



# Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives

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## ABSTRACT

It is uncertain whether a Canadian orphan drug policy, similar to those used in the US and EU, will be given further consideration. The justification for having an orphan drug policy is initially discussed, with this article 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 'orphan drug' should be defined and, accordingly, how incentives should be allocated. Three pharmaceutical industry incentives are then evaluated in order to identify how the needs of patients with rare diseases can be addressed. Market exclusivity has effectively encouraged investment in orphan drugs and therefore it is recommended that the incentive be implemented in Canada. Priority review voucher programs are still in their infancy, making it difficult to draw strong conclusions about these programs. Introducing a voucher program in Canada is nevertheless not recommended because priority review in Canada is unlikely to be sufficiently valuable. An orphan drug-specific tax credit offers a convenient means of subsidizing orphan drug development without being overly costly, given the narrow parameters within which the credit would operate. Therefore, a Canadian orphan drug tax credit is also recommended.

**KEYWORDS:** Health Canada, pharmaceutical incentives, market exclusivity, orphan drug policy, priority review vouchers, rare diseases

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## INTRODUCTION

In what may be a significant turning point for many Canadian patients, policymakers in Canada recently reversed their decision to follow in the footsteps of other jurisdictions by introducing an orphan drug policy. Until October of 2017,<sup>1</sup> Health Canada was considering how to amend the *Food and Drug Regulations* in order ‘to encourage the development of orphan drugs (ie drugs for rare diseases) and increase the availability of these products on the Canadian market’.<sup>2</sup> Several other jurisdictions already provide orphan drug incentives to varying degrees, with the US and the EU having the most extensive policies. In 2012, a draft framework for a Canadian orphan drug policy was the subject of some discussion, though no legislative changes were made as a result.<sup>3</sup>

The term ‘orphan’ refers to the fact that rare diseases were historically neglected, or ‘orphaned’, by the pharmaceutical industry.<sup>4</sup> Rare diseases, by definition, provide only a small pool of potential buyers, making it less likely that a rare disease treatment will be very profitable. It can also be especially challenging and expensive to develop treatments for rare diseases because of insufficient information about the natural course of a disease (which makes it difficult to identify validated clinical end points that can be used to test a treatment’s efficacy),<sup>5</sup> and problems with recruiting enough clinical trial participants and conducting trials where participants may be widely spread across a jurisdiction.<sup>6</sup> A number of authors agree that without orphan drug policies many treatments for rare diseases would never have been developed and brought to market.<sup>7</sup> That being said, there is some debate over whether orphan drugs are always going to be unprofitable to invest in, in light of both the incentives and regulatory assistance for orphan drug developers and the high price points that are typical of orphan drugs.<sup>8</sup>

Responding to concerns that rare diseases were being neglected by drug developers in favor of more profitable diseases, in 1983 the US introduced legislation that was intended to promote the development and market availability of rare disease

<sup>1</sup> For example, see Maura Forrest, *Health Canada Gives ‘Kiss Of Death’ To Planned Policy For Rare-Disease Drugs*, NATIONAL POST, Oct. 16, 2017, <http://nationalpost.com/news/politics/health-canada-gives-kiss-of-death-to-planned-policy-for-rare-disease-drugs> (accessed Mar. 26, 2018).

<sup>2</sup> At the date of writing, it is unclear whether, or in what form, this initiative will be pursued, though Health Canada has recently stated that its initiative to improve the review of drugs is also intended to ‘increase the availability of drugs that meet the needs of the health care system, including drugs for rare diseases’. Health Canada, *Improving The Regulatory Review Of Drugs And Devices*, <https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html?wbdisable=true> (accessed Mar. 20, 2018).

<sup>3</sup> Health Canada Office of Legislative and Regulatory Modernization, *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework*, Dec. 13, 2012, <https://www.raredisorders.ca/content/uploads/Proposal-for-Orphan-Drug-Framework.dec-12-2012.pdf> [hereinafter *Health Canada Draft Orphan Drug Framework*].

<sup>4</sup> Pedro Franco, *Orphan Drugs: The Regulatory Environment*, 18 DRUG DISC. TODAY 163, 163 (2013).

<sup>5</sup> Erik Tambuyzer, *Rare Diseases, Orphan Drugs and Their Regulation: Questions and Misconceptions*, 9 NAT. REV. DRUG DISC. 921, 923 (2010).

<sup>6</sup> Charles Oo & Lorraine M. Rusch, *A Personal Perspective of Orphan Drug Development for Rare Diseases: A Golden Opportunity or An Unsustainable Future?*, 56 J. CLIN. PHARMACOL. 257, 257 (2016).

<sup>7</sup> For example, Franco, *supra* note 4, at 163.

