $350 million.[375] Several companies appear to have benefited from using a voucher. For example, Sanofi-Aventis purchased a PRV from BioMarin for $67 million and used it to get Praluent, a cholesterol-lowering drug, on the market before a competitor; as sales for this drug are expected to be $2 billion annually, getting to market six months earlier may have earned the company an additional $1 billion.[376]

As evidenced by the recent expansion to the voucher program to include medical countermeasures,[377] and discussions about proactively expanding the list of eligible tropical diseases,[378] vouchers are a politically popular incentive.[379] This may be largely because, at least at first glance, they appear to be cost-free.[380] However, for a number of reasons, many academics urge caution and restraint when considering further augmentations to the voucher program. Some argue that expanding the voucher program will drive down the market value of vouchers and therefore reduce the effectiveness of the incentive,[381] while other argue that vouchers are unlikely to be effective at all and that the use of vouchers incurs unacceptable costs and risks.[382] The following sections describe the concerns raised in the literature about PRV programs and attempts to critically analyze the arguments for and against using vouchers to encourage orphan drug development.

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[374] See e.g. *ibid.*

[375] See e.g. Gaffney, Mezher & Brennan, *supra* note 60. See also Aaron S Kesselheim & Jerry Avorn, "Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy" (2016) 316 JAMA 2357 for a discussion about the controversial circumstances under which the seventh drug to receive a RPD PRV was granted regulatory approval.

[376] Kevin Khachatryan, "Incentivizing Drug Development: Novel Reforms of Pharmaceutical Innovation" (2016) 18 Colum Sci & Tech L Rev 139 at 148.

[377] See above, at 61-63, for a description of the initial adoption and subsequent growth of PRV programs.

[378] See e.g. Kenneth Gustavsen, "To Improve Pandemic Preparedness, Update The Priority Review Voucher Program", *Health Affairs* (22 March 2016) online: Health Affairs Blog http://healthaffairs.org.

[379] Ana Santos Rutschman, "The Priority Review Voucher Program at the FDA: From Neglected Tropical Diseases to the 21st Century Cures Act" (2017) 26 Annals Health L 71 at 94.

[380] *Ibid.*

[381] See e.g. David B Ridley & Stephane A Regnier, "The Commercial Market for Priority Review Vouchers" (2016) 35 Health Affairs 776 at 782.

[382] See e.g. AS Kesselheim, "Priority Review Vouchers: An Inefficient and Dangerous Way to Promote Neglected-Disease Drug Development" (2009) 85 Clin Pharma & Therapeutics 573 [Kesselheim, "Inefficient and Dangerous"].

5.3 PRVs May Create Concerns Regarding Drug Safety and Agency Autonomy

Putting aside, for the moment, questions about the effectiveness of the voucher programs, this section considers whether PRVs are fundamentally flawed from a public policy perspective to such an extent that they should not be used regardless of their effect. Recall that vouchers are intended to function as a "pull" mechanism; they reward behaviour by creating a financial incentive as a prize for socially desirable outcomes. This is considered by some to be, in and of itself, problematic because "such initiatives may achieve short-term gains, but they do not consistently lead to sustained improvement and may have important unintended consequences"[383] because they rely on the desire of pharmaceutical companies to increase its profits. Specifically, Kesselheim argues that sustainable interest in rare disease drug development is unlikely to result from financial incentives because unanticipated changes in the pharmaceutical industry that decrease the value of an incentive would likely prompt companies to cease with any drug development projects initiated in response to that incentive.[384] Market exclusivity is also a "pull" incentive and, as was made apparent in the discussion above, does seem to have incurred some unintended consequences such as the complications introduced by scientific advances that permit "salami slicing" of diseases, though whether exclusivity has led to only short-term gains is debateable. Critics have also stated that vouchers would be questionable from a public policy perspective, regardless of whether or not they are effective, citing increased safety risks associated with priority review as a fundamental problem with voucher programs.[385] This section first addresses concerns about the FDA's priority review process in general and how these concerns might be strengthened when vouchers are redeemed before discussing issues that are specific to the voucher programs.

5.3.1 Potential Safety Issues with "Vouchered" Drugs

Potential safety issues with drugs that have been subjected to a priority review represent a major concern about PRVs, and FDA officials have in fact questioned the wisdom of subjecting

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[383] Aaron S Kesselheim, "Drug Development for Neglected Diseases – The Trouble with FDA Review Vouchers" (2008) 359 N Engl J Med 1981 at 1982 [Kesselheim, "Trouble with Vouchers"].

[384] *Ibid*. Therefore, Kesselheim argues, funding of basic research is preferable from a public policy perspective and likely to have a greater impact on public health outcomes than rewards for targeted drugs.

[385] See e.g. *ibid.*

potential "blockbuster drugs" to priority review.[386] The term "blockbuster drug" refers to drugs that make over $1 billion in sales within five years of being on the market.[387] Pressure to review applications for blockbuster drugs within a limited, six-month time-frame may indeed create legitimate concerns about the safety of "vouchered" drugs because "there is a different benefit-risk balance to be considered" when reviewing drugs that will likely be widely used.[388] The drugs for which vouchers are most likely to be redeemed are ones that are expected to be used by millions of patients, such as drugs to treat Type II diabetes and high cholesterol, and therefore are typically submitted for approval with applications that are much more complex and take longer to review.[389] Additionally, drugs that are granted priority review status based on their own merits are drugs that are expected to address an unmet medical need and the risk-benefit analysis performed by the FDA takes this into account.[390] Vouchers will be redeemed for drugs that would not otherwise qualify for priority review and, therefore, the increased risk of an expedited process may not be balanced by the increased benefit that is expected where an unmet medical need is present.

That being said, the increased risk associated with priority review may not be as great as some suggest. As mentioned above, Novartis was the first company to redeem a voucher, and in that case rather than granting approval, the agency instead requested that more data be submitted in support of the application.[391] This example suggests that the FDA is not necessarily going to compromise on its safety standards when conducting priority reviews of vouchered drugs.[392] The priority review system is not new, and it is unclear whether or not the priority review of potential blockbuster drugs truly creates a safety problem, with some authors stating that safety concerns are likely to be unfounded given that the FDA already "fast-tracks" drugs through priority

[386] "FDA Insider Shares Thoughts on Priority Review Vouchers", *The Weinberg Group* (12 October 2015) online: The Weinberg Group https://weinberggroup.com/ ["FDA Insider"].
[387] Ridley, Grabowski & Moe, *supra* note 19 at 314.
[388] US, Government Accountability Office, *Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program* (Report to Congressional Committees, GAO-16-319) (Washington, DC: US GAO, 2016), online: US GAO https://www.gao.gov/assets/680/675544.pdf at 14.
[389] "FDA Insider", *supra* note 386.
[390] Government Accountability Office, *supra* note 388 at 14.
[391] See e.g. "First Priority Review Voucher Wasted" (2011) 10 Nat Rev Drug Discov 721.
[392] See e.g. Hamming, *supra* note 367 at 405.

review.[393] As noted in the original proposal for PRVs, faster review by the FDA does not mean that the safety and efficacy standards for approval are lowered.[394]

NDAs approved by the FDA between November 21, 1997 and December 31, 2009 that underwent priority review were more likely to subsequently receive a post-marketing boxed warning than drugs that were given standard review during that time, but not more likely to result in serious post-marketing safety incidents compared with drugs that receive standard review.[395] The authors attribute the association between priority review and subsequent boxed warnings to the fact that priority review is granted only for drugs that treat serious conditions and are expected to "provide a significant improvement in safety or effectiveness"; [396] as such, any benefits of such drugs may outweigh serious safety risks, thereby making it more likely that drugs that have warranted priority review will subsequently receive boxed warnings. These findings align with the FDA's assertion that drugs that receive priority review have different risk-benefit considerations than potential blockbuster drugs.[397] While the priority review process itself may not create an additional safety risk, there may be some cause for concern about granting drugs priority review status that would not otherwise merit an accelerated review.

Overall, there seems to be little concrete evidence to support the argument that vouchers will in fact compromise the safety of drugs for which a voucher has been redeemed. That being said, as the FDA is the agency tasked with conducting drug reviews, some acknowledgement of the concerns expressed by agency staff is warranted. FDA experts are likely the most qualified to say whether or not there are safety concerns with the agency's priority review process. Furthermore, the findings of previous investigations into the safety of priority reviewed drugs cannot necessarily be translated to the blockbuster drugs for which vouchers are most likely to be

[393] Rutschman, *supra* note 379 at 76.
[394] Ridley, Grabowski & Moe, *supra* note 19 at 321-22.
[395] Andreas Schick et al, "Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals" (2017) 40 Drug Safety 497 at 501-02. Priority reviewed drugs were not, however, more likely to be associated with safety-related withdrawals or restricted indications. The authors concluded that this was likely because "the median time from approval to the addition of a post-marketing boxed warning was similar for drugs that underwent priority review as well as for drugs that underwent standard review."
[396] *Ibid* at 502.
[397] "FDA Insider", *supra* note 386 (the different risk-benefit consideration is particularly relevant where a drug offers little to no therapeutic advantage over treatments that are already on the market, as may be the case with many drugs for which vouchers are redeemed).

redeemed. As it stands, it remains to be seen whether the voucher programs will actually create a safety problem. The mandated report of all three voucher programs should help to inform this issue. In the meantime, recall that vouchers are not a guarantee of either a shorter review time or that FDA will grant market approval.[398]

5.3.2 Indirect Costs of Voucher Programs

Voucher programs have been defended on the grounds that they "[do] not require public funds",[399] but critics have noted that this is a misconception.[400] Voucher programs rush non-priority drugs (i.e. drugs for which there is not an urgent public health need) to the market, thereby resulting in a longer time during which taxpayer-funded health care plans must pay for them.[401] While vouchers technically operate off-budget, they are not "free" in the broader sense because the value of a voucher comes from the ability to get a drug to market more quickly, and the additional costs of early entry to the market are paid for by drug consumers, both directly and indirectly through insurance payments, as well as by taxpayers in general via government-funded pharmaceutical cost-assistance programs.[402] That being said, such costs may be mitigated to the extent that generic versions of a vouchered drug will also be available on the market earlier because the effective patent life of a drug for which a voucher was used is not impacted much, if at all, by an accelerated review.[403]

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[398] See e.g. Department of Health and Human Services, *Tropical Disease PRVs*, *supra* note 364 at 9 (the FDA has made it clear that the agency does not guarantee that the review of vouchered drugs will be completed within six months, only that its targeted review time will be six months).
[399] David B Ridley, Jennifer Dent & Christopher Egerton-Warburton, "Efficacy of the Priority Review Voucher Program" (2016) 315 JAMA 1659 at 1660.
[400] See e.g. Kesselheim, "Inefficient and Dangerous", *supra* note 382 at 573.
[401] Ameet Sarpatwari & Aaron S Kesselheim, "Efficacy of the Priority Review Voucher Program" (2016) 315 JAMA 1660 at 1660.
[402] Kesselheim, "Inefficient and Dangerous", *supra* note 382 at 573.
[403] Alfonso Calles Sanchez, "The 'Priority Review Vouchers' for Neglected Pharmaceutical Innovation and their Impact on Pharmaceutical Patents" (2014) 16 Pharmaceuticals Pol'y & L 167 (In the United States, the Hatch-Waxman Act extends a drug's patent term by adding half of the time that the drug spent under FDA review; therefore, reduced FDA review time will result in a reduced patent extension. Therefore, "the effective patent life of the vouchered drug remains the same and this drug obtains earlier market access. Thus, its generic versions will also obtain earlier market access" at 169). See also J Matheny et al, "Drug and Vaccine Development for Infectious Diseases: The Value of Priority Review Vouchers" (2009) Clin Pharma & Therapeutics 571 at 572 (in the United States priority review will not have the effect of

Interestingly, in the original proposal for PRVs, the accelerated approval and marketing of blockbuster drugs was suggested as an advantage of voucher programs because consumers would have faster access to blockbuster drugs, including faster access to generic versions.[404] Whether faster access to blockbuster drugs actually provides a significant benefit to patients is questionable and will vary drug by drug. Some blockbuster drugs are likely to have such a significant therapeutic advantage over previously existing treatments that speeding them to market via a PRV will be beneficial to the general public. For other drugs, ones that offer little therapeutic advantage or create a potential safety risk, this will not be the case. It is, therefore, uncertain whether speeding blockbuster drugs to market is generally an advantage or disadvantage of voucher programs. Regardless, what needs to be borne in mind is that voucher programs are not, as they may initially appear to be, cost-free. The cost to be paid (in the form of earlier and therefore longer payments for blockbuster drugs) may or may not be acceptable, but it certainly is a cost that policy-makers should consider.

5.3.3 Additional Burden on FDA Reviewers

Priority review does not entail a different assessment of the safety and efficacy of a drug, it only means that the FDA will perform the same assessment within a shortened timeframe, which will naturally require more resources. It is conceivable that vouchers will slow the review of drugs for which priority status is actually warranted by redirecting FDA resources to meet the demand of a voucher redemption.[405] As described above, sponsors who wish to redeem a PRV must pay a special user fee to the FDA, which is intended to off-set the additional costs involved in giving priority to a NDA.[406] The 90 day notice requirement is also intended to reduce undue strain on the agency by allowing time to allocate its resources accordingly.[407] However, some academics argue that these measures are insufficient to alleviate the additional workload because

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extending the effective patent life of a drug because the length of the patent extension is based on the duration of FDA review under the Hatch-Waxman Act, and therefore any time gained from an accelerated review does not affect the patent's expiration date); Ridley, Grabowski & Moe, *supra* note 19 at 322 .

[404] Ridley, Grabowski & Moe, *supra* note 19 at 322.

[405] Anne M Readal, "Finding a Cure: Incentivizing Partnerships Between Disease Advocacy Groups and Academic Commercial Researchers" (2013) 26 J L & Health 285 at 306.

[406] 21 USC § 360ff(c) (2012); Ridley, Grabowski & Moe, *supra* note 19 contemplated the use of an additional fee to offset the additional FDA costs of performing priority review, at 318.

[407] 21 USC § 360ff(b)(4) (2012).

it "will not change the institutional hiring and organizational parameters that ultimately shape FDA's review capabilities."[408] The user fee also risks incurring cuts to the FDA's budget because the payment is added to an offsetting collections account, which may prompt the appropriations committee to reduce the FDA budget.[409] While it is not yet clear whether this will actually occur, the reality is that in any event the FDA cannot simply hire more reviewers each time a voucher is submitted. According to the Director of FDA's Office of New Drugs, the user fee will not address the additional workload because the 90 days notice that a company must give before redeeming a voucher does not allow the agency sufficient time to hire and train the additional staff members, nor would it be reasonable to hire additional reviewers only to let them go after the priority review is completed and the additional burden caused by a voucher redemption is relieved.[410]

At the moment, the FDA's workload-related complaints about the voucher program are not corroborated by the evidence.[411] At least one study has found that the FDA "has been able to maintain [its] standards for reviewing drug applications on schedule" and that "the FDA has continued to function efficiently and effectively at drug approval, despite the increased workload generated by PRVs."[412] The GAO report regarding all three voucher programs, due by the end of January 2020, must include an analysis of the extent to which vouchers impact FDA's ability to complete its review of other drugs. [413] As with the potential safety concerns discussed above, increases to FDA workload are a potential concern that warrants ongoing attention and

[408] Sana Mostaghim & Aaron S Kesselheim, "Suitability of Expanding the Priority Review Voucher into Rare Disease Drug Development" (2016) 4 Expert Opinion on Orphan Drugs 1001 at 1002.
[409] Readal, *supra* note 405 at 307-08.
[410] "FDA Insider", *supra* note 386. But see David B Ridley, "Priorities for the Priority Review Voucher" (2017) 96 Am J Trop Med Hyg 14 for a response to these concerns. David Ridley has argued that rather than a lack of available financial resources, the real problem for the FDA is federal pay limits that make it difficult to offer a competitive salary and thereby attract new reviewers. He suggests that Congress give the FDA more flexibility with respect to pay limits in order to attract more reviewers, and that regular voucher redemptions would make it reasonable to hire these additional reviewers.
[411] Chris Bialas et al, "Analyzing the FDA Priority Review Voucher Program's Stimulation of Research and Public Health Impact" (2016) 3 Tech Transfer & Entrepreneurship 131 at 137.
[412] *Ibid* at 134.
[413] *21st CC Act*, *supra* note 341, § 3014(c)(3)(A).

monitoring, but at this stage it is too early to consider this to be a serious issue with voucher programs.

5.3.4 Interference with FDA Priority Setting

Voucher programs are particularly unique because they directly involve the FDA "as an integral component of the economic incentive."[414] Whether this is an appropriate use of a government function is certainly open to debate. "Linking an essential government public health function – namely the regulatory review of investigational drugs – with a way of generating monetary value for private companies" [415] may be inherently problematic regardless of how effective the incentive may be. A frequent criticism is that the voucher programs interfere with the FDA's ability to set its own priorities with respect to reviewing drugs. [416] Normally, priority review, and the associated additional expense, is reserved for drugs for which there is an urgent public health need, i.e. those that deserve priority.[417] The submission of a voucher has the effect of disrupting this process. For what it is worth, the FDA has explicitly stated that the agency does not support the continuation of the voucher programs and would prefer that other incentives (e.g. pediatric exclusivity) be used. [418] The GAO report on the RPD voucher program includes statements from the FDA that "the [voucher] program interferes with its ability to set priorities on the basis of public health needs" and that, by allowing companies to effectively purchase a priority review the program "undermines FDA's public health mission and the morale of its professional review staff."[419]

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[414] Rutschman, *supra* note 379 at 97.
[415] Mostaghim & Kesselheim, *supra* note 408 at 1001.
[416] *Ibid*.
[417] See generally Aaron S Kesselheim et al, "Trends in the Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014: Cohort Study" (2015) 351 Brit Med J h4633 at 3-5 for some context to these FDA concerns. A study of drugs approved by the FDA from 1987 to 2014 shows that an increasing number of products are being subject to priority review and expedited development programs; however, throughout this time a greater proportion of priority review was being granted for drugs that were not the first in their class (for drugs are more likely to provide only incremental benefits over existing products). These findings suggest that over time the FDA priority review program is being increasingly applied to products that are less innovative. While the agency's use of priority review and expedited development programs increased from 1987 to 2014, this trend is not being driven by associated increased development of innovative (i.e. first in class) drugs.
[418] Government Accountability Office, *supra* note 388 at 14.
[419] *Ibid*.

Voucher programs will undoubtedly interfere with the FDA's autonomy with respect to setting its own priorities and allocating resources for the review of NDAs. While the concerns expressed by the FDA should be taken into consideration, without clear evidence that vouchers are actually having a detrimental impact on FDA performance, this concern is speculative. In a sense, priority setting arguably *is* occurring, in that Congress has deemed it appropriate to award the products that are the targets of the voucher programs, and it is not clear that the FDA is better equipped to set priorities. In order to accurately assess the impact of PRVs more information is needed about whether or not the voucher programs actually interfere with the FDA's ability to prioritize drugs based on their own merits, i.e. those for which there truly is an urgent public health need.[420] The recently mandated GAO report, due in 2020, should provide further insight.[421] In the interim, perhaps concerns can be alleviated by early observations indicating that the FDA is still functioning well in spite of the voucher programs.[422]

5.3.5 Access to the Drugs that Qualify for a Voucher

Finally, what may be the most common complaint about PRVs is that the programs do not specifically promote affordable access to qualifying drugs.[423] The guidance for the tropical disease voucher program makes it clear that there is no requirement whatsoever to market or distribute a drug for which a voucher is awarded.[424] Under the RPD program, a sponsor who does not market their qualifying RPD drug within one year of receiving market approval will risk having the FDA revoke the voucher.[425] More importantly, however, voucher programs do not require companies to market qualifying drugs at affordable prices.[426] The ultimate goal of pharmaceutical incentives, including vouchers, must be to get safe and effective treatments to patients who need them. In light of this, it seems incongruent that the eligibility criterion does

[420] Rutschman, *supra* note 379 at 98 ("the impact and consequences of allowing private parties to influence agency goal setting has yet to be fully addressed in the literature").
[421] *21st CC Act*, *supra* note 341, § 3014(c)(3)(A) (the report must include an analysis of the effect of vouchers on the FDA's ability to review drugs for which vouchers were not awarded or used).
[422] Bialas et al, *supra* note 411 at 134.
[423] See e.g. Kesselheim, Maggs & Sarpatwari, *supra* note 11 at 1688.
[424] Department of Health and Human Services, *Tropical Disease PRVs*, *supra* note 364 at 8. It is unclear how the FDA would approach this decision, as the legislation does not make revocation mandatory, nor is it clear whether a transferred voucher would be revoked.
[425] 21 USC § 360ff(e) (2012).
[426] Khachatryan, *supra* note 376 at 168.

not require any effort be made by the drug developer to achieve this.[427] PRVs, as with market exclusivity, arguably do promote access to a certain extent because a company is only eligible for a voucher (or exclusivity) once it applies for market approval. Obtaining market approval may be seen as the final step that must be taken to make drugs available to patients. However, as discussed above, availability on the market does not necessarily equate to affordable access to a treatment. Unlike market exclusivity and its potentially monopoly-related price effects, voucher programs likely will not contribute to high prices for orphan drugs, but in any event vouchers do not explicitly promote affordable access. As with many orphan drugs, some of the products for which vouchers have been awarded are incredibly expensive. For example, Vimizim, for which the first RPD voucher was awarded, costs $380,000 per patient annually, making it one of the top five most expensive drugs in the world.[428] As such, it is questionable whether vouchers will actually have a positive impact on patient health outcomes.

It is possible that the issue of affordable access needs to be addressed by amending the legislation. One suggestion to address the access problem has been to require that drug developers forego patent rights in order to be eligible for a voucher.[429] The original proposal for PRVs did in fact contemplate such a requirement.[430] This requirement, which probably could have made some headway to facilitate access to qualifying treatments, did not ultimately make it into the legislation, probably because it would have been extremely unpopular with the pharmaceutical industry. To be fair, the lack of popularity may signal that the incentive effect would be dampened if patent protection were lost. A more common suggestion is to require that companies show the FDA a plan to make their drug accessible.[431] As originally proposed by Ridley, Grabowski and Moe, voucher programs would have required sponsors to have at least one manufacturer lined up for the product.[432] This is particularly relevant to the tropical disease program, in order to address the "last mile" problem (i.e. where problems are frequently faced in low-income countries with transportation, organization, and lack of qualified personnel involved

[427] See e.g. Bernard Pécoul & Manica Balasegaram, "FDA Voucher for Leishmaniasis Treatment: Can Both Patients and Companies Win?" *Speaking of Medicine* (20 January 2015), online: PLoS Speaking of Medicine Community Blog http://blogs.plos.org/speakingofmedicine/.
[428] Rutschman, *supra* note 379 at 86.
[429] Jorn Sonderholm, "In Defence of Priority Review Vouchers" (2009) 23 Bioethics 413 at 418.
[430] Ridley, Grabowski & Moe, *supra* note 19 at 314.
[431] See e.g. Ridley & Regnier, *supra* note 381 at 782.
[432] Ridley, Grabowski & Moe, *supra* note 19 at 314.

with administering treatments),[433] although it would do nothing to address the affordability concerns in any event. Others suggest that the eligibility criteria should include some guarantee from the sponsor that the drugs for which vouchers are awarded will be made available at affordable prices.[434] Notwithstanding how unpopular these suggestions are likely to be with the pharmaceutical industry, they would serve to further promote the objective of increasing patient access to treatment. That being said, putting limits on what a company could charge for their eligible product would in all likelihood significantly impair the effectiveness of voucher programs.

Alternatively, it may be inappropriate to address the access issue by amending the voucher programs. In reality the point of the voucher programs is to address the market failures that lead to diseases being neglected, and to do so specifically by increasing the expected rate of return on R&D investments. As discussed above, companies have historically neglected to develop treatments for tropical diseases and rare pediatric disorders because these are not typically expected to be profitable markets; further limiting what a company can expect to receive would increase the financial disincentive, which is the exact opposite of what the voucher programs are trying to do.

The issue of affordable access is not suited to being addressed via a "revenue-side" incentive such as voucher programs. It may simply be the case that these types of financial incentives are generally not the best means for promoting affordable access to treatments.[435] Innovation and access to innovative products are two distinct issues, and the creators of the voucher program note that it encourages innovation and acknowledge that the program does not necessarily promote access.[436] Pharmaceutical innovation for neglected diseases is a socially valuable goal in and of itself because without the development of urgently needed products there can be no access to such drugs. Amending the eligibility criteria so as to require that companies guarantee affordable access would likely severely undermine the value of vouchers and the program's effectiveness. Other mechanisms for ensuring affordable access, such as tax credits

[433] See e.g. Michael Ravvin, "Incentivizing Access and Innovation for Essential Medicines: A Survey of the Problem and Proposed Solutions" (2008) 1 Pub Health Ethics 110 at 113.
[434] See e.g. Pécoul & Balasegaram, *supra* note 427.
[435] Kesselheim, "Trouble with Vouchers", *supra* note 383 ("such initiatives may achieve short-term gains, but they do not consistently lead to sustained improvement and may have important unintended consequences" at 1982).
[436] Ridley & Regnier, *supra* note 381 at 782.

that would lower the costs of development or direct grants for drug development that are contingent upon reasonable prices, may be more appropriate means of addressing the access issue.

5.4 Effectiveness and Impact of the Voucher Programs

As discussed above,[437] it is inherently difficult to determine the effectiveness and impact of a sole incentive on decisions about drug development because such decisions are naturally going to be influenced by any number of factors. Perhaps taking a cue from concerns about the lack of formal evaluation of other pharmaceutical incentives, some attempt has been made to formally analyze the effectiveness of the voucher programs.[438] In accordance with the original enactment of the RPD voucher program, a GAO assessment was completed, details of which are discussed below. The recently enacted *21st Century Cures Act* further requires that, by January 31, 2020, the GAO conduct and submit a study of all three voucher programs and, among other issues, specifically assess "whether any improvements to such programs are necessary to appropriately target incentives for the development of drugs that would likely not otherwise be developed, or developed in as timely a manner."[439] As such, while the Act may not address the concerns and perceived problems with vouchers, at least it does create "a better normative framework for evaluating the successes and failures of the program as an incentives mechanism."[440]

The initial GAO report on the effectiveness of the RPD voucher program was published in March, 2016. Mirroring the academic literature on the subject, the general consensus about the RPD voucher is that, given how long drug development takes, it is too early to tell whether or not the program provides an effective incentive.[441] Drug development typically takes over a decade to complete and, therefore, it is unsurprising that every drug for which a voucher has been awarded was already in the process of being developed when the voucher program was

[437] Section 4.3 discusses the impact that market exclusivity is considered to have had on drug development decisions.
[438] See e.g. 21 USC § 360ff(i) (2012) (required "a study of the effectiveness of awarding rare pediatric disease priority vouchers"); *21st CC Act*, *supra* note 341, § 3014 also requires formal assessment of all three voucher programs.
[439] *21st CC Act*, *supra* note 341, § 3014 (c)(3)(B).
[440] Rutschman, *supra* note 379 at 96.
[441] Government Accountability Office, *supra* note 388 at 9.

implemented.[442] However, requests for vouchers, and for RPD designation, may be indicative of interest in the program.[443] One study considers that the 52 requests for RPD designation (as of December 2015) are demonstrative of "considerable enthusiasm for the PRV program."[444] As such, there may be some indication that voucher programs are "on track" to encouraging the targeted drug development. [445] Nevertheless, more time and information is needed to really understand the impact that these programs are having on public health outcomes.

5.4.1 Voucher Programs May Not Effectively Encourage Valuable Innovation

A couple of distinct lines of criticism about voucher programs have been raised in the literature regarding what constitutes a qualifying drug. These concerns ultimately relate to what is and is not required by the eligibility criteria. The first concern is that vouchers can provide developers with a windfall because they are awarded for getting a drug approved in the United States, regardless of the time and money (or lack thereof) that a company actually invested in developing the drug. The second concern is that the eligibility criteria do not sufficiently promote *valuable* drug innovation. This section assesses each of these issues in turn.

5.4.1.1 Windfall Potential of Vouchers

Vouchers, as with market exclusivity regimes, are intended to address a market failure, not to provide companies with a sort of windfall. A frequent complaint is that voucher programs allow companies to receive potentially significant financial gain without having had to do any of the legwork or otherwise provide any additional amount of investment to develop a qualifying drug. The eligibility criteria require that a drug has not been previously approved in the United States,[446] but there are no conditions regarding drugs that have been already approved and used in other jurisdictions. A company can, therefore, obtain a voucher, and the associated profits, by simply registering a qualifying drug with the FDA, a practice alleged to be one which "pointlessly rewards old innovation."[447] Clearly this can and has happened. In March 2014, Knight Therapeutics was awarded a voucher for miltefosine, a leishmaniasis treatment, but

[442] *Ibid*.
[443] *Ibid* at 10.
[444] Bialas et al, *supra* note 411 at 134.
[445] *Ibid* at 139.
[446] 21 USC §§ 360ff(a)(4)(A)(ii), 360n(a)(4)(C) (2012); *21st CC Act*, *supra* note 341, § 3086(a)(4)(D).
[447] Arnold & Pogge, *supra* note 11 at 231.

miltefosine had already been approved and widely used in other countries for that indication.[448] Knight is reported to have spent roughly $10 million to purchase the rights to the drug and obtain FDA approval; as a result of these "efforts" the company was subsequently able to sell its voucher for $125 million.[449] In this instance the voucher program was "effective" only to the extent that it encouraged Knight to seek market approval in the United States for a drug. Obtaining market approval for miltefosine in the United States likely had little effect, if any, on access to a necessary treatment because patients needing leishmaniasis drugs are typically not in the United States.[450] This narrative is used as one example of how the program "is subsidizing the non-negligible, yet modest costs (by pharmaceutical industry standards) of bringing existing drugs into the United States market."[451] The Knight example offers clear evidence that voucher programs can be used by pharmaceutical companies to obtain windfall profits without producing any significant benefit.