<sup>8</sup> For example, see Kiran N. Meekings, Cory S.M. Williams & John E. Arrowsmith, *Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D*, 17 DRUG DISC. TODAY 660 (2012).

treatments.<sup>9</sup> Australia, Singapore, Japan, the EU, and Taiwan followed suit in 1989, 1991, 1993, 1999, and 2000, respectively.<sup>10</sup> Orphan drug policy in the US is primarily based in the *Orphan Drug Act of 1983* (ODA),<sup>11</sup> though a number of other policy instruments supplement the ODA by also facilitating orphan drug development.<sup>12</sup> Orphan drugs are defined under the ODA as drugs that are intended to treat a rare disease,<sup>13</sup> and a rare disease is one that ‘affects less than 200,000 persons in US’ 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 US a drug for such disease or condition will be recovered from sales in the US’.<sup>14</sup>

Under the ODA, a sponsor may apply for its drug to be granted orphan drug designation at any time throughout the drug development process.<sup>15</sup> Orphan drug designation does not exempt a treatment from needing to obtain regulatory approval prior to being marketed to the public.<sup>16</sup> Rather, orphan drug designation permits access to a number of incentives that are designed to facilitate the development and marketing of orphan drugs. Under the ODA, a sponsor receives exclusive approval (ie market exclusivity) once its designated orphan drug has been approved for market.<sup>17</sup> 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 7 years.<sup>18</sup> Additional 7-year periods of exclusivity can be obtained if the drug is subsequently approved as a treatment for another orphan indication.<sup>19</sup> Market exclusivity can be ‘broken’ in favor of a new orphan product that is essentially the same drug intended for the same indication but which demonstrates clinical superiority (ie is safer, more effective, or significantly more convenient to administer than the first orphan drug),<sup>20</sup> in circumstances where the original orphan product can no longer be supplied in sufficient quantities, or otherwise by consent of the market exclusivity holder.<sup>21</sup>

Other incentives and means of regulatory assistance also exist to facilitate orphan disease research and development (R&D) activity and to help sponsors navigate the

<sup>9</sup> Office of Inspector General, Department of Health and Human Services, *The Orphan Drug Act Implementation and Impact*, May, 2001, at 4, <http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf> (accessed Mar. 26, 2018); Orphan Drug Act, Pub. L. No. 97-414, § 1, 96 Stat 2049 (1983).

<sup>10</sup> 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: Franco, *supra* note 4, at 165.

<sup>11</sup> 21 U.S.C. § 360bb(a)(2).

<sup>12</sup> For example, see 42 U.S.C. § 281.

<sup>13</sup> 21 C.F.R. § 316.3(b)(10).

<sup>14</sup> 21 U.S.C. § 360aa.

<sup>15</sup> 21 C.F.R. § 316.23(b).

<sup>16</sup> That being said, the FDA has permitted flexibility with respect to how clinical trials for orphan drugs are designed. For example, see Aaron S. Kesselheim, Jessica A. Myers & Jerry Avorn, *Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer*, 22 JAMA 2320, 2324 (2011).

<sup>17</sup> 21 C.F.R. § 316.31(a) (2011).

<sup>18</sup> *Id.*

<sup>19</sup> 21 C.F.R. § 316.31(b).

<sup>20</sup> See generally 21 U.S.C. § 360aa-360dd. See also 21 C.F.R. § 316.3(b)(3); Carolyne Hathaway, John Manthey & Cassie Scherer, *Exclusivity Strategies in the United States and European Union*, UPDATE, May/June 2009, at 36, [https://www.lw.com/upload/pubcontent/\\_pdf/pub2655.1.pdf](https://www.lw.com/upload/pubcontent/_pdf/pub2655.1.pdf) (accessed July 21, 2018).

<sup>21</sup> 21 C.F.R. § 316.31(a)(3)-(4).

approval process. For example, the application fee to submit a New Drug Application (NDA) is waived,<sup>22</sup> the ODA provides for direct funding to be allocated for orphan drug R&D, the recipients of which are determined according to a (competitive) applications process,<sup>23</sup> and the Orphan Drug Tax Credit (ODTC), a non-refundable credit, can be claimed for qualified clinical trials costs incurred in the development of designated orphan drugs and is equal to 50% of the costs incurred.<sup>24</sup>

Since the implementation of the ODA, other orphan drug incentives have been introduced that supplement the Act. Priority review vouchers (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 (RPDs).<sup>25</sup> Initially proposed as an incentive to promote the development of treatments for neglected tropical diseases,<sup>26</sup> under the FDASIA, PRVs may be awarded to a drug sponsor who obtains marketing approval for an RPD drug.<sup>27</sup> A PRV entitles the holder to have a subsequent NDA for a different drug product be subject to priority review.<sup>28</sup>

EU orphan disease legislation, introduced in 1999 following the apparent success of the ODA in the US, was largely modeled on the ODA<sup>29</sup> but with a few key changes. One important difference is that the EU Regulations take disease severity and the existence of previously approved treatments into consideration when determining orphan status. Orphan drug designation is granted to medicinal products intended for the diagnosis, prevention, or treatment of either a 'life-threatening or chronically debilitating condition' that affects fewer than 5 in 10,000 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'.<sup>30</sup> There must also be no authorized 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.<sup>31</sup>

<sup>22</sup> FDA, *Designating an Orphan Product: Drugs and Biological Products*, online: US Food and Drug Administration <http://www.fda.gov>. US Food & Drug Administration, *Designating an Orphan Product*, <https://www.fda.gov/forindustry/developingproductsforrareconditions/howtoapplyfororphanproductdesignation/default.htm> (accessed July 21, 2018).