Knight Therapeutics is not the only company to benefit from the voucher program in this manner. The first voucher under the Tropical Disease program went to Novartis in 2009 for a malaria treatment that had already been approved in over 80 countries.[452] United Therapeutics was awarded a RPD voucher for a drug that was largely developed by the National Cancer Institute; the company sold this voucher in 2015 for $350 million.[453] The CEO of one drug company who initially stood to be a potential recipient of a tropical disease voucher noted that within his company the voucher was referred to as the "Willy Wonka ticket" because it was regarded as an unexpected bonus of their drug development activities.[454] Furthermore, Ebola and Zika viruses have recently been added to the list of qualifying tropical diseases, but only after a number of development activities were commenced for these diseases.[455] These examples suggest that voucher programs may simply be providing a reward for treatments that would have

[448] Kesselheim, Maggs & Sarpatwari, *supra* note 11 at 1687.
[449] *Ibid.*
[450] Notable exceptions include military personnel and medical staff who travel to low income countries where tropical diseases are most prevalent (see e.g. Department of Health and Human Services, *Tropical Disease PRVs*, *supra* note 364 at 2).
[451] Rutschman, *supra* note 379 at 85.
[452] Kesselheim, Maggs & Sarpatwari, *supra* note 11 at 1687.
[453] *Ibid.*
[454] Kate Traynor, "FDA Program could Boost Treatments for Neglected Diseases" (2008) 65 Am J Health-Syst Pharma 1595 at 1596.
[455] Rutschman, *supra* note 379 at 89-91.

been developed regardless, such that "all resulting biopharmaceutical innovation [is] completely detached from this type of incentive program".[456]

Some argue that the legislation should be fixed in order to prevent companies from obtaining windfalls.[457] A common recommendation is to amend the legislation to require that companies show that they have invested some minimum amount in R&D for an eligible product in order to qualify for a voucher.[458] Alternatively, a two-year window of eligibility could be imposed on drugs that have already been approved in other jurisdictions.[459] It is notable that these two suggestions address "windfalls" occurring where the value of the voucher exceeds costs of drug approval; they do not address situations where the drug approval would have occurred even if the voucher program were not available, (i.e., the "Willy Wonka ticket" scenario). As of now, it is unclear how great of a problem this potential for windfalls truly is. With respect to vouchers, it may simply be a matter of giving the program time and it has been noted that in any event these examples should diminish as the programs continue because obvious sources of these types of drugs will "dry up".[460] To reiterate, it is hardly surprising that vouchers have thus far been awarded for treatments that were already developed or being developed before the voucher programs were implemented. Over time, more information will be made available that will help determine whether or not the voucher programs are effective at encouraging innovative drug development.

5.4.1.2 Disconnection between the Value of Eligible Drugs and the Reward of a Voucher

A second, and perhaps more significant, concern about the eligibility criteria is that they fail to connect the size of the reward (the voucher) with the value or utility of the drug for which a voucher is awarded.[461] With respect to the tropical disease voucher, the program may be unlikely to encourage the development of cures (e.g. vaccines) over symptomatic relief because eligibility is not linked with the effectiveness of the qualifying drug.[462] On the other hand, drugs

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[456] *Ibid* at 91.
[457] E.g. Pécoul & Manica Balasegaram, *supra* note 427.
[458] See e.g. Ridley & Regnier, *supra* note 381 at 782.
[459] Bialas et al, *supra* note 411 at 138; Arnold & Pogge, *supra* note 11 at 231 (an alternative suggestion is that drugs that are approved elsewhere prior to a specified date (e.g. the date the PRV program was implemented) be ineligible for a voucher).
[460] *Ibid*.
[461] See e.g. Kesselheim, "Trouble with Vouchers", *supra* note 383 at 1981-82.
[462] Ravvin, *supra* note 433 at 418.

must be eligible for priority review on their own merits in order to qualify for a voucher;[463] therefore there is arguably some degree of assurance that they meet an unmet need. However, this only partially addresses the issue. The threshold for priority review designation is not necessarily that high. One review of drugs submitted between 1987 and 2014 indicates that priority review status is increasingly being granted for drugs that are not first in class; in other words, some drugs that are not necessarily that innovative are already being deemed eligible for priority review.[464] Therefore, the FDA may not be currently using the priority review program to give priority solely to drugs which are the most innovative, indicating that the impact of vouchers will not be as detrimental to their operations as the agency has suggested. At the same time, this means that the requirement that a drug be eligible for priority review is likely to be of relatively little consequence.

Furthermore, the voucher programs do not encourage companies to make valuable improvements to existing treatments because in order to be eligible for a voucher a drug must not contain a previously approved active ingredient (including an ester or salt of a previously approved active ingredient).[465] Restricting the eligibility criteria in this manner might needlessly discourage the development of valuable innovation that takes advantage of previously approved active ingredients. This requirement may prevent a lot of valuable drugs from being encouraged by voucher programs, particularly given that, for example, the best new treatments for malaria and tuberculosis often contain previously approved active ingredients.[466] Changes made to "known" ingredients can actually be of significant benefit to patients, but would be ineligible for a voucher.[467] As a result, for example, a new malaria treatment that is effective but must be administered six times a day and degrades in the heat would be eligible for a voucher but an

[463] 21 USC §§ 360ff(a)(4)(C), 360n(a)(4)(A)(ii) (2012); *21st CC Act*, *supra* note 341, § 3086(a)(4)(B).
[464] Kesselheim et al, *supra* note 417 at 4. "First in class" refers to drugs that are the "first agent approved within its respective drug class". The authors used the "first in class" to categorizes drugs according to their innovativeness, with first in class drugs being more innovative than drugs that were not first in class.
[465] Department of Health and Human Services, *Tropical Disease PRVs*, *supra* note 364 at 7.
[466] Lisa M Jarvis, "Filling Drug Gaps" (2009) 87 Chem & Engineering News 38 at 40.
[467] Kesselheim, "Inefficient and Dangerous", *supra* note 382 at 574.

improved formula of that same drug that would greatly enhance its usefulness in lower income countries would not be rewarded.[468]

Finally, the eligibility criterion for the RPD program states that qualifying NDAs must "not seek approval for an adult indication in the original rare pediatric disease product application".[469] While the FDA guidance makes it clear that they interpret this to mean that applications seeking approval as a treatment for a RPD and as a treatment for adults with the *same* disease will not be ineligible,[470] it unclear why the legislation should dissuade sponsors from seeking approval as a treatment for a different adult indication at the same time. This nuance of the policy could needlessly delay the approval of treatments for different adult indications and further disconnects the reward from public health benefits.[471]

To more closely link the reward of a voucher with a positive impact on public health, some have suggested that the eligibility criteria require some evidence that the drug is likely to have a therapeutic advantage over existing treatments[472] or that the award of a voucher be contingent on a demonstration of a plan to make the eligible drug available at affordable prices.[473] Neither of these suggestions is likely to gain popularity with the pharmaceutical industry, nor is adding such requirements likely to encourage companies to make risky investments under even less certainty that they will receive a voucher. It is also unclear how feasible this requirement would be to implement and administer because of difficulties with designing and applying such criteria in a fair and predictable manner. While it is likely important to dissuade companies from making minor or otherwise meaningless alterations to existing treatments solely in order to obtain a voucher, relaxing the restrictions about known active ingredients could serve to encourage valuable improvements to previously approved drugs and,

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[468] Kesselheim, "Trouble with Vouchers", *supra* note 383 at 1981-82.
[469] 21 USC § 360ff(a)(4)(E) (2012).
[470] US, Department of Health and Human Services, *Rare Pediatric Disease Priority Review Vouchers: Guidance for Industry (Draft Guidance),* (Silver Spring, MD: Office of Communications, Division of Drug Information, 2014) online: US Food & Drug Administration https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf at 5-6 [Department of Health and Human Services, *Rare Pediatric Disease PRVs*].
[471] Hamming, *supra* note 367 at 411.
[472] See e.g. Ridley, Grabowski & Moe, *supra* note 19 at 314 (the original proposal for voucher programs does call for this requirement).
[473] See.e.g. Arnold & Pogge, *supra* note 11 at 231-32.

therefore, strengthen the connection between the reward of a voucher and the value of the qualifying drug.

5.4.2 Vouchers May be an Ineffective Incentive for Pharmaceutical Innovation

Despite the political popularity of voucher programs, there is room to question whether vouchers can actually encourage the targeted drug development. In some ways, much of this scepticism stems from the novelty of vouchers as an incentive and the resulting uncertainty about how the voucher programs will be administered. Additionally, some argue that the value of a voucher will never be sufficient to influence R&D decisions given the costs of drug development.[474] There are reasons to question how great of an impact vouchers can have (i.e. estimations of potential voucher prices are very small relative to the cost of drug development) but there are reports from the pharmaceutical industry indicating that at least some drug companies are using the voucher program as a means to attract additional investment.[475] This section discusses the potential impact that vouchers are likely to have on drug development decisions in further detail.

5.4.2.1 Uncertainty about how the Voucher Programs will be Administered

To begin, there is uncertainty surrounding the voucher programs in general which may inhibit their effectiveness. Drug companies may not be strongly influenced by vouchers because the program is so novel and unique. Uncertainty about how the programs would work and how the FDA would interpret the criteria likely has impaired the effectiveness of the programs, particularly when the tropical disease voucher program was first introduced.[476] Adding to the uncertainty is the fact that vouchers only reward successful development efforts. Drug development is an inherently uncertain process, with many drugs and potential treatments never showing sufficiently positive clinical results. As a "pull" mechanism, vouchers are a reward for research output or, more specifically, for *successful* research output. It is difficult to predict years in advance whether a drug will eventually obtain FDA approval and therefore be eligible for a voucher. As such, vouchers are unlikely to be an effective incentive in the early decision-making stages.

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[474] See e.g. Rutschman, *supra* note 379 at 93.
[475] See e.g. Waltz, *supra* note 8 at 1316.
[476] Robertson et al, *supra* note 11 at 2.

However, uncertainty about receiving a voucher does not mean that the program cannot still encourage companies to continue with or re-direct a project toward developing an eligible drug. For example, vouchers could provide the necessary encouragement that will ensure a company sees a project fully through to completion. There is some suggestion that companies are using the potential to receive a voucher in exactly this manner.[477] For example, one non-profit organization reports having used the voucher program to attract the additional investment it needed to complete the clinical trials and registration of a drug that "had been languishing for years".[478] Furthermore, a company can apply in advance to have their drug designated as a RPD treatment,[479] an aspect of the program that can provide some degree of certainty about whether a drug will eventually be eligible for a voucher.[480] The uncertainty about obtaining a voucher likely does inhibit any impact that the incentive will have on early decision-making but vouchers can nevertheless still be an effective tool to encourage companies to see projects fully through the development pipeline.[481]

The original enactment of the RPD program contained a sunset clause that likely contributed to the uncertainty about obtaining a voucher. The GAO report describes how at least two drug sponsors have reported a hesitation to invest years and money to develop a qualifying drug because they could not be sure that the program would still exist by the time the development process could be completed.[482] Until the *21st Century Cures Act* was enacted in December of 2016, the RPD was set to terminate in 2016.[483] The Act amends section 529 of the *Food, Drug, & Cosmetics Act* and provides for the RPD program to continue until September

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[477] Ridley, Dent & Egerton-Warburton, *supra* note 399 at 1660.
[478] *Ibid*.
[479] 21 USC § 360ff(d) (2012).
[480] But see Department of Health and Human Services, *Tropical Disease PRVs*, *supra* note 364 at 7; Department of Health and Human Services, *Rare Pediatric Disease PRVs, supra* note 470 at 12 (the FDA makes it clear that eligibility cannot be fully determined in advance of a NDA being submitted because of the criteria that eligible drugs cannot contain a previously approved active ingredient).
[481] See e.g. Ridley, Dent & Egerton-Warburton, *supra* note 399 at 1660.
[482] Government Accountability Office, *supra* note 388 at 17.
[483] 21 USC § 360ff(b)(5) (2012) provides for no more vouchers to be awarded after one year from the day on which the third RPD voucher is awarded; Alexander J Varond & Josephine M Torrente, "One, Two, Three . . . and They're Out! FDA Issues Third Rare Pediatric Disease Priority Review Voucher, Triggering One-Year Sunset Clause" (23 March 2015), online: FDA LawBlog www.fdalawblog.net (the third RPD voucher was awarded in March 2015).

2020.[484] While the *21st Century Cures Act* does provide an additional two years during which time vouchers can be awarded for treatments that were designated as RPD drugs prior to September 2020,[485] any potential effectiveness of the vouchers is likely impaired by this clause because drug companies are understandably unlikely to be encouraged by a program that may terminate before they can complete the drug development process and therefore be eligible for the reward.[486]

Uncertainty about the continuation of the RPD voucher program and any resulting decreased effectiveness of the incentive should be accepted as a reasonable price to pay given that there are legitimate questions and concerns about voucher programs, as outlined above. The benefits to be gained from a formal assessment of the impact and effect of all three voucher programs, as required by the *21st Century Cures Act*,[487] outweigh the disadvantages that may be incurred because of the sunset clause. As discussed above, voucher programs may interfere with the FDA's ability to prioritize urgently needed treatments and have raised some reservations about the safety of blockbuster drugs that are granted priority review. The merits of these concerns should be formally assessed before the voucher programs are allowed to continue indefinitely. The additional two years granted to companies who receive RPD designation for their drug will help to mitigate this uncertainty and much of the related impairment of the program's effectiveness.

5.4.2.2 Uncertainty about the Value of Vouchers

Even if a company could be certain they would receive a voucher for their development efforts, it would nevertheless be difficult, if not impossible, for them to accurately predict how valuable their voucher would be to them. The value of a voucher can be realized in one of two ways: a company can use the voucher itself to get a drug of its own on the market more quickly, or it can sell the voucher to another company. It has been suggested that voucher programs will be more influential for companies that also have a potential blockbuster drug in development, because the value of using a voucher to accelerate their own drug to market will typically be

[484] *21st CC Act*, *supra* note 341, § 3013.
[485] *Ibid*, § 3013(a).
[486] Bialas et al, *supra* note 411 at 137.
[487] *Supra* note 341, § 3014.

greater than what they would gain by selling the voucher.[488] Getting a blockbuster drug to market even four months quicker can be significantly profitable for a company. As discussed above, Sanofi-Aventis's cholesterol treatment, for which it redeemed a voucher, is expected to bring in $2 billion annually.[489] Accelerating that drug to market resulted in the company obtaining significantly greater profit. In this instance, the voucher also enabled Sanofi-Aventis to get its drug on the market ahead of a competitor,[490] which can have additional advantages for a company as well.[491] Therefore, redeeming a voucher has been shown to result in some additional financial gain for drug developers, at least for companies that have additional drugs in the development pipeline.

However, it is primarily small companies that are doing research on rare and neglected diseases; these companies are far less likely to have potential blockbuster drugs also in development and, therefore, are less likely to benefit from a voucher.[492] If a company cannot take advantage of a voucher itself, any value must come from a sale of the voucher, which is problematic because it relies on negotiations between private bodies.[493] The resulting lack of transparency between a seller and a potential buyer can reduce the price that a developer of a qualifying drug can expect to receive from selling a voucher.[494] The market value of a voucher is inherently uncertain. The value of vouchers is dependent on how much it is worth to a drug developer to have their drug subject to priority review (i.e. a voucher is going to be worth a lot more to developers that have a promising blockbuster drug in development), which is not necessarily going to be fully understood.[495] A number of attempts have been made to estimate the commercial value of a voucher, and previous voucher sales can help to inform this estimate,

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[488] Nicola Dimitri, "The Economics of Priority Review Vouchers" (2010) 15 Drug Discovery Today 887 at 890.
[489] Khachatryan, *supra* note 376 at 148.
[490] *Ibid.*
[491] Andrew S Robertson, "Preserving an Incentive for Global Health R&D: The Priority Review Voucher Secondary Market" (2016) 42 Am J L & Med 524 at 534 (though Robertson also notes that this effect is not the most significant, and that other factors (e.g. therapeutic advantage) play a far more significant role in determining sales/competition, at 538).
[492] Lexchin, "One Step Forward", *supra* note 11 at 7.
[493] *Ibid.*
[494] *Ibid.*
[495] See e.g. Dimitri, *supra* note 488 ("the bearer would not necessarily know if and when there would be a potentially profitable drug in its portfolio worth prioritizing" at 888).

but it remains fairly speculative.[496] The difficulty of estimating the value of a voucher has been cited by pharmaceutical companies as limiting how influential the incentive is.[497] The reality is that the value of a voucher depends on what a company is willing to pay at the time a company is looking to sell (which is dependent on many other factors such as the potential buyer's confidence in their drug that they are considering using a voucher for and the number of vouchers available at the time). Therefore, vouchers are a reward of a very uncertain and highly speculative value, an aspect of the program that surely impairs its effectiveness.

As the value of a voucher cannot be known ahead of time (particularly for companies that will have to sell a voucher in order to realize its value), it is reasonable to question how effective of an incentive vouchers ever could be. The value of market exclusivity is more certain; at the very least companies will know how long the period of protection will last, and will have a rough estimate of the market demand for a particular orphan drug.[498] Not much can be done to address the uncertainty about the "size" of the reward, except to keep one thing in mind: the value of vouchers will decrease if the number of vouchers available for sale is increased. In this sense, the effectiveness of the PRV programs creates a paradox: the more successful they are at encouraging drug development, the more vouchers will be awarded. More vouchers available for sale will reduce the market value of a voucher and, therefore, the effectiveness of the incentive.[499] This needs to be borne in mind when policymakers start to consider possible expansions to the voucher programs.[500] Proposals to expand the voucher program into other disease areas likely create further uncertainty about the value of vouchers, and expansions would reduce the price that companies could expect to get for a voucher by flooding the market.[501] In order to ensure that the value of a voucher remains relatively high, policy makers should be hesitant to make expansions and seek to keep the eligibility criteria for awarding vouchers fairly narrow.[502]

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[496] Kesselheim, "Trouble with Vouchers", *supra* note 383 at 1981.
[497] Robertson et al, *supra* note 11 at 2.
[498] Companies will already have a rough understanding of a disease's prevalence given that they will have applied for orphan designation (presumably using the prevalence-based definition).
[499] See e.g. Ridley & Regnier, *supra* note 381 at 782.
[500] *Ibid.*
[501] *Ibid.*
[502] *Ibid.*

5.4.2.3 (In)Sufficient Value of Vouchers

Critics of PRVs also assert that vouchers are not and never will be sufficiently valuable to encourage companies to invest in R&D for rare diseases because of how expensive the drug development process is.[503] Even though the selling price for a voucher has gone as high as $350 million, this price is unlikely to be sufficient to encourage large drug companies to alter their investment strategy to include tropical or rare pediatric diseases.[504] To illustrate, it costs roughly $1 billion to develop a vaccine; a voucher of unknown value is not a sufficiently strong incentive to encourage investment in vaccine development.[505] At least one author has suggested that, in order to alleviate this concern, developers of qualifying drugs should receive three vouchers instead of just one.[506] However, this would likely introduce too many vouchers and drive down the market value and, accordingly, the effectiveness of vouchers. Vouchers may simply be "too small" of an incentive to influence behaviour and, therefore, as discussed above, vouchers may only be rewarding behaviour that would have occurred in any event.

Undoubtedly the value of PRVs alone is insufficient to trigger an orphan drug development project; however, this does not lead to the conclusion that vouchers are altogether insufficiently valuable to have an impact on behaviour. The creators of the voucher programs acknowledge that vouchers alone are unlikely to be a sufficiently large financial incentive but nevertheless defend their utility, arguing that vouchers were never intended to operate as a stand-alone incentive.[507] It was always anticipated that vouchers would work in conjunction with other push and pull mechanisms such as the Orphan Drug Tax Credit, research grants, and market exclusivity, as evidenced by the original proposal in which the authors take into account the tax credit available to orphan drug developers in their estimate of the potential value of a PRV.[508] It

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[503] See e.g. Rutschman, *supra* note 379 ("it might be that the program will always be too small to truly impact allocation of R&D resources within the pharmaceutical industry" at 93).
[504] Kesselheim, Maggs & Sarpatwari, *supra* note 11 at 1688.
[505] Arnold & Pogge, *supra* note 11 at 231.
[506] Sonderholm, *supra* note 429 at 417.
[507] Ridley, Grabowski & Moe, *supra* note 19 at 319.
[508] *Ibid*. Another relevant major incentive is pediatric exclusivity, whereby an additional six months of exclusivity is available for developers that conduct, in response to a Written Request from the FDA, pediatric studies of new and previously approved drug products (21 USC § 355a(b) (2010)). See also Government Accountability Office, *supra* note 388 at 13-14 (in response to the expansion of PRVs to rare pediatric diseases the FDA has suggested that reliance on this incentive is preferable to the use of PRVs as an incentive to encourage companies to

is nevertheless possible that vouchers do play a valuable role in innovation policy by encouraging drug sponsors to see the development process through to completion. While acknowledging the importance of funding basic science and providing other incentives, Ridley and colleagues nevertheless continue to support the utility of vouchers as a means of getting products fully through the development pipeline.[509] In addition, voucher programs can encourage drug developers to "salvage existing projects that were initiated for other diseases"[510] or otherwise operate to "motivate developers to continue with existing programs".[511] In this manner, vouchers will function as the necessary "nudge" to get a company to apply for FDA approval for a targeted drug by offering a way for companies to attract the investment needed for late-stage trials in circumstances where the commercial potential of neglected diseases is too small, making it difficult to get the necessary additional investment.[512]

Some reports from the pharmaceutical industry indicate that vouchers are in fact currently being used as part of a business strategy. The CEO of Kineta, a company that has investments in drugs for dengue and Ebola, has stated that the tropical disease voucher program has been "critical in making the business case to our investors to advance this research".[513] Additionally, the CEO of a Vancouver-based company has also reported that the possibility of receiving a voucher has been useful in attracting potential buyers or partners for the company.[514] In this example, the company had already started to develop a treatment for leishmaniasis prior to the implementation of PRVs but are now using the program to attract necessary additional investment.[515] Surveys and follow-up interviews with drug companies involved in developing treatments for tropical diseases indicate that PRVs are a major consideration for investment decisions, though other factors play a greater role in influencing their decisions.[516] Finally, the

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conduct pediatric studies because it is an effective incentive that, unlike vouchers, does not interfere with FDA autonomy with respect to priority setting).

[509] Ridley, Dent & Egerton-Warburton, *supra* note 399 at 1659.

[510] Ridley, Grabowski & Moe, *supra* note 19 at 321.

[511] *Ibid* at 322.

[512] Jarvis, *supra* note 466 at 39.

[513] Ridley, Dent & Egerton-Warburton, *supra* note 399 at 1660.

[514] Waltz, *supra* note 8 at 1316.

[515] *Ibid.*

[516] Robertson et al, *supra* note 11 at 2. The most significant factor cited was the potential market value of a particular tropical disease drug project, and other factors such as a sense of corporate social responsibility and contracts and grants were also ranked as more influential than PRVs.

responses do indicate that vouchers alone are not sufficient to encourage the desired drug development, a finding that echoes the original proposal for the voucher incentive: that vouchers need to be paired with other incentives in order to be useful.[517] This may be evidence that, in spite of their limitations, vouchers are nevertheless "a valuable and highly cost-effective addition" to pharmaceutical incentive schemes.[518]

The *21st Century Cures Act* requires that the GAO determine "whether, and to what extent, the voucher impacted the sponsor's decision to develop [a] drug."[519] Therefore, this report can be expected to shed further light on the effectiveness of the voucher programs. The impact of vouchers on R&D decisions must be weighed against the potential policy issues discussed above; the GAO is mandated to evaluate these as well. In the interim, a relatively small impact on decision-making (that is suggested by these early surveys) does not warrant prematurely abandoning the incentive. Provided that the risks and costs associated with vouchers do not outweigh any benefits then the program may be worthwhile even though it may not create a sufficiently large incentive to operate independently as a catalyst for drug development.

5.5 Potential for a Canadian PRV program

Generally speaking, as the costs and impact of vouchers in the United States have yet to be adequately determined, other jurisdictions should be hesitant to introduce similar programs. Furthermore, the administrative burden created by voucher redemptions is likely to be exaggerated in Canada because Health Canada is a smaller agency than the FDA, and the already small impact of vouchers can be expected to be further impaired by the significantly smaller pharmaceutical market here.

As in the United States, Health Canada has a priority review mechanism in place. Priority review is limited to drugs that are "intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses or conditions where a) there is no existing drug on the Canadian market with the same profile or b) where the new product represents a significant improvement in the benefit/risk profile over existing products."[520] Priority review status means that Health Canada will approach a drug submission with a shortened review target

[517] *Ibid.*
[518] Matheny et al, *supra* note 403 at 572.
[519] *Supra* note 322, § 3014(c)(1)(B).
[520] Health Canada, *Priority Review of Drug Submissions (Therapeutic Products)*, online: online: Government of Canada www.canada.ca.

in mind, one of 180 days instead of the standard 300 days.[521] The agency strives to meet this accelerated target by inserting these applications into the queue with this review target in mind (i.e. by reviewing it in advance of other, non-priority drug submissions).[522]

Unfortunately, there is relatively little literature about Health Canada's priority review system, and therefore any conclusions will have to be extrapolated from what information is available. The timeliness of the review of new drugs in Canada has long been criticized, with Canada historically lagging well behind the United States, the United Kingdom, Sweden, and Australia.[523] An Auditor General report of Health Canada's review performance in 2009 and 2010 found that only 70% of new drug submissions ("NDS") were reviewed within the targeted 300 days, a figure significantly short of Health Canada's target of completing 90% of reviews within the targeted timeframe.[524] A number of factors were offered in explanation of this, including the various duties that reviewers must undertake in addition to their review duties.[525] Health Canada implemented a cost recovery framework in April 2011 that included increased user fees and was intended to improve review times.[526] Nevertheless, two more recently published articles investigated the timeliness of cancer-treating drug reviews across jurisdictions and found that Health Canada still takes significantly longer than the FDA to review drug submissions.[527] However these articles only considered drugs that were approved up to June 2013, and marketing applications for cancer-treating drugs may be particularly large and complex.[528] The most recent performance report from the Therapeutic Products Directorate is

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[521] *Ibid.*
[522] *Ibid.*
[523] See generally Nigel SB Rawson, "Timeliness of Review and Approval of New Drugs in Canada from 1999 Through 2001: Is Progress Being Made?" (2003) 25 Clin Therapeutics 1230.
[524] *2011 Fall Report of the Auditor General of Canada*, online: OAG http://www.oag-bvg.gc.ca/internet/English/parl_oag_201111_04_e_35936.html#hd4b, at exhibit 4.2.
[525] *Ibid* at para 4.49.
[526] *Ibid* at para 4.50.
[527] Doreen Ezeife et al, "Comparison of Oncology Drug Approval Between Health Canada and the US Food and Drug Administration" (2015) 121 Cancer 1688 at 1690; N Samuel & S Verna, "Cross-comparison of Cancer Drug Approvals at Three International Regulatory Agencies" (2016) 23 Current Oncology e454 at e455.
[528] See e.g. Joseph A DiMasi, Christopher-Paul Milne & Alex Tabarrok, "An FDA Report Card: Wide Variance in Performance Found Among Agency's Drug Review Divisions" (2014) Project FDA Report, online: Manhattan Institute https://www.manhattan-institute.org/pdf/fda_07.pdf, at 10-11 (while FDA's Oncology review department actually appears to be faster at reviewing

more illuminating. The report shows that, on average, Health Canada did not meet its review target of 300 days for standard review during the fiscal years 2011 up to 2015-2016.[529] With approval times ranging from a maximum of 1119 calendar days in fiscal year 2011-12 to a minimum of 63 calendar days in 2012-13 this average is not necessarily an accurate representation of Health Canada's performance.[530] Of greater significance is Health Canada's performance with respect to priority review of NDSs. No NDS given priority status during the time-period was reviewed within the targeted 180 days.[531] This data is particularly relevant to a consideration of the PRV program because it suggests that, as Health Canada currently does not meet its targeted timeframe for reviewing "priority" drug applications, PRVs therefore would likely introduce an additional burden that could not be met by the agency. Nor could PRVs be an effective incentive if companies could not rely on Health Canada being able to complete an accelerated review in a sufficiently timely manner.

Furthermore, safety issues with drugs that receive priority review may be a legitimate concern in the Canadian context. One study found that drugs approved via Health Canada's priority review system between 1995 and 2010 are significantly more likely to subsequently have a serious safety issue than drugs that were approved via standard review during the same timeframe.[532] Unfortunately, this investigation defines "serious safety issue" to mean *either* the acquisition of a serious safety warning *or* the withdrawal from the market for safety reasons.[533] As discussed above, subsequent acquisition of a safety warning may simply be a consequence of a different risk-benefit consideration that may be appropriate for drugs that merit priority review, rather than evidence of any deficiencies in the priority review process itself. Of greater concern are drugs that are approved via priority review then subsequently withdrawn for safety reasons. Of the 84 products that experienced a "serious safety issue" after approval, only 16 were ultimately withdrawn from the market and it is unclear how many of these were subject to

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NDAs than other departments, the authors estimate that oncology drugs are more scientifically complex than average, using clinical development times as an indicator of complexity).

[529] Health Canada, *Therapeutic Products Directorate Drug Submission Performance Annual Report Fiscal Year 2015-2016*, (8 June 2016) at 18.

[530] *Ibid.*

[531] *Ibid.*

[532] Joel Lexchin, "New Drugs and Safety: What Happened to New Active Substances Approved in Canada between 1995 and 2010?" (2012) 172 Arch Intern Med 1680 at 1681.

[533] *Ibid.*

standard or priority review.[534] Therefore, there is not enough information to conclude whether or not the additional burden of vouchers could be imposed on the agency without incurring further delays and potential problems with the safety of vouchered drugs.

Even if Health Canada is adequately prepared to take on the additional workload, the benefits to drug developers of a priority review voucher, and therefore the effectiveness of the incentive, are likely to be far less in the Canadian context because of the significantly smaller market for pharmaceutical products. In general, companies are choosing to not market products in Canada, possibly because "[a] small Canadian market and/or limitations on introductory prices imposed by the Patented Medicines Prices Review Board may mean that expected sales are too low to warrant the costs of getting a drug approved and then promoting it in Canada."[535] If companies currently cannot be bothered to market their product in Canada, it is reasonable to expect that a potential priority review in Canada is going to be of very little value to a drug sponsor. Given that the effectiveness of the program in the United States, particularly in relation to the costs and risks of vouchers, has yet to be determined, it is unlikely to be worthwhile to introduce a voucher program in Canada at this time.