<sup>23</sup> 21 U.S.C. § 360ee; Franco, *supra* note 4, at 167.

<sup>24</sup> Office of Inspector General, *supra* note 9, at 7.

<sup>25</sup> Alexander Gaffney, Michael Mezher & Zachary Brennan, *Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers*, <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fda%E2%80%99s-priority-review-vouchers> (accessed Mar. 26, 2018).

<sup>26</sup> David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313, 313 (2006).

<sup>27</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No 112-144, § 360ff, 126 Stat 993, 1094 (2012) (codified as amended at 21 U.S.C. § 360ff).

<sup>28</sup> *Id.* Vouchers can be used for any drug, including non-orphan drugs.

<sup>29</sup> Orphanet, *Orphan Drugs in Europe*, [http://www.orpha.net/consor/cgi-bin/Education\\_AboutOrphanDrugs.php?lng=EN&stapage=ST\\_EDUCATION\\_EDUCATION\\_ABOUTORPHANDRUGS\\_EUR](http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_EUR) (accessed Mar. 26, 2018).

<sup>30</sup> European Commission, Commission Regulation (EC) 141/2000 of 16 December 1999 on orphan medicinal products, 2000 O.J. (L 18/1) 3(1)(a) [hereinafter EC Regulation 141/2000].

<sup>31</sup> *Id.* at 3(1)(b).

Industry incentives for pharmaceutical development are not limited to orphan diseases. Pediatric diseases<sup>32</sup> and tropical diseases<sup>33</sup> are two examples where similar incentives have been introduced because these areas are also likely to be neglected by the pharmaceutical industry. As with rare diseases, developing new antimicrobials is unlikely to be lucrative, thereby making incentives necessary.<sup>34</sup> An evaluation of initiatives used by the EU, US, and UK revealed that pull incentives as well as other measures (such as tax credits) that will assist companies in the later stages of developing new antimicrobials are lacking.<sup>35</sup> This finding is echoed by calls from the pharmaceutical industry for legislation that ‘addresses the failure of the marketplace to incentivize investment in the development of antimicrobials’.<sup>36</sup> Both market exclusivity and PRVs have been considered with respect to antimicrobial innovation.<sup>37</sup> Antimicrobial resistance is a global issue that is increasing in severity.<sup>38</sup> By shedding light on the advantages, anticipated impact, and potential risks associated with different incentives, this article may be of assistance to future discussions about incentivizing antimicrobial innovation.

The ultimate goal of orphan drug policy is to improve the lives and well-being of patients with rare diseases<sup>39</sup>; this can be accomplished by both promoting access to appropriate treatments and facilitating the development of novel drugs.<sup>40</sup> This article proceeds from an 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 R&D for orphan drugs, encouraging companies to launch orphan drugs in Canada is a matter of greater importance and urgency. This article considers three potential orphan drug incentives in a Canadian context, and analyses whether it would be reasonable to expect the incentives to have an impact in terms of increasing access to rare disease treatments in Canada.

First, the justification for introducing orphan drug incentives in Canada is considered. Concluding that introducing some form of orphan drug incentive(s) in Canada would be a good policy decision, the issues and anticipated impact of three incentives

<sup>32</sup> Edward Connor & Pablo Cure, ‘Creating Hope’ and Other Incentives for Drug Development for Children, 3 SCI. TRANS. MED. 66cm1 (2011).

<sup>33</sup> Nicola Dimitri, *R&D Incentives for Neglected Diseases*, 7 PLOS ONE e50835 (2012).

<sup>34</sup> Chris Dall, *\$1 Billion Reward Proposed for New Antibiotics*, CENTER FOR INFECTIOUS DISEASE RESEARCH AND POLICY, Jan. 24, 2018, <http://www.cidrap.umn.edu/news-perspective/2018/01/1-billion-reward-proposed-new-antibiotics> (accessed Mar. 26, 2018).

<sup>35</sup> Victoria L. Simpkin et al., *Incentivising Innovation in Antibiotic Drug Discovery and Development: Progress, Challenges and Next Steps*, 70 J. ANTIBIOT. 1087, 1092 (2017).