5.6 Summary

The above evaluation of how the voucher programs are functioning in the United States leads to the conclusion that, to echo the GAO report, it is too early to say with confidence whether or not vouchers are an effective and efficient incentive for drug development. While the vouchers may be small and uncertain in value relative to market exclusivity, they may nevertheless be a worthwhile supplement to other incentives, particularly when one considers how they have been drafted so as to more specifically target subsets of orphan diseases that are especially likely to be neglected (i.e. tropical and pediatric diseases).[536] If the policy concerns (i.e. drug safety and FDA workload) are determined to be unfounded then the program may be

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[534] *Ibid.*

[535] Lexchin, "A Comparison", *supra* note 148 at 219. In light of this finding, a "fee waiver voucher", awarded to companies who apply for Health Canada approval for a qualifying drug, that could be redeemed to have the Health Canada NDA fee waived for any drug of a company's choosing could be a potentially useful alternative incentive. While the value of such a voucher would be relatively low, it could nevertheless provide the necessary encouragement to get companies marketing their orphan products in Canada at a timelier rate.

[536] The question of how the definition "orphan drug" could be drafted so as to align with the spirit of orphan drug policies was discussed above, at 26-27, 32-33.

justified even though it has only a relatively small impact on decision-making and investment in rare diseases. A relatively small impact is acceptable from a policy perspective provided that the benefits of the incentive outweigh the disadvantages. The same considerations would apply to a voucher program in Canada, though the costs-benefit analysis would change because Canada's pharmaceutical market is significantly smaller. Questions about the value of a priority review voucher and concerns about the burden placed on the review agency are likely exaggerated in the Canadian context. Overall, a PRV program in Canada cannot be recommended because it is likely to create too much additional workload for Health Canada and, in any event, accelerating drugs to the Canadian market is not particularly valuable to companies with the result that PRVs would not be an effective incentive in Canada. While it is possible that the program may become a good policy choice in the future (if further study of the United States PRV programs show stronger and more convincing results), Canada's smaller pharmaceutical market means that any advantage to be gained from priority review is also going to be smaller.

CHAPTER 6: INCENTIVE OPTION 3 – TAX CREDIT FOR DRUG DEVELOPMENT

6.1 The Nature of Tax-based Incentives

Market exclusivity and PRVs are examples of "pull", or "revenue-side", incentives because they reward the ultimate product of R&D projects; both are designed to increase a drug's profitability through increasing revenues (as opposed to decreasing costs). The tax system offers an alternative means of providing an incentive for orphan drug development. Referred to in the literature as "push" (also called "supply-side") mechanisms, tax-based incentives for innovation operate by lowering the costs of doing R&D. This has important implications for both policymakers and the pharmaceutical industry, including the timing of the incentive and the targeted behaviour. Tax incentives are available throughout the drug development process and are not dependent upon ultimately getting a drug approved for market. Therefore, unlike market exclusivity and PRVs, tax-based incentives specifically facilitate the actual process of drug development rather than "simply" encouraging companies to get regulatory approval for an orphan drug.

This Chapter assesses the use of the tax system to encourage orphan drug development activity in Canada. Section 6.2 describes the justification for government subsidization of R&D in general, either via tax expenditures or through direct funding programs. Canada's general R&D tax incentive, the Scientific Research and Experimental Development ("SR&ED") program, is described, followed by a description of the Orphan Drug Tax Credit ("ODTC"), which is an orphan drug-specific incentive available in the United States. Section 6.3 discusses the issues associated with using the tax system to provide an incentive for R&D. Notably, using the tax system generally has consequences for the amount of government oversight that will be given to a program. Tax-based incentives also offer taxpayers a degree of certainty that is not available with market exclusivity and PRVs because drug developers will obtain a tax credit regardless of whether their R&D activities ultimately yield a marketable product. This section concludes with Section 6.4, which provides a summary of the findings and recommendations arrived at through the analysis of tax incentives for orphan drug development. Specifically, a tax-based incentive would be a valuable orphan drug incentive in Canada that would promote the interests of rare disease patients without placing undue financial strain on taxpayers.

6.2 Tax Incentives for Innovation

Policymakers frequently use tax expenditures to promote socially desirable behaviour, including innovation.[537] Tax-based incentives for innovation can be designed in a number of different ways, including deductions, exclusions, exemptions, credits (refundable and non-refundable), deferrals, and lower tax rates.[538] The financial benefit for taxpayers is in the form of reduced tax liability, which in turn is a cost to governments (and, by extension, other taxpayers) in the form of forgone government revenue.

As discussed in Chapter 3, market failures are frequently cited as providing a strong rationale for governments to provide incentives that will encourage socially valuable behaviour.[539] It is uncertain whether or not tax expenditures are the best way to effect behaviour changes,[540] and it can be difficult to assess the effectiveness of tax expenditures that are intended to modify behaviour.[541] Many economic and political variables are going to influence a company's ability and willingness to undertake R&D projects.[542] As a result, it is difficult to determine the extent to which tax benefits actually encourage increased R&D activity as opposed to merely providing financial support for R&D projects that would have been undertaken in the absence of the incentive. However, the extent to which a business is willing to undertake R&D activities is certainly going to be influenced by the costs of doing so.[543] Therefore, government programs that reduce a company's costs of doing R&D are likely to facilitate greater innovative activity by that business,[544] and empirical evidence generally indicates that government subsidies for R&D, either via direct funding programs or through the tax system, "are an effective means

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[537] See e.g. Peter Hogg, Joanne E Magee & Jinyan Li, *Principles of Canadian Income Tax Law*,7th ed (Toronto: Carswell, 2010) at 51-52.
[538] *Ibid* at 51.
[539] See e.g. Busom, Corchuelo & Martinez-Ros, *supra* note 128 at 572.
[540] See e.g. Christopher Heady, "Tax Expenditures: Definitional and Policy Issues" in Lisa Philipps, Neil Brooks, and Jinyan Li, eds, *Tax Expenditures: State of the Art*, (Toronto: Canadian Tax Foundation, 2011) 2:1 at 2:14 ("it seems very few incentives can be shown to work better when delivered through the tax system than through an expenditure program.").
[541] Hogg, Magee and Li, *supra* note 537 at 58.
[542] Barry Bozeman & Albert N Link, "Tax Incentives for R&D: A Critical Evaluation" (1984) 13 Research Pol'y 21 at 27.
[543] Expert Panel Report, *supra* note 129 at 2-1.
[544] *Ibid* at 2-10.

of encouraging innovative activity."[545] The following discussion describes how tax expenditures are being used to promote R&D and attempts to evaluate whether the benefits of using the tax system outweigh the costs of doing so.

6.2.1 Scientific Research & Experimental Development

Canada already uses its tax system to subsidize R&D activity in general via SR&ED, a federal tax program that is meant to encourage innovative activity.[546] The scope of SR&ED is very broad; eligibility is not limited to any particular industry and the R&D activities that qualify for the tax benefits include everything from basic research (that which seeks to advance scientific knowledge without reference to a specific practical application) up to experimental development (activities that are intended to produce technological achievement).[547] As such, SR&ED is not specifically designed to encourage the pharmaceutical industry to invest in R&D for orphan diseases.

Three forms of tax benefits are available via SR&ED: an income tax deduction,[548] an investment tax credit ("ITC"),[549] and, for small Canadian-controlled private corporations ("CCPCs"), a refundable ITC.[550] The SR&ED ITC can be claimed by a corporation, partnership, individual for all qualifying R&D costs for eligible activities carried on in Canada.[551] Eligible research activities are defined in subsection 248(1) of the *Income Tax Act*.[552] It should be noted that the SR&ED ITC is a comprehensive credit, meaning that the credit can be claimed for almost all R&D spending.[553] Comprehensive credit schemes operate differently from incremental credit schemes, whereby a credit rate is applied only to the amount of R&D expenses that

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[545] Jacob Nussim & Anat Sorak, "Theorizing Tax Incentives for Innovation" (2017) 36 Va Tax Rev 25 at 43, 51(i.e. government-provided subsidization does not merely replace or substitute money that would have been spent regardless).
[546] Department of Finance Canada & Revenue Canada, *supra* note 132 at 42.
[547] *Income Tax Act*, RSC 1985, c 1 (5th Supp), s 248(1).
[548] *Ibid*, s 37.
[549] *Ibid*, s 127(5).
[550] *Ibid*, s 127.1.
[551] Canada Revenue Agency, *Claiming SR&ED Tax Incentives*, online: CRA https://www.canada.ca.
[552] *Supra* note 5547.
[553] See generally Benjamin Russo, "A Cost-Benefit Analysis of R&D Tax Incentives" (2004) 37 Can J Econ 313 at 319, 327.

exceeds a "base amount".[554] Many other jurisdictions, including the United States, use incremental credit schemes to provide R&D tax benefits.[555]

SR&ED is the "single largest federal program" to provide financial support for commercial R&D in Canada, with the program providing "more than $3 billion in tax incentives to over 20,000 claimants annually."[556] An Independent Panel report on government R&D spending, mandated by the Minister of State (Science and Technology), noted that SR&ED accounts for 70% of federal government spending to facilitate R&D.[557] The projected cost of the SR&ED credit for 2018 is $2,905 million.[558] SR&ED is perceived to be overly expensive, as evidenced by recommendations that changes be made to the provisions in order to reduce the cost of the program.[559] Some relatively recent changes have in fact been made, including a reduction of the credit rate from 20% to 15% and exclusion of capital expenditures and lease payments from being eligible for a deduction,[560] presumably with the intention to cut back on SR&ED spending.

A report by an Independent Panel was commissioned in response to concerns about low rates of business innovation in Canada relative to other countries.[561] The Panel found that Canada does indeed lag behind other countries with respect to the rate of innovation and that, compared with other countries, Canada relies very heavily on SR&ED to subsidize R&D activity as opposed to direct funding schemes.[562] It is possible that these two findings are related, in other words, that SR&ED is not as effective as it could be and that the level of innovation in Canada suffers as a result. One study found that firms who took advantage of *both* innovation tax credits and an R&D grant program "not only introduced more innovations but made more world-first

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[554] *Ibid*.
[555] *Ibid*.
[556] Canada Revenue Agency, *Evolution of the SR&ED Program – A Historical Perspective*, online: CRA https://www.canada.ca.
[557] Expert Panel Report, *supra* note 129 at 3-8.
[558] Department of Finance Canada, *Report on Federal Tax Expenditures 2017 - Concepts, Estimates and Evaluations 2017*, online: FIN http://www.fin.gc.ca/fin-eng.asp.
[559] Expert Panel Report, *supra* note 129 at E-10.
[560] See Minister of Finance, *Jobs, Growth and Long-Term Prosperity: Economic Action Plan 2012* (Ottawa: Public Works and Government Services Canada, 2012) at 70.
[561] Expert Panel Report, *supra* note 129 at E-1.
[562] *Ibid* at 1-2, 6-1, & 6-2.

innovations and were more successful in commercializing their innovations,"[563] indicating that innovative activities may be more effectively encouraged when both tax credits and grants are used compared to the use of only a tax incentive. This finding is mirrored by the Independent Panel's recommendation that SR&ED spending be reduced in favour of more direct spending.[564] It is, therefore, open to suggest that Canada's reliance on the SR&ED program at the expense of decreased resources being available for direct spending programs at least contributes to Canada's perceived lack of innovation.[565]

Several issues with the SR&ED program have been cited as impairing its effectiveness. As with other tax expenditures, SR&ED appears to be prone to uneven distributional effects, or in other words, creating an upside down effect whereby larger and more established companies benefit more from the program than smaller or newer publically traded companies that are not eligible for refundable credits.[566] SR&ED's eligibility provisions have also been noted as being overly complex, perhaps further contributing to an upside-down effect by making it more difficult for less sophisticated, but potentially very innovative, companies to identify eligible expenditures.[567] There is empirical evidence indicating that smaller companies are in fact generally less able to benefit from R&D tax incentives precisely for this reason.[568] This uneven distributional effect seems to be the combined result of a lack of awareness of the potential tax benefits,[569] the complex eligibility criteria (which make it difficult for businesses to accurately estimate their eligibility), and the high costs of claiming (i.e. sufficient record-keeping).[570] The

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[563] Charles Berube & Pierre Mohnen, "Are Firms that Receive R&D Subsidies More Innovative?" (2009) 42 Can J Econ 206 at 222.
[564] Expert Panel Report, *supra* note 129 at 6-4-5.
[565] *Ibid* at 1-2.
[566] See e.g. Andrew Wahl, "Thanks for Nothing" (2002) 75 Canadian Business 56.
[567] Donalee Moulton, "Science Grant Ignorance not Blissful" (March 2010) 26 The Bottom Line. One problem with SR&ED is that the complexity of the provisions results in many companies not making a claim because they or their tax preparer have misunderstood the rules. The claiming process is complex and onerous (in terms of record-keeping and reporting requirements), and many companies might not realize that they are undertaking eligible activities. See also Expert Panel Report, *supra* note 129 at 5-4.
[568] See e.g. M Beatriz Corchuelo & Ester Martínez-Ros, "Who Benefits from R&D Tax Policy?" (2010) 45 Cuadernos de Economía y Dirección de la Empresa 145 at 160.
[569] *Ibid* at 147, 160.
[570] Expert Panel Report, *supra* note 129 at 5-4. See also Francis Chittenden & Mohsen Derregia, "The Role of Tax Incentives in Capital Investment and R&D Decisions" (2010) 28 Env & Planning C: Gov & Pol'y 241 (smaller firms are likely to experience greater difficulty in

report of the Independent Panel suggests that SR&ED could be made more effective, particularly for small and medium-sized corporations, if the eligibility provisions were simplified.[571] Specifically, making certain expenditures ineligible was recommended in order to reduce the compliance costs associated with identifying eligible expenditures and maintaining the documentation necessary to claim the benefit.[572]

While available to the pharmaceutical industry,[573] SR&ED does not encourage orphan drug development specifically. Given that availability of approved treatments for rare diseases is still very much an issue, SR&ED is likely insufficient as a means of encouraging orphan drug development in Canada. The initial draft discussion document for a Canadian orphan drug policy does not contemplate using the tax system to provide an orphan drug-specific incentive, possibly because the SR&ED program is already available. Nevertheless, the United States has a tax credit specifically for orphan drug development in addition to a general research tax credit. If Canada were to introduce an orphan drug framework, SR&ED would undoubtedly be used by companies that invest in orphan drugs. However, the subsidization provided by SR&ED may not be sufficient, and a tax credit that specifically encourages orphan drug development could be a valuable and effective incentive.

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claiming R&D tax incentives because they have invested less time and energy in maintaining the required documentation, at 252).

[571] Expert Panel Report, *supra* note 129 at E-10.

[572] *Ibid* at E-10. See also Canada Revenue Agency, *CRA Delivers Enhanced Administration and Predictability for SR&ED Claimants*, online: CRA https://www.canada.ca/en/news/archive/2013/01/cra-delivers-enhanced-administration-predictability-sr-ed-claimants.html; Canada Revenue Agency, *The First-time Claimant Advisory Service*, online: CRA https://www.canada.ca/en.html; Canada Revenue Agency, *Pre-Claim Consultation*, online: CRA https://www.canada.ca/en.html (intended to help business identify eligible projects, was launched in June 2016); Canada Revenue Agency, *Pre-Claim Review*, online: CRA https://www.canada.ca/en.html (intended to provide assurance to claimants that the CRA will accept their entire claim as filed, piloted in August 2016). The CRA has implemented these measures to make the program more user-friendly, but it is too soon to determine whether these changes will successfully increase the predictability, and consequently the effectiveness, of the program.

[573] Patented Medicine Prices Review Board, *supra* note 136 at 48. The Annual Report shows that patentees spent $869.1 million on R&D (defined according to eligible SR&ED expenditures) in 2015. Though note that this figure is not necessarily representative of the entire amount being spent on pharmaceutical research in Canada because companies without sales of patented drugs do not need to report their R&D spending to the PMPRB and therefore the Report will not include the R&D activity by firms that, for example, only conduct research.

6.2.2 The Orphan Drug Tax Credit

In addition to a general R&D tax benefit and direct research grants, the United States also uses its tax system to specifically promote orphan drug development. Implemented as part of the ODA in 1983, the ODTC is considered to have played a significant role in encouraging orphan drug development and is thought to be a necessary incentive in order to ensure continued interest in developing orphan drugs.[574] The ODTC subsidizes the costs of orphan drug development by providing a non-refundable tax credit for "up to 50 percent of qualified clinical trial costs related to the development of designated orphan drugs".[575] In order to claim clinical testing costs, the drug under development must have been designated "orphan" status by the FDA.[576]

As discussed above, investment in orphan drug development increased significantly following the introduction of the ODA, and the ODTC is considered to have significantly contributed to this by lowering the costs of conducting clinical trials.[577]As the ODTC was implemented at the same time as other important incentives for orphan drug development (i.e. market exclusivity, orphan drug research grants) it is difficult to accurately gauge the impact of the credit alone,[578] however, a formal assessment of the ODTC estimates that the credit is responsible for facilitating up to one third of orphan drug development projects and approvals, noting that without the ODTC many companies could not otherwise have afforded to complete the drug development process.[579] Certainty and stability surrounding the ODTC are cited as features that make it a particularly effective incentive because, even though tax credits require companies to initially make an investment, drug developers can rely on subsequently receiving

[574] National Organization for Rare Disorders, Biotechnology Industry Organization & Ernst & Young, "Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases" (June 2015) online: NORD https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf at 24 [NORD, BIO & E&Y].
[575] *Ibid* at 7.
[576] *Ibid*.
[577] *Ibid* ("[l]acking sufficient market size or economic incentive, new treatments might not be developed to treat rare diseases. ODA provisions, like the Orphan Products Grant Program and the ODTC, were designed specifically to combat such barriers and increase orphan drug development" at 24).
[578] The analysis necessarily describes the combined effect of these two push incentives. The ODA introduced a number of incentives and therefore any estimate of the effectiveness of an incentive is going to be complicated by the existence of other incentives.
[579] NORD, BIO & E&Y, *supra* note 574 at 20-21.

the benefits.[580] More will be said about the value of this certainty to drug companies in the following section.

That being said, the ODTC is not without its limitations. The ODTC is of greater benefit to established drug developers (i.e. companies with prior drug approvals and tax liability) than to "pre-market companies" (i.e. those without prior drug approvals and no expectation that they will have tax liability in the near future).[581] Pre-market companies still benefit from the ODTC but to a lesser extent, particularly as they often have to wait longer before the tax credits can be used to off-set tax liability.[582] As a significant portion of orphan drug R&D activities are being completed by less established companies,[583] this may be an example of how the ODTC, like SR&ED, provides the greatest benefit where it is needed the least.

Furthermore, tax-based incentives do not affect revenue margins and, therefore, unlike market exclusivity, cannot be expected to increase the expected return on a developer's investment.[584] Therefore, the ODTC seems to be less effective at generating investment for less prevalent rare diseases, i.e. diseases that have an especially small pool of potential drug consumers and are therefore less potentially profitable than more prevalent diseases.[585] One author suggests that even full subsidization of clinical trial costs will be insufficient to stimulate development for particularly rare diseases.[586] As such, to encourage development for especially rare diseases, subsidization (either via tax incentives or direct funding) needs to be paired with "revenue-side" incentives that increase profitability of R&D activities.

6.3 Issues with Tax-Based Incentives for Orphan Drug Innovation in Canada

Historically there has been strong criticism about using the tax system for purposes other than generating government revenue.[587] According to the concerns expressed by Surrey, a leading tax scholar, tax expenditures that promote innovation can lead to wasted resources and

[580] *Ibid* at 9.
[581] *Ibid* at 13-17.
[582] *Ibid* at 15.
[583] See e.g. Sean Ekins & Jill Wood, "Incentives for Starting Small Companies Focused on Rare and Neglected Diseases" (2016) 33 Phamr Res 809 at 810.
[584] Wesley Yin, "Market Incentives and Pharmaceutical Innovation" (2008) 27 J Health Econ 1060 at 1073.
[585] *Ibid*.
[586] *Ibid*.
[587] Stanley S Surrey & Paul R McDaniel, *Tax Expenditures* (Cambridge, Mass: Harvard University Press, 1985) at 99-108.

market distortions.[588] Nevertheless, the *Income Tax Act*[589] is currently used to promote a wide variety of government policies. Tahk says that many of the original concerns about tax expenditures are no longer relevant in light of how they are now structured, (at least in the United States context) and that there are distinct advantages to promoting government policies via the tax system.[590] In light of the amount of government spending that is accomplished through tax expenditures, one would expect that there are, in fact, sufficient advantages that justify such wide-spread use of this policy mechanism. This section describes the implications of using the tax system to provide an incentive for R&D in general and orphan drug development in particular.

This Chapter is not intended as a thorough comparison of tax incentives with direct grants, however, because tax-based incentives and grants both function as an incentive by subsidizing R&D costs, some degree of comparison with direct funding programs is unavoidable throughout the following discussion. Further, the policy analysis of tax expenditures requires investigation into whether the tax system is the optimal means of implementation, which necessarily entails some comparison with offering subsidies outside of the tax system.

6.3.1 "Control" Concerns

Using the tax system has implications for the degree of control that policy-makers will be able to exercise over an incentive program. Overall, tax expenditures tend to have less frequent and less detailed government oversight than other incentive mechanisms, such as direct funding programs.[591] This section, therefore, addresses how using the tax system to provide incentives can generate concerns about insufficient government control and oversight.

As with market exclusivity and PRVs, tax credits are not cost-free. They are certainly "paid for" in the form of lost government revenue. In terms of fairness, it may be appropriate to disperse the costs of incentivizing pharmaceutical innovation across all taxpayers in society as opposed to placing the burden of paying for an incentive directly on the consumers of orphan

[588] Russo, *supra* note 553 at 315.
[589] *Supra* note 547.
[590] Susannah Camic Tahk, "Everything is Tax: Evaluating the Structural Transformation of U.S. Policymaking" (2013) 50 Harv J on Legis 67 at 68.
[591] Expert Panel Report, *supra* note 129 at 5-2. Although this does not necessarily have to be the case because tax-based incentives could be re-designed in such a manner that increases government control over the program (See e.g. Nussim & Sorak, *supra* note 545 at 58-59).

drugs (as market exclusivity does) or drug consumers more generally (as PRVs would do), and any third party who ultimately pays for those drugs.[592] Unlike direct spending programs, tax-based incentives do not have a pre-determined government spending limit and therefore can become incredibly expensive for the government and, in turn, taxpayers.[593] While there is typically a maximum amount that any individual taxpayer may claim, the total amount of money that a tax expenditure will cost in a given year can only be roughly estimated. Consequentially, the government may end up spending more in support of R&D activity than is truly justified, with little ability to curb this expenditure. However, this factor merely gives some context to the rest of the analysis. A significant cost may, in fact, be reasonable in circumstances where there is a strong justification for the tax expenditure (such as the unmet medical needs of patients with rare diseases) and the incentive being offered is actually effective in achieving its objectives. As discussed above, SR&ED is perceived to be very costly and efforts have been made to reduce SR&ED spending.[594] A targeted, orphan-specific tax incentive would, of course, be less expensive than the SR&ED program because it would be available for a significantly smaller subset of R&D activities. As the costs of a tax credit for orphan drug development expenses would be dispersed across all Canadian taxpayers, the resulting positive impact on public health could justify this collective burden. Increasing available treatments would likely generate improved health outcomes, resulting in more patients and their families being able to return to and/or contribute more to the workforce and, consequently, contribute more to paying for orphan drug incentives through their income taxes.

A second important aspect of tax expenditures is that, once implemented, they tend to enjoy a level of stability that is generally not afforded to other government programs.[595] This has been suggested as one of the most powerful arguments in favour of using tax expenditures to

[592] Nussim & Sorak, *supra* note 545 at 47-48.
[593] A concern also noted by Office of the Auditor General of Canada, *Report 3 Tax-Based Expenditures* (Ottawa: Public Works and Government Services, 2015) ("tax expenditures are not subject to a spending limit authorized by Parliament and may put pressure on the federal government's finances" at 6).
[594] At 97-98.
[595] At least in the American context (see e.g. Tahk, *supra* note 590 at 88), though a report from the Auditor General of Canada also noted that, unlike direct program spending, tax-based expenditures are not required to be annually approved by Parliament or be the subject of expenditure reviews. (Office of the Auditor General of Canada, *supra* note 584 at 12).

promote R&D activity.[596] This stability is related to the lack of regulatory oversight given to tax-based incentives, compared with other incentive programs.[597] Tax incentives tend to be more stable and permanent than grant programs because they are not typically subject to annual budget reviews, which may mean that tax incentives are more likely to lead to behaviour adjustments than a grant program that could undergo dramatic changes on a yearly basis.[598] While direct funding schemes can be thought of as more predictable in the sense that they permit a company to receive financial support before an R&D project has even been commenced, this predictability is relatively short-lived; SR&ED is firmly ensconced in the Canadian tax system, which facilitates planning of R&D investment and activities over the long-term. Given that drug development often takes over a decade, a tax incentive that can be relied upon throughout that time facilitates planning of the development process better than a direct funding program that is subject to annual review, amendments, and possible termination.

While not necessarily a disadvantage per se, the stability of tax expenditures certainly permits reasonable concerns about the extent to which public resources are being spent via the tax system to encourage innovation. Some authors suggest that, with respect to R&D tax incentives, "unless there is a clear conviction that policies implemented via tax expenditures merit an immunity not granted to other R&D assistance programs, the result is an unnecessary abrogation of policy leadership."[599] Given how much government spending is provided via SR&ED one could reasonably argue that the program should be regularly evaluated. Being set within the tax system makes SR&ED difficult to regularly assess; however, increased oversight by government actors, in and of itself, is not necessarily desirable. A lack of regular scrutiny is merely a potential concern with tax expenditures in general and may not actually operate as a disadvantage with respect to SR&ED or an orphan drug-specific tax credit. Regular evaluation also requires significant government resources to accomplish and whether frequent assessment is worth it to ensure that a program continues to function as intended will vary by program. Careful policy planning could reduce the need to regularly assess a subsidy because if its provisions have been sufficiently well thought out the government will retain a sufficient amount of control over its spending. A tax incentive targeting orphan drug development would have the advantage, for

[596] Bozeman & Link, *supra* note 542 at 26.
[597] *Ibid* at 27.
[598] *Ibid* at 26.
[599] *Ibid* at 28.

policymakers, of specifically directing the pharmaceutical industry toward socially valuable innovative efforts, while also affording drug companies a degree of predictability that is not often available through direct funding programs.

Furthermore, as a supply-side incentive, tax benefits are available "up-front"; in other words, companies receive the subsidy prior to product approval. For drug companies, this is an especially important advantage of tax incentives and other push mechanisms because they can rely on receiving the benefit regardless of whether or not the R&D activities they invest in ultimately yield a marketable product. Supply-side incentives are considered to be effective because they are available throughout the process of R&D, which is precisely the time when expenses are high.[600] Revenue-side incentives, such as PRVs and market exclusivity, "suffer from time-inconsistency",[601] whereby incentives that are not awarded until the completion of R&D activities are associated with decreased certainty and the possibility that the incentive will no longer be available once a drug developer has an eligible product. Recall that this has been noted as a short-coming of the PRV programs.[602] Uncertainty about whether a project will yield a marketable product combined with the enormous expense of the drug development process might strongly discourage companies from investing in R&D.[603] On the other hand, there is no guarantee that the costs of the tax expenditure will result in "successful" drug development, and some concern has been expressed that supply-side incentives allows for potentially wasteful government spending because there is no guarantee that a product will be successfully developed.[604] Nevertheless, for some pharmaceutical companies supply-side incentives like tax credits may be the only way they will be able to complete (or even begin) the drug development process. The cost of greater certainty and perhaps, therefore, greater impact, may be some waste in the form of funding being paid for research activities that ultimately do not result in a marketable product. Furthermore, "unsuccessful" drug development is arguably still socially

[600] Yin, *supra* note 584 at 1073.
[601] *Ibid.*
[602] See e.g. Government Accountability Office, *supra* note 388 at 17.
[603] Yin, *supra* note 584 ("[g]iven that upfront R&D costs tend to swamp marginal costs of drug or vaccine production, this uncertainty may deter firms from investing in R&D. For these reasons, supply-side incentives that occur contemporaneously with R&D expenditures are thought to be an effective tool for stimulating innovation" at 1073).
[604] Sonderholm, *supra* note 429 at 418.

valuable because it can add to the knowledge base of the broader scientific and pharmaceutical industry.[605]

6.3.2 Effectiveness and Impact of Tax Incentives

While tax incentives are available throughout the drug development process, they also require that a company make the initial investment in a development project in order to receive the subsidy. In other words, while the money is available sooner than under revenue-side incentives, it may not be soon enough for some companies. Smaller or otherwise less financially stable companies may not be able to make that initial investment and, therefore, be unable to take advantage of tax-based incentives.[606] R&D tax incentives seem to primarily assist firms that are not operating under significant financial constraints.[607] As noted by one author, "tax incentives as a policy tool toward R&D are most effective when they are least necessary and may influence those firms who need them the least."[608] Particularly for small, start-up enterprises, the requirement to pay up-front may be detrimental to their innovative potential and therefore basing an orphan drug incentive in the tax system operates as a disadvantage to the extent that it does not facilitate R&D efforts from companies that do not have sufficient capital to start or continue with a project. Arguably, the issue of requiring businesses to make an initial investment can be addressed through direct funding schemes,[609] though companies could face similar difficulty in obtaining assistance in this manner, depending on the eligibility criteria, because of uncertainty around a project's feasibility.