<sup>36</sup> Jeffrey Stein, *Developers of Antibiotics Urgently Need Government Help*, WASHINGTON POST, Feb. 28, 2018, [https://www.washingtonpost.com/opinions/developers-of-antibiotics-urgently-need-government-help/2018/02/28/8805b386-1b42-11e8-98f5-ceecfa8741b6\\_story.html?utm\\_term=.63fd08163278](https://www.washingtonpost.com/opinions/developers-of-antibiotics-urgently-need-government-help/2018/02/28/8805b386-1b42-11e8-98f5-ceecfa8741b6_story.html?utm_term=.63fd08163278) (accessed Mar. 26, 2018).

<sup>37</sup> Seth Seabury & Neeraj Sood, *Toward A New Model For Promoting The Development Of Antimicrobial Drugs*, HEALTH AFFAIRS BLOG, May 18, 2017, <https://www.healthaffairs.org/doi/10.1377/hblog20170518.060144/full/> (accessed Mar. 26, 2018).

<sup>38</sup> For example, see Simpkin et al., *supra* note 35, at 1087.

<sup>39</sup> For example, see Canadian Organization for Rare Disorders, *Our Work*, <https://www.raredisorders.ca/our-work/> (accessed Mar. 23, 2018) [hereinafter CORD, *Our Work*].

<sup>40</sup> Orphan Drug Act, *supra* note 9.

that could be used (market exclusivity, PRVs, and an orphan drug tax credit) are then assessed, according to how they have operated in the US and EU thus far. Market exclusivity and an orphan drug tax credit, while not without their issues, have been observed to be useful incentives, and are therefore recommended as part of a Canadian orphan drug framework. The costs and utility of PRVs have yet to be fully evaluated and therefore a PRV program in Canada is not recommended, at least not in the near future. One limitation of this paper is that it only considers incentives that are already being used; it has been suggested that Canadian policymakers should develop novel incentives in order to avoid some of the pitfalls that have been observed with the US and EU policies.<sup>41</sup>

### JUSTIFYING ORPHAN DRUG INCENTIVES

The need for a Canadian orphan drug policy was originally rejected in 1997 on the basis that Canadian patients with rare diseases can take advantage of orphan drugs being developed in other jurisdictions, including the ability to access treatments that are not approved in Canada via the Special Access Program (SAP).<sup>42</sup> The assertion that Canadian patients have adequate access to rare disease treatments developed in other jurisdictions is certainly open for debate. Firstly, there is evidence indicating that orphan drugs are not available on the Canadian market to a satisfactory degree. Over the years, the Canadian Organization for Rare Disorders (CORD), a patient advocacy group, has persistently lobbied for an orphan drug framework,<sup>43</sup> asserting that ‘only 60% of treatments for rare disorders make it into Canada and most get approved up to 6 years later than in the US and Europe’.<sup>44</sup> A ‘significant disparity’ between the number of orphan drugs available in Canada and the number of orphan drugs available in the US has in fact been observed.<sup>45</sup> The extent to which orphan drugs are not available on the Canadian market remains somewhat uncertain, with Divino et al. finding that between the years 2007 and 2013, 47% of orphan drugs available in the US were also available in Canada,<sup>46</sup> while another investigation indicates that roughly 75% of orphan drugs approved in the US are eventually approved in Canada.<sup>47</sup> In any event, there is almost always a delay between when companies apply for market approval in the US or the EU and when they

<sup>41</sup> Hugh J. McMillan & Craig Campbell, *We Need a “Made in Canada” Orphan Drug Policy*, 189 CMAJ E1274 (2017).

<sup>42</sup> Franco, *supra* note 4, at 165.

<sup>43</sup> For example, see Ben Spurr & Allan Woods, *Canadian Families Pushing for a Rare Diseases National Strategy*, THE STAR, Jan. 20, 2016, <https://www.thestar.com/news/canada/2016/01/20/canadian-families-pushing-for-a-rare-diseases-national-strategy.html> (accessed Mar. 26, 2018); Canadian Organization for Rare Disorders, *CORD Statement in the House of Commons on March 10, 2016*, <https://www.raredisorders.ca/cord-statement-in-the-house-of-commons-on-march-10-2016/> (accessed Mar. 23, 2018).

<sup>44</sup> CORD, *Our Work*, *supra* note 39.

<sup>45</sup> 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*, 11 ORPHANET J. RARE DIS. 68, 5 (2016).

<sup>46</sup> *Id.* Of the 316 orphan drugs available in the US, 147 were also available in Canada.

<sup>47</sup> Specifically, 74% of orphan drugs approved by the FDA between 1997 and 2012 were also given at least one market approval in Canada: 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*, 11 HEALTH POL’Y 70, 75 (2016).

apply for approval in Canada.<sup>48</sup> While Herder and Krahn attribute delays primarily to Health Canada's longer review process,<sup>49</sup> Shajarizadeh & Hollis state that differences in review times play a relatively smaller role and that '[i]n general, orphan drugs were submitted much later in Canada than in the EU and the US'.<sup>50</sup> Given that many rare diseases are serious in nature, one priority should be to minimize delays in availability on the Canadian market. Secondly, patients who must use the SAP to access orphan drugs that are not yet approved in Canada are put at a financial disadvantage relative to other patients because drugs that are accessed through this program are usually not covered by either public or private health care plans.<sup>51</sup> McMillan and Campbell note that the SAP is more appropriate for cheaper, generic drugs, and is not suitable for accessing orphan drugs.<sup>52</sup> Therefore, without orphan drug incentives in Canada, the needs of Canadians with rare diseases are not being met at a satisfactory rate.

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.<sup>53</sup> Patients with rare diseases can face additional challenges specifically because they have a rare disease as opposed to a more common one; for example, the first doctor that a patient with a rare disease visits is often unlikely to have seen that disease before, thereby making a timely diagnosis difficult.<sup>54</sup> *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.<sup>55</sup> Given the value that Canadians purportedly give to equality, policy makers should attempt to relieve this disproportionate burden. While pharmaceutical incentives will not address the issues that patients with rare diseases initially encounter (such as misdiagnosis), policy measures that minimize other disadvantages that patients with rare diseases face (ie problems with timely access to appropriate treatment) aligns with the value of equality. Canadian orphan drug incentives should be designed primarily to motivate drug companies to seek Health Canada approval for their orphan drugs. This should be the primary objective because it more directly supports the ultimate goal of providing patients with access to the drugs they need, and because it is likely to have a greater impact than attempts to encourage innovative drug development for rare diseases.

<sup>48</sup> *Id.*; Ali Shajarizadeh & Aidan Hollis, *Delays in the Submission of New Drugs in Canada*, 187 *CMAJ* E47, E59 (2015).

<sup>49</sup> Herder & Krahn, *supra* note 47, at 75–78.

<sup>50</sup> Shajarizadeh & Hollis, *supra* note 48, at E49.

<sup>51</sup> This disadvantage is exacerbated by the generally high costs of orphan drugs relative to drugs for more common disorders: Carly Weeks, *Without Rare-Disease Policy, Patients in Canada Face Steep Costs for Drugs*, *GLOBE AND MAIL*, Feb. 24, 2017, <https://www.theglobeandmail.com/life/health-and-fitness/health/without-rare-disease-policy-patients-in-canada-face-steep-costs-for-drugs-health/article34129051/> (accessed Mar. 26, 2018).

<sup>52</sup> McMillan & Campbell, *supra* note 41, at E1274.

<sup>53</sup> Eline Picavet et al., *Orphan Drugs for Rare Diseases: Grounds for Special Status*, 73 *DRUG DEV. RES.* 115, 116 (2012) [hereinafter Picavet et al., *Special Status*].

<sup>54</sup> Christopher D. Moen, *Helping 'Orphans' Grow: Fostering Rare Disease Drug Development*, 33 *DELAWARE LAWYER* 24, 26 (2015).

<sup>55</sup> Much 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': *CORD, Our Work*, *supra* note 39.

Some authors have made the argument that governments are legally obligated to fund rare disease treatments.<sup>56</sup> 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.<sup>57</sup> This argument could reasonably be expanded to suggest that governments, at the very least, must provide incentives that promote the development and marketing of rare disease treatments. If there is in fact a legal obligation to provide orphan drug incentives, one example may be found in Canada's international human rights commitments. In 2010, Canada ratified the 2007 United Nations Convention on the Rights of Persons with Disabilities.<sup>58</sup> The definition of 'persons with disabilities' is not fixed and arguably can include patients with rare diseases.<sup>59</sup> 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.<sup>60</sup>

Neglecting 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. 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.<sup>61</sup> 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'.<sup>62</sup> If the pharmaceutical industry ignores certain types of diseases because they are not sufficiently profitable, then patients who suffer from those diseases

<sup>56</sup> See Hanna I. Hyry et al., *The Legal Imperative for Treating Rare Disorders*, 8 ORPHANET J. RARE DIS. 135 (2013).

<sup>57</sup> *Id.* at 2.

<sup>58</sup> For example, see Government of Canada, *Reports on United Nations Human Rights Treaties*, <https://www.canada.ca/en/canadian-heritage/services/canada-united-nations-system/reports-united-nations-treaties.html> (accessed Mar. 26, 2018).

<sup>59</sup> 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'. Division for Social Policy and Development of the United Nations, *Frequently Asked Questions regarding the Convention on the Rights of Persons with Disabilities*, <https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities/frequently-asked-questions-regarding-the-convention-on-the-rights-of-persons-with-disabilities.html> (accessed Mar. 26, 2018). See also Hyry et al., *supra* note 56, at 3, where the authors point out that rare diseases are 'understood to fall within the definition of disability under the US Social Security Act'.