As mentioned previously, a common concern about tax expenditures is that they can create an "upside-down" effect whereby tax benefits are worth more to those who have more money, an issue that has been referenced with respect to both SR&ED and the ODTC.[610] Some authors have suggested that upside-down effects are particularly problematic in the case of R&D

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[605] Of course, the extent to which "unsuccessful" R&D projects will actually prove beneficial depends on the extent to which companies make the resulting information accessible. One way to promote the dissemination of research information could be to make doing so necessary in order to be eligible for an orphan drug tax credit.
[606] Busom, Corchuelo & Martinez-Ros, *supra* note 128 at 577.
[607] *Ibid* at 590.
[608] Bozeman & Link, *supra* note 542 at 27.
[609] Expert Panel Report, *supra* note 129 at 6-3-6-5 (in its report on government spending on R&D the Expert Panel recommended that SR&ED spending be reduced in favour of allocating more resources to direct funding schemes).
[610] See e.g. Tahk, *supra* note 590 at 77 for further description of these concerns.

tax incentives because newer companies may not have sufficient tax liability or profitability to benefit from the credit when they are just starting out, but these may be the companies that are most deserving of assistance.[611] The upside-down effect can be mitigated to the extent that refundable, instead of non-refundable, tax credits are used because the value of refundable credits is not dependent on a taxpayer having tax liability.[612] This effect is in fact reduced to some extent in Canada because small CCPCs are able to receive refundable credits. However, SR&ED has been accused of being "woefully ineffective for publicly traded tech companies"[613] that are not eligible for refundable credits, a complaint that is underscored by the fact that in 2007 only 4% of SR&ED benefits were received by small non-CCPCs.[614] In any event, the use of refundable credits for orphan drug development is not recommended as this would greatly increase government spending in a manner that is not necessarily justified by an equally significant impact on public health outcomes. On the other hand, the additional costs associated with providing a refundable credit could be reduced by providing the credit at a lower rate (e.g. 35 percent instead of 50).[615]

An alternative arrangement that warrants further consideration has been suggested by Valverde, Reed, and Schulman.[616] Their proposed "grant-and-access" program would give companies the choice between a tax credit and a direct research grant (subject to a price cap on the orphan drug).[617] Such a program would offer an additional means of subsidizing orphan drug development while addressing the uneven distributional effects observed with the ODTC in the United States. One significant limitation on this alternative is that it requires a "robust" grant program be set up, in order to sufficiently subsidize development costs.[618] As will be discussed

[611] Bozeman & Link, *supra* note 542 at 27.
[612] Tahk, *supra* note 590 at 78.
[613] Wahl, *supra* note 566.
[614] Expert Panel Report, *supra* note 129 at 3-9 (in 2007 56% of SR&ED benefits went to large businesses and 40% went to small CCPCs). Of course, the advantage of having minimal to no refundable credits is the reduced government spending. Additionally, non-refundable credits can be carried forward so the benefit is not altogether lost.
[615] The author thanks Professor Tamara Larre for this suggestion.
[616] "Proposed 'Grant-And-Access' Program With Price Caps Could Stimulate Development Of Drugs For Very Rare Diseases" (2012) 31 Health Aff 2528.
[617] *Ibid* at 2530.
[618] *Ibid* at 2531.

in greater detail below,[619] it may not be politically feasible to introduce a large direct funding scheme for orphan drug development in Canada.

As already discussed, the complexity of tax provisions can contribute to undesirable distributional effects as well. This issue would likely be less of a concern with respect to an orphan drug-specific tax incentive because companies undertaking R&D in the pharmaceutical field are more likely to be equipped to accurately identify qualifying research activities. Even small pharmaceutical companies can be expected to realize that their activities are eligible for an orphan drug tax credit. Given the importance of maintaining detailed and accurate research documents in order to gain regulatory approval, it is also likely that having the records required to successfully claim the tax credit will present very little difficulty for companies engaged in pharmaceutical research.

Finally, with respect to the ability of tax incentives to bring about the desired changes in behaviour (i.e. to get pharmaceutical companies investing in developing orphan drugs), as discussed above, the ODTC appears to be effective only to a certain extent.[620] Less prevalent diseases are less likely to receive attention from the pharmaceutical industry, even when the costs of drug development are being subsidized.[621] This finding highlights the importance of having both supply-side and revenue-side incentives; supply-side incentives will make it easier for a company to carry out R&D and see the development process through to completion while revenue-side incentives may be necessary to encourage companies to invest in drug development projects that would otherwise be unprofitable.[622] Although not without its problems, a similar orphan drug-specific credit in Canada may complement a Canadian market exclusivity regime.

6.3.3 Implementation Costs

Government subsidization of research can be accomplished in a number of manners, either directly, such as through research grants, or indirectly as with tax credits. One final issue about a tax credit to facilitate orphan drug development remains to be considered and that is whether a tax agency is well-suited to administering an orphan drug incentive or, more specifically, whether a tax agency represents the optimal policy means to provide an orphan drug

[619] At 112-13.
[620] See e.g. Yin, *supra* note 584 at 1073.
[621] *Ibid.*
[622] *Ibid.*

subsidy. An orphan drug tax credit will involve the Canada Revenue Agency ("CRA") in administering what is essentially a health policy. This is not necessarily a problem per se, but does warrant further consideration because the institution, or agency, that is tasked with administering a program has implications for the design and accuracy of the program; some agencies are better suited to administering a particular program and may therefore be able to do so more cheaply and accurately than another agency.[623]

Incentives that are based in the tax system often have characteristics that differentiate them from direct spending programs, but these differences may simply be a matter of how these programs are typically designed. Arguably, both tax expenditures and cash-based transfers ("CBTs") can "always be redesigned in an equivalent manner"[624] so as to "take the same form and be contingent on the same variables" [625] and therefore "generate identical effects on behaviour".[626] Where CBTs and tax-based incentives may actually differ is with respect to implementation costs, political constraints, and international commitments.[627] Therefore, decisions about whether to use a direct or indirect means of providing a subsidy should involve a consideration of the implementation costs associated with each agency.

Implementation costs refer to the capital (human, tangible, intangible, or financial) that is needed to apply the rules that govern the allocation of the subsidy.[628] With respect to programs that are intended to encourage innovation, assessments have to be made about what qualifies as innovative activity in order to ensure that government subsidization is only being granted for appropriate activities (i.e. those for which public spending is justified).[629] In order to avoid undue implementation costs when making these assessments, the agency tasked with administering a program needs to possess a sufficient degree of expertise in the incentive program's subject matter.[630] Weisbach & Nussim discuss an "integration theory", which posits that whether a government program should be implemented as a part of the tax system depends on the extent to

[623] David A Weisbach & Jacob Nussim, "The Integration of Tax and Spending Programs" (2004) 113 Yale LJ 955 at 982.
[624] Nussim & Sorak, *supra* note 545 at 29.
[625] *Ibid* at 65.
[626] *Ibid* at 29.
[627] *Ibid* at 65.
[628] *Ibid* at 65-66.
[629] *Ibid* at 73.
[630] *Ibid* at 73.

which the program's function complements the functions that are already performed by the tax system.[631] Integration theory suggests that if the areas that the CRA already specializes in involve skills that are necessary to implement a particular program, then integrating that program into the tax system would be advantageous.[632] Innovation incentives require knowledge of scientific or technological matters; an incentive for orphan drugs requires an even narrower area of expertise.[633] Tax agencies do not inherently possess this specialized expertise, nor is it necessarily desirable for tax agencies to develop expertise in scientific and technological matters because such expertise is not otherwise complementary to administering the other tasks of a tax agency (i.e. measuring and assessing means to pay, etc).[634] According to integration theory, R&D incentives will incur high implementation costs when administered by the tax agency (because the tax agency will have to develop or out-source the necessary expertise) and therefore, tax incentives for innovation should be redesigned as CBTs and the task of administering these programs allocated to another agency.[635] With respect to an incentive program that specifically promotes orphan drug development, a drug regulatory agency would be better suited to administering it because it already has the expertise required to design, monitor and enforce the rules, and doing so complements the other activities of that agency.[636]

The definition of "scientific research and experimental development" used to determine an eligible expense under SR&ED does involve a degree of scientific or technological

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[631] *Supra* note 623 at 980.
[632] *Ibid* at 994.
[633] Nussim & Sorak, *supra* note 545 ("[p]referably, public funds should support R&D activity, for example, and nothing else….Therefore, these policies must insist, as they do in reality, on making sure only "appropriate" R&D activities receive cash transfers. This set of requirements and conditions that designate "appropriate" R&D activities is scientific or technological in nature. It takes the forms of scientific or technological thresholds for receiving public support, monitoring the technological progress over time, evaluating the final outcome of the R&D process, or assessing the scientific or technological source of resulting products…All of these requirements command scientific or technological expertise on the part of the government" at 73).
[634] *Ibid* at 75 ("[t]he point is that the activities required by the Service to run a technological/scientific tax scheme – e.g. monitoring, auditing, ruling – are not complementary with those used in the regular production process of this agency" at 75); But see Tahk, *supra* note 590 who argues the opposite; that it *is* desirable to have incentives for innovation administered by the tax agency *specifically* because it will require the agency to develop a new set of specialized knowledge, at 102-03.
[635] *Ibid* at 75-76.
[636] *Ibid* at 75.

knowledge on the part of CRA.[637] In response to criticism about SR&ED's complexity and the associated problems with making a successful claim, CRA has introduced a number of support services including the First-Time Claimant Advisory Service and Pre-claim Project Review.[638] Empirical evidence is needed to make any conclusive statement but it is reasonable to question whether it really is efficient to introduce these services into the tax system. These seem to be non-tax-related administrative tasks that would be better left to a different government agency. Tax agencies specialize in "observing, measuring, and enforcing ability-related variables such as income, expenses, family structure, business entities, financial instruments, etc."[639] CRA's support services for SR&ED claimants require expertise that is not otherwise related to the other activities of the agency.[640]

With respect to a broad incentive program like SR&ED it is not clear which government agency should administer it, and, given this breadth, they may not be another government agency in Canada that would be an obvious candidate to administer an equivalent program. However, an orphan drug-specific incentive program allows for a more straightforward application of the integration theory that was discussed above. Orphan drug policy is of course a public health policy and perhaps "health-related innovation, for example, should be entirely managed by the Department of Health, which enjoys the necessary scientific expertise, economies of scope with

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[637] *Income Tax Act*, *supra* note 547, s 248(1) states "scientific research and experimental development means systematic investigation or search that is carried out in a field of science or technology by means of experiment or analysis and that is (a) basic research, namely, work undertaken for the advancement of scientific knowledge without a specific practical application in view, (b) applied research, namely, work undertaken for the advancement of scientific knowledge with a specific practical application in view, or (c) experimental development, namely, work undertaken for the purpose of achieving technological advancement for the purpose of creating new, or improving existing, materials, devices, products or processes, including incremental improvements thereto…".

[638] *CRA Delivers Enhanced Administration and Predictability for SR&ED Claimants*, *supra* note 572 (the First-Time Claimant Advisory Service is available for first-time potential SR&ED claimants who wish to benefit from an in-person meeting with CRA staff who will provide advice about how to identify potentially eligible projects and maintain the documentation necessary to make a claim and Pre-Claim Review is available for all potential SR&ED claimants and involves an identification of projects that may qualify).

[639] Nussim & Sorak, *supra* note 545 at 75.

[640] With the amount of money that is spent via SR&ED it is possible accurate assessments of "appropriate" R&D activities are *not* being made, with the result that SR&ED benefits are being paid out where not truly warranted.

its other health-related activities, and low intra-agency coordination costs".[641] The CRA does not specialize in identifying what constitutes qualified clinical trial costs, or what qualifies as an orphan drug. Health Canada is likely to be better suited to this task because the agency already possesses the specialized knowledge regarding orphan drugs and clinical testing, and identifying eligible activities (i.e. clinical trials for designated orphan drugs) relates to the other activities of that agency. A tax-based incentive for orphan drug development would fail to take advantage of Health Canada's existing expertise in that subject matter. As such, the theory would suggest that an orphan drug subsidy should be administered by Health Canada rather than the CRA.

On the other hand, as the CRA already administers SR&ED, a tax credit for orphan drug development could reasonably be added to their tasks with relatively little additional burden to the agency. Drug developers in Canada already make use of SR&ED benefits,[642] and there would be minimal additional compliance costs for them in claiming an orphan drug tax credit. Having an orphan drug subsidy in the tax system would also have the advantages associated with yearly filing. Specifically, annual filing of taxes can increase awareness, and therefore take-up, of the program,[643] and offers companies a convenient way to apply for the subsidy.[644]

Furthermore, while implementation costs provide one basis for deciding how to provide a subsidy, the political costs are also acknowledged as a means to distinguish between essentially equivalent programs.[645] An incentive that stands no reasonable chance of being implemented cannot be expected to have an impact on orphan drug development. Directly funding orphan

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[641] Nussim & Sorak, *supra* note 545 at 80.
[642] See e.g. Patented Medicine Prices Review Board, *supra* note 136 at 46.
[643] See e.g. Tahk, *supra* note 590 (discusses how filing tax returns provides "automatic notification" of tax-based programs at 93).
[644] As companies will already be filing a tax return, applying for an orphan drug tax credit can be a relatively simple matter, compared with the additional time and complexity that having to apply to a separate program would incur. See e.g. Tamara Larre, "The Children's Fitness Tax Credit: Right Message, Wrong Policy Instrument" in Neil Brooks, Jinyan Li & Lisa Philipps, eds, Tax Expenditure Analysis: State of the Art (Toronto: Canadian Tax Foundation, 2011) 12:1 (discusses how annual filing can make it easier on companies by reducing the costs of complying with a program at 12:7).
[645] Nussim & Sorak, *supra* note 545 (for the purposes of their analysis the authors "assume away" the political reasons for the design and allocation of innovation-inducing mechanisms, specifically stating "[w]e ignore in this article principal-agent problems within the organization (which are the essence of political theories of government), and focus on the "team theory" tradition. Assuming away political causes for an organizational structure of government, a "team theory" framework focuses the analysis on specialization and coordination" at 71).

drug development may be politically unfeasible in light of the public controversy over the high prices for orphan drugs and pharmaceutical companies that "game" the system by exploiting loopholes in orphan drug policies. For better or worse, the voting public perceives tax expenditures to be less costly than direct grants even in the face of information that says otherwise.[646] The political popularity that tax incentives typically enjoy relative to direct spending programs, combined with the concerns about orphan drug prices, may mean that the tax system will be the only way policymakers could actually get an orphan drug subsidy implemented. Assuming that some subsidization of orphan drug development is necessary, a tax-based program that could be introduced without insurmountable opposition may in fact be a better policy choice than a direct funding program that would attract significant opposition.

6.4 Summary

This Chapter leads to the conclusion that an orphan drug subsidy should be implemented in the form of an orphan-specific tax credit. This incentive, unlike market exclusivity, will have the advantage of lowering the costs of drug development and may therefore permit R&D activity that could not occur without the additional assistance from the government. A commitment to equality makes it fair to widely disperse the costs of a tax-based subsidy across all Canadian citizens, as orphan drug development is likely to have broader societal benefits. Furthermore, the ODTC used by the United States has a sufficiently narrow window of eligibility that the cost of such a program in Canada would be relatively modest. The limitations of a tax credit or indeed, any subsidy for drug development, reinforce the importance of using the tax system in conjunction with a revenue-side incentive such as market exclusivity that will be able to further encourage companies to development and market orphan drugs. Finally, while this discussion found that an orphan drug development subsidization program would be more appropriately administered by Health Canada as a direct funding program, the high costs of orphan drugs and controversy of orphan drug policies place political constraints on the choice of policy mechanism that cannot be ignored. CRA is already involved in administering a research-based incentive (SR&ED) and tax expenditures tend to be politically popular relative to direct funding schemes, thus making it more likely that a tax expenditure would be a preferred policy instrument. Given

[646] Conor Clarke & Edward Fox, "Perceptions of Taxing and Spending: A Survey Experiment" (2015) 124 Yale LJ 1252 at 1257, 1287.

the importance of providing *some* form of subsidy, a tax credit, as a "second best" option, will have to suffice.