<sup>60</sup> Convention on the Rights of Persons with Disabilities, *acceded by Canada* May 19, 1976, 2515 U.N.T.S. 3, emphasis added.

<sup>61</sup> *Acceded by Canada* May 19, 1976, 993 U.N.T.S. 3.

<sup>62</sup> *Id.* 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



are unable to enjoy ‘the highest attainable standard’ of health and are being denied ‘the benefits of scientific progress and its applications’.

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’<sup>63</sup> because they could result in R&D for treatments of more common diseases being neglected because companies will pursue the incentives available for rare diseases. Admittedly, it is not obvious that diseases should be given priority based on prevalence, and one could legitimately question whether public resources should focus instead on diseases that presumably create a lesser burden on society.<sup>64</sup> Firstly, 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 calculations yield to a morality-based need to ‘rescue’ identifiable individuals (or a group of individuals so small that its members are in effect ‘identifiable’), suggests there may be a moral obligation to provide orphan drug incentives.<sup>65</sup> The moral imperative for directing resources toward orphan drug development may be strengthened by the fact that many orphan diseases are serious in nature,<sup>66</sup> and frequently suffered by children.<sup>67</sup> Furthermore, it is actually relatively common to have a rare disease. Roughly 6000 to 8000 rare diseases have been identified worldwide<sup>68</sup> and CORD estimates that 1 in 12 Canadians (roughly 3 million) have a rare disease.<sup>69</sup> Therefore, the total number of Canadians suffering from a rare disease is relatively substantial (and the total economic impact of rare diseases is not insignificant). Accordingly, it is incorrect to assume that rare diseases do not impose a large impact on society, particularly when one also considers the family of a patient with a rare disease (and, given how many rare diseases affect children,<sup>70</sup> it is likely that many parents withdraw from the workforce to act as caregivers). That being said, limits will need to be placed on the extent to which public funds are allocated to incentives. The anticipated impact of incentives will inform the cost–benefit analysis that should be

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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.

<sup>63</sup> Michael Palmer & Dyfrig A. Hughes, *Orphan Drug Legislation: Heyday or Had Their Day?*, 16 VALUE HEALTH A491 (2013).

<sup>64</sup> For example, see Michael Drummond & Adrian Towse, *Orphan Drugs Policies: A Suitable Case for Treatment*, 15 EUR. J. HEALTH ECON. 335, 339 (2014).

<sup>65</sup> ‘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’. David C. Hadorn, *Setting Health Care Priorities in Oregon: Cost-Effectiveness Meets the Rule of Rescue*, 265 JAMA 2218, 2219 (1991) (as cited in John McKie & Jeff Richardson, *The Rule of Rescue*, 56 SOC. SCI. & MED. 2407, 2408 (2003)).

<sup>66</sup> Picavet et al., *Special Status*, *supra* note 53, at 116. See also *Health Canada Draft Orphan Drug Framework*, *supra* note 3, at 4.

<sup>67</sup> CORD, *Our Work*, *supra* note 39.

<sup>68</sup> *Health Canada Draft Orphan Drug Framework*, *supra* note 3, at 4.

<sup>69</sup> CORD, *Our Work*, *supra* note 39.

<sup>70</sup> CORD, *Our Work*, *supra* note 39.

used to determine where those limits should lie. Orphan drug incentives can be limited by both maintaining the ability to terminate an incentive and by narrowing the criteria that will be used to determine what qualifies for an incentive. Both of these measures will be discussed in greater detail below.

Orphan drug policies have generally been positively received. The ODA has been hailed as ‘one of the most successful health-care laws that has been passed in the late twentieth century’<sup>71</sup> because it has directly resulted in greater availability of approved treatments for patients with orphan diseases. According to the FDA ‘the [ODA] has unquestionably stimulated the development of drugs for rare diseases’.<sup>72</sup> Market approvals for rare disease treatments in the US have significantly increased,<sup>73</sup> from 2 in 1983 to 49 in 2014,<sup>74</sup> up to a total of 637 approvals for orphan products as of September 2017.<sup>75</sup> Similar results have also been observed in Europe, where the EU has granted orphan designation at a steadily increasing rate, suggesting that the incentives have successfully stimulated R&D of products for rare diseases.<sup>76</sup>

On the other hand, in spite of this success, 95% of orphan diseases still do not have any approved treatments.<sup>77</sup> Several authors have discussed concerns that orphan drug incentives ‘promote the concentration of marketing activities in a few profitable therapeutic areas at the expense of others that are equally, if not more, important’.<sup>78</sup> The type of rare disease that a patient suffers from is a significant factor in determining the likelihood that a treatment will be developed and approved.<sup>79</sup> Cancer-treating drugs in particular dominate the orphan drug market, likely because drug companies can expect to profit more from cancer treatments (especially when one considers that off-label use of drug products is particularly common in oncology) than from other orphan drugs.<sup>80</sup> This is not, however, necessarily an argument against providing incentives of any sort, but rather an indication that what does need to be amended is how ‘orphan drug’ is defined. In other words, the eligibility criterion that governs how orphan drug

<sup>71</sup> Marlene E. Haffner, Janet Whitley & Marie Moses, *Two Decades of Orphan Product Development*, 1 NATURE 821, 823 (2002).

<sup>72</sup> Office of Inspector General, *supra* note 9, at 7.

<sup>73</sup> For example, see Richard Y. Cheung, Jillian C. Cohen & Patricia Illingworth, *Orphan Drug Policies: Implications for the US, Canada, and Developing Countries*, 12 HEALTH L.J. 183, 184 (2004).

<sup>74</sup> Kurt R. Karst, *The 2014 Numbers Are In: FDA's Orphan Drug Program Shatters Records*, FDA LAW BLOG, Feb. 15, 2015, <http://www.fdalawblog.net/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records/> (accessed Mar. 26, 2018).

<sup>75</sup> US Food & Drug Administration, *Search Orphan Drug Designations and Approvals*, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/> (accessed Mar. 26, 2018).

<sup>76</sup> Eline Picavet, David Cassiman & Steven Simoens, *Evaluating and Improving Orphan Drug Regulations in Europe: A Delphi Policy Study*, 108 HEALTH POL'Y 1, 1–2 (2012).

<sup>77</sup> Moen, *supra* note 54, at 25.

<sup>78</sup> For example, see Andre Cote & Bernard Keating, *What is Wrong with Orphan Drug Policies?*, 15 VALUE HEALTH 1185, 1190 (2012).

<sup>79</sup> For example, see Aaron S. Kesselheim, Carolyn L. Treasure & Steven Joffe, *Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage*, 14 PLOS MED. e1002190, 4 (2017).

<sup>80</sup> Matthew Herder, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the USA and Canada*, 3 J. L. & BIOSCI. 158, 160 (2016). 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’. Olivier Wellman-Labadie & Youwen Zhou, *The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?*, 95 HEALTH POL'Y 216, 218, 220, 225 (2010).

incentives are allocated should be refined to ensure that the pharmaceutical industry is being directed toward diseases that are truly at risk of being orphaned.

Companies do not have to demonstrate that they incurred any additional risk or cost to develop an orphan drug in order to obtain the incentives. Orphan drug policies in both the US and EU allow it to be assumed that there is a financial risk associated with developing a treatment for a rare disease.<sup>81</sup> Under the original enactment of the ODA, orphan status would be granted only 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 US.<sup>82</sup> Drug developers would therefore have had to provide information about their anticipated costs of bringing a drug to market. The regulations were quickly amended to include a prevalence-based definition of rare disease, which allows financial risk to be assumed if a disease is suffered by less than 200,000 people.<sup>83</sup> In at least some cases this assumption is likely false, particularly in light of scientific advances and changes in the pharmaceutical industry that have made the orphan drug market more attractive to drug developers.<sup>84</sup> Furthermore, some orphan drugs are approved to treat multiple indications, including some common diseases, and therefore have a relatively large pool of potential buyers.<sup>85</sup> 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’.<sup>86</sup>

Interest in the orphan drug market could simply indicate that the industry is using orphan drug incentives as they were always intended to make developing and marketing orphan drugs commercially viable.<sup>87</sup> Increasing the profitability of orphan drugs, and thereby removing the financial disincentive, was *the* point of the ODA.<sup>88</sup> This argument has been countered by pointing out that increasing use of disease stratification (to demonstrate that a disease falls within the prevalence-based definition of rare disease) coupled with the disproportionate development of cancer-treating orphan drugs does not allow for such a simple explanation.<sup>89</sup> This argument calls into question the original justifications for orphan drug policies. Nevertheless, this issue remains unsettled and the pharmaceutical industry contends that the incentives for orphan drugs are still necessary to ensure continued investment in what remains a financially risky endeavor.<sup>90</sup> The reality likely lies somewhere in the middle: some orphan drugs will have

<sup>81</sup> 21 U.S.C. § 360ee(a)(2); EC Regulation 141/2000, *supra* note 30, at 3(1)(a).

<sup>82</sup> Orphan Drug Act, *supra* note 9, § 526(a)(2).

<sup>83</sup> 21 U.S.C. § 360ee(a)(2).