CHAPTER 7: SUMMARY AND CONCLUSIONS

Rare diseases historically created a market failure where the costs of developing a drug to treat a small number of people are likely to outweigh the expected return on investment to the developer. Diseases of low prevalence can also create unique challenges for drug developers with respect to obtaining a sufficiently workable understanding of the progress of a given disease and conducting clinical trials for relatively few patients who may be widely dispersed across a jurisdiction. As a result, these diseases were ignored, or "orphaned", by the pharmaceutical industry. Orphan drug frameworks have been enacted in a number of jurisdictions in order to address this problem. The United States has led the way for orphan drug policies and its ODA, enacted in 1983, is generally hailed as a successful policy move. The number of treatments being developed for rare diseases increased dramatically following the enactment of the ODA and the Act is frequently cited as having had a significant impact on public health. A similar policy was subsequently implemented in the European Union; Australia, Singapore, Japan, and Taiwan also have orphan drug legislation that provide incentives to varying degrees. Orphan drug incentives have, in concert with other factors, made orphan drugs a more profitable and attractive investment for drug companies. This thesis sought to evaluate three orphan drug incentives with the goal of understanding how well they could be expected to operate in Canada and to identify whether it would be advisable to modify how they are currently being used in other jurisdictions.

In the 1990s a Canadian orphan drug policy was rejected as being unnecessary, largely on the basis of two reasons: one, that Canadian patients can use the SAP to apply for access to medicines that are not yet approved in Canada and, two, low levels of pharmaceutical innovation in Canada were taken to imply that orphan drug incentives would be unlikely to have an impact in any event due to lack of capacity. Nevertheless, with no orphan drug framework in place, Canadian patients with rare diseases can face additional challenges with respect to accessing treatment. With nothing that encourages companies to market their orphan drug products here, developers of orphan drugs tend to delay obtaining market authorisation in Canada, if they do so at all. Unapproved drugs that are accessed through the SAP are not usually covered by healthcare plans with the result that patients with rare diseases often have to pay for them. This puts patients with rare diseases at a disadvantage relative to those with more common diseases.

Government interventions that address market failures are often considered valid public policy. Further justification for providing orphan drug incentives may be found in the "rule of rescue" line of reasoning, whereby a disproportionate allocation of resources can be considered acceptable public policy in order to "rescue" a small group of people. Many orphan diseases are serious to life-threatening in nature and are frequently suffered by children; these are circumstances that make the argument in favour of providing orphan drug incentives all the more compelling. It could even be argued that Canada has a legal obligation to promote development and access to orphan drugs through various policy mechanisms. At the very least, it is reasonable to argue that Canada should provide incentives that will encourage drug companies to market their orphan drugs here in a more timely manner in order to relieve the current barriers to treatment faced by rare disease patients relative to patients with more common disorders.

That being said, it is not entirely clear how "orphan" status should be determined, and how the resources associated with that designation should be allocated. Increasingly vocal concerns about wildly expensive orphan drugs also highlight the importance of careful policy planning. The success of orphan drug policies is tempered by the outstanding issues of availability and affordable access. In acknowledgment of the concerns about exploitation of orphan drug policies and undue strain on public healthcare budgets as a result of increased stratification of disease subsets, it is recommended that careful consideration be given to the definition of "orphan". Rarity alone may not be sufficient to justify the provision of incentives and it may be more appropriate for a Canadian orphan drug framework to take disease severity, or some additional criteria, into consideration. Without seeking to conclusively state how "orphan" should be defined, in all likelihood factors in addition to disease prevalence should be included in Canada's "orphan drug" definition.

Market exclusivity may be the most powerful incentive offered through orphan drug policies and, unsurprisingly, the above evaluation arrived at the conclusion that it should be introduced in Canada as part of an orphan drug framework. The relatively narrow scope of protection combined with the strength of the protection (due to how exclusivity is enforced) would address both public policy concerns and perceived shortcomings of patent law. The requirements that an invention must be novel and inventive can result in what is perceived to be an under-protection of a drug developer's investment and, therefore, patent protection is not necessarily sufficient to encourage valuable drug development to a satisfactory degree.

Furthermore, the subjective nature of the patent application process results in an indeterminacy that can further impair the impact that patent regimes can have on drug development. Market exclusivity, as it is offered in the United States and the European Union, provides a degree of certainty and predictability that is not available under patent schemes, and may therefore operate more effectively as an incentive for drug development in general.

Market exclusivity likely functions as a strong incentive for pharmaceutical companies to invest in developing and marketing rare disease drugs, however, the incentive does not appear to be sufficiently targeted from a public policy perspective with the result that patients with less prevalent rare diseases are still without approved treatments. This issue needs to be addressed beyond the level of any individual incentive (i.e. in identifying the drugs that should be eligible for incentives in the first place). The high cost of drugs that are approved for rare diseases creates an additional barrier to patient access, but it is debateable whether market exclusivity is the primary cause of these high prices. To an extent, the costs of developing a drug will dictate what companies need to charge for an orphan drug, but at the very least it can be acknowledged that exclusivity protection does little to alleviate the cost concerns.

Concerns about sky-rocketing prices for orphan drugs are not unwarranted, and scientific advances in the field of pharmacogenomics are such that Canadian policymakers should make some modifications to how the United States and European Union have drafted the rules governing exclusivity. In recognition that a small market can make it difficult to profit from orphan drug development, providing a longer period of protection may partly address concerns about affordable access because companies would have a longer period of time during which they can rely on market protection. At the very least, it is not recommended that exclusivity be provided for only a few years because this would likely put pressure on companies to increase prices in an effort to make a profit in a much more limited timeframe. Including the ability to terminate the exclusivity period once an orphan drug has become "sufficiently profitable" is recommended in order to avoid prolonged application of an incentive where it is no longer necessary. That being said, the term "sufficiently profitable" must be clearly defined and should take into consideration the additional indications for which an orphan drug is approved, at least those that are bio-marker-defined subsets of the original orphan condition. The potential to extinguish exclusivity protection once it appears no longer justifiable could hopefully quell

public concerns about orphan drug policies being vulnerable to exploitation by pharmaceutical companies.

Implementing market exclusivity along with a European Union-inspired provision allowing for the exclusivity period to be prematurely extinguished once a drug becomes "sufficiently profitable", as suggested above, would make the incentive somewhat more closely related to the actual risks and costs incurred in developing a drug. In theory, the potential to terminate the exclusivity protection could weaken the market exclusivity as an incentive in the eyes of pharmaceutical companies. On the other hand, such a provision could be more clearly worded to allow it to be known in advance roughly how and when that clause would be applied, thereby tempering any concerns that exclusivity would be taken away too early or without just cause. This solution will of course require companies to be more forthcoming and transparent about their R&D investments and marketing expenditures to be effective, and Health Canada's experience of administering its NOC/c program suggests that care should be taken to ensure that the agency is able to adequately assess profitability and respond accordingly (i.e. by terminating market exclusivity).

Public controversy over orphan drug prices and incentives in general may have a detrimental effect on Canadian patients with rare diseases. Allocation of public resources, as would be required to provide orphan drug incentives, should be done in a manner that reflects the values and priorities of society as a whole. If the public perceives orphan drug incentives to be overly generous toward drug developers, or otherwise unnecessary, then patients with rare diseases in Canada will continue to be disadvantaged. In order to smooth the path for an orphan drug framework to be enacted in Canada, policymakers should be proactive in their efforts to prevent exploitation by the pharmaceutical industry (i.e. through careful wording of the definition for "orphan drug") and to tie the provision of incentives to a positive impact on public health outcomes. This applies to all potential incentives but probably more so to market exclusivity because it is seen as such a powerful and valuable incentive, whereas vouchers are perceived to be of uncertain and insufficient value and tax credits, as a supply-side incentive, simply operate differently (by lowering the costs of R&D rather than increasing the profits of doing so).

The possibility to terminate exclusivity protection, combined with regulation that would "add up" profitability of the drug as a treatment for related disease subsets will help to address

concerns about misuse of orphan drug incentives, particularly if these provisions successfully encourage companies not to set unreasonably high prices. While the recommendation to provide longer market exclusivity periods is unlikely to garner strong political support, including the possibility of ending market protection for "sufficiently profitable" drugs should alleviate the anticipated initial resistance to this. For this reason it is especially important to flesh out the term "sufficiently profitable"; doing so will give the provision real meaning and avoid the appearance of being an empty threat. As the provision to shorten the exclusivity period has never been used in the European Union this would be a legitimate concern, one that Canadian policymakers can avoid by elaborating on the meaning of "sufficiently profitable" and giving clear guidance about when and how it will be applied.

Priority review vouchers, while a unique and interesting incentive, are not recommended as part of an orphan drug framework in Canada. There are outstanding questions about the safety of "vouchered" drugs and the additional burden that will be placed on the review agency when a voucher is redeemed. Furthermore, the value of vouchers remains uncertain and, in any event, is arguably always going to be a weak influence on decisions about drug development. Although vouchers may be insufficient to act as the catalyst for a drug's development, they may provide a sufficient financial incentive to allow smaller companies to attract the investment they need to complete the development process. Safety concerns about drugs that are reviewed via Health Canada's priority review mechanism and legitimate questions about the agency's ability to meet its review targets even without the additional burden that would be imposed by a voucher program should be sufficient to conclude that it would be inappropriate to implement a PRV program in Canada at this time. This conclusion is reinforced by the fact that Canada has a significantly smaller population than the United States, and therefore, presumably, represents a smaller market for blockbuster drugs. As the impact of voucher programs comes from the value of accelerating a blockbuster drug to market, this value (which is already questionable in the United States) surely would be insufficient in the Canadian context to have an impact on drug development and marketing decisions.

While recognizing the importance of having a revenue-side incentive such as market exclusivity, the need to subsidize the costs of orphan drug development cannot be overlooked. Therefore, an orphan drug-specific tax credit should be introduced in Canada. Subsidies, tax-based or otherwise, have been demonstrated to be an effective means of achieving policy

objectives. Canada already provides a tax-based subsidy for R&D activity with its SR&ED program. However, this program is not specifically directed at orphan drug development. The United States, on the other hand, uses an orphan drug-specific tax credit in addition to its general R&D tax expenditure. The ODTC is considered to be a valuable and necessary part of orphan drug policy in the United States. Restricting eligible expenses to "qualified clinical testing costs" for orphan drug development projects would result in a program that is sufficiently narrow so as to keep the cost of a Canadian orphan drug subsidy reasonable.

No matter how "off-budget" or indirect the government costs may seem, providing incentives for drug development will always come at a price. It is not obvious who should bear the costs of providing orphan drug incentives. Where a commitment to equality provides a strong justification for having orphan drug incentives it is, therefore, also appropriate to disperse (at least partly) the costs of an incentive broadly across all (tax-paying) members of a society, as a tax-based incentive would do. Using the tax system places the costs of an orphan drug development incentive on taxpayers in general, as opposed to drug consumers (and any third party payer) of either orphan drugs (as is the case with market exclusivity) or blockbuster drugs (that have been accelerated to the market by a PRV). The improved treatment options that would hopefully result from such an incentive could subsequently bring about improved health outcomes for rare disease patients. Significant improvements in the health of these patients could result in cost savings to the public health care system and increased economic contributions from the treated patients and their caregivers.

Tax-based subsidies for R&D have several distinct benefits for pharmaceutical companies. Once introduced, tax expenditures tend to be stable relative to other funding schemes that often undergo regular review and potential changes. This offers pharmaceutical companies a degree of predictability that enables them to plan and invest in drug development accordingly. On the other hand, the lack of regular scrutiny does call for careful drafting, implementation, and discipline in government-prompted review of effectiveness.

For pharmaceutical companies, the importance of supply-side incentives cannot be overstated. As such, they may be a necessary component of an orphan drug policy because they can enable companies to undertake R&D projects that could not otherwise afford to in the absence of such assistance. While the fact that SR&ED and ODTC benefits are paid out regardless of whether the subsidized activity is ultimately successful (i.e. by resulting in a

marketable product) may elicit concerns about wasteful government spending, for many companies the high costs of drug development will often require such up-front government spending. Many companies will simply be unable to undertake orphan drug development projects in the absence of subsidization. While the money may not flow as quickly as would be optimal where the company must wait for a profitable tax year, a tax credit will yield benefits more quickly than revenue-side incentives such as market exclusivity. Furthermore, even apparently unsuccessful drug development, like other R&D, can produce spill-overs of knowledge that ultimately benefit society in any event.

While Canada's general R&D tax program, SR&ED, is the subject of criticism regarding the distributional consequences of the program, such concerns would exist to a lesser degree, if at all, with an orphan drug tax credit. Smaller, less sophisticated companies in Canada have cited the complexity of SR&ED provisions as creating difficulty with identifying eligible activities and successfully claiming expenses. The breadth of SR&ED's scope undoubtedly creates confusion over what qualifies; an orphan drug tax credit for "qualified clinical testing costs" would be unlikely to generate such uncertainty. Furthermore, difficulties with maintaining the documentation required to support a claim, observed with the SR&ED program, will not be faced by drug developers because the clinical trial process already requires meticulous record-keeping.

That being said, an orphan drug tax credit in Canada will admittedly suffer from similar uneven distributional effects that are observed with the ODTC in the United States, where larger, more established firms receive a greater benefit from non-refundable tax credits because they are able to use them immediately to off-set current tax liability. While refundable credits can ensure a more even distribution of the tax benefit, unless the credit rate was reduced accordingly, a refundable orphan drug credit is not recommended because it would increase the cost of the program. Uneven distributional effects could be also addressed by directly funding orphan drug development in lieu of using the tax system. Furthermore, an orphan drug subsidy is arguably better suited to being administered by Health Canada, which already possesses expertise in classifying diseases and the clinical trial process. However, introducing large-scale research grant schemes for orphan drug development is unlikely to be a popular policy choice with the voting public and therefore a tax-based incentive is still the recommended means for subsidizing orphan drug development in Canada. Further, there is the potential for administrative cost savings for the government and taxpayers by implementing the subsidy though the existing

income tax system. An orphan drug tax credit would not create unreasonable resource demands on CRA, as the agency already administers the SR&ED program. As such, an orphan drug tax credit is a recommended component, in addition to market exclusivity, of any orphan drug framework implemented in Canada.

With lower rates of pharmaceutical innovation and a significantly smaller market it is unlikely that any orphan drug incentive in Canada would have as dramatic of an impact as the incentives appear to have had in the United States. At the date of writing, it is unclear if a Canadian orphan drug policy will be pursued again in the near future. Nevertheless, offering market exclusivity to foreign drug developers could have facilitated rare disease patients in accessing orphan drugs without the additional cost and burden of using the SAP, and a tax credit for orphan drug development would have been a convenient means of encouraging valuable drug development here, without incurring too great of a cost to Canadian taxpayers. Given that there are ongoing challenges faced by patients with rare diseases in Canada it is hoped that some measures will nevertheless be taken to encourage companies to obtain Health Canada approval for orphan drugs. For example, Health Canada could waive the application fees for a second (non-orphan) New Drug Submission for companies that obtain market approval of a qualifying orphan drug here (i.e. a slightly different take on the PRV programs). Alternatively, some form of a tax break could be offered to companies that market their orphan drug(s) in Canada.[647] In any event, any future discussions about a Canadian orphan drug framework could benefit from taking into account the issues with orphan drug incentives described in this thesis.

[647] For that matter, there seems to be no reason why a tax credit for orphan drug development could not be offered as a stand-alone incentive (notwithstanding the issues described above about the ideal definition of "orphan drug").

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