<sup>84</sup> For example, see Steven Simoens, *Pricing and Reimbursement of Orphan drugs: The Need for More Transparency*, 6 ORPHANET J. RARE DIS. 42, 2 (2011). At least some orphan drugs can be more profitable than non-orphan drugs because of a number of factors that both increase potential revenue (eg higher price points, larger market shares, exclusivity protection, and faster uptake) and decrease development costs (eg shorter and smaller clinical trials, fee waivers, and subsidies): Meekings, Williams & Arrowsmith, *supra* note 8, at 663. This is partly contributed to by the fact that once labeled an ‘orphan’, drug prices are substantially increased: for example, see Eve A. Roberts, Matthew Herder & Aiden Hollis, *Fair Pricing of ‘Old’ Orphan Drugs: Considerations for Canada’s Orphan Drug Policy*, 187 CMAJ 422, 422–23 (2015).

<sup>85</sup> *Id.* at 3.

<sup>86</sup> *Id.* at 6.

<sup>87</sup> 21 U.S.C. § 360aa § 1.

<sup>88</sup> For example, see Franco, *supra* note 4, at 165.

<sup>89</sup> Matthew Herder, *When Everyone is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada*, 20 ACCOUNT. RES. 227, 243 (2013) [hereinafter Herder, *When Everyone is an Orphan*].

<sup>90</sup> For example, see Tambuzyer, *supra* note 5, at 928.

sufficient potential profitability that they would be developed in the absence of incentives, while other orphan drugs will only reach the market if incentives are provided.

In order to address the rare diseases that continue to be neglected, Canadian policymakers should refrain from blindly copying the orphan drug policies in the US and EU.<sup>91</sup> These orphan drug policies are relatively blunt instruments. In 1984, when the prevalence-based definition was added to the ODA,<sup>92</sup> 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 lucrative business opportunity,<sup>93</sup> ‘rarity’ alone may be insufficient to justify the allocation of government resources.<sup>94</sup> In order to avoid overburdening public resources, disease severity arguably should be a consideration, as is required by the European Regulations.<sup>95</sup> 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 whatever reason, regardless of prevalence or severity.<sup>96</sup> The EU Regulations, unlike in the US, require that applicants demonstrate a lack of alternative treatments, or that their drug offers a significant benefit over existing treatments, in order to access orphan drug incentives.<sup>97</sup> Including this requirement would have the benefit of tying incentives to a demonstration of an actual problem and is one opportunity to avoid providing incentives where they are not necessary. With no orphan drug policy at the moment, Canada is well positioned to give careful consideration to the definition of ‘orphan’, and policymakers should take advantage of this when drafting the eligibility criteria for orphan drug incentives.

There has also been some suggestion that a Canadian orphan drug policy would be unlikely to have a significant impact because of relatively low levels of innovative drug research in Canada.<sup>98</sup> Potentially low levels of pharmaceutical innovation in Canada provide a relatively weak argument against providing *any* orphan drug incentives; the Canadian pharmaceutical industry may be able to innovate at a rate that is, while not globally significant, at least *sufficient* to justify incentives. While Canada does lag behind other countries with respect to the amount of money being invested in pharmaceutical R&D compared to the amount being spent via pharmaceutical sales,<sup>99</sup> Canada’s pharmaceutical industry is second only to its IT industry in terms of innovative levels.<sup>100</sup> At

<sup>91</sup> Herder, *When Everyone is an Orphan*, *supra* note 89, at 242.

<sup>92</sup> 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 that there is ‘no reasonable expectation’ that a drug would be profitable. David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, 31 *AM. J. L. & MED.* 365, 376 (2005).

<sup>93</sup> Shannon Gibson, Hamid R. Raziee & Trudo Lemmens, *Why the Shift? Taking a Closer Look at the Growing Interest in Niche Markets and Personalized Medicine*, 7 *WORLD MED. & HEALTH POL’Y* 1, 5 (2015).

<sup>94</sup> For example, see Herder, *When Everyone Is an Orphan*, *supra* note 89, at 244.

<sup>95</sup> EC Regulation 141/2000, *supra* note 30, at 3(1)(a).

<sup>96</sup> Matthew Herder, *What is the Purpose of the Orphan Drug Act?*, 14 *PLOS MED.* e1002191,5 (2017).

<sup>97</sup> Genevieve Michaux, *EU Orphan Regulation - Ten Years of Application*, 65 *FOOD DRUG L. J.* 639, 641 (2010).

<sup>98</sup> Cheung, Cohen & Illingworth, *supra* note 73, at 190.

<sup>99</sup> Patented Medicine Prices Review Board, *Annual Report 2015*, July 29, 2016, at 52, [http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2015/2015\\_Annual\\_Report\\_Final.EN.pdf](http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2015/2015_Annual_Report_Final.EN.pdf) (accessed Mar. 26, 2018).

<sup>100</sup> Innovation, Science and Economic Development Canada, *Canadian Pharmaceutical Industry Profile*, at 4, <http://npaf.ca/wp-content/uploads/2015/11/Pharmaceutical-industry-profile-Canadian-Life-Science-Industries.pdf> (accessed Mar. 26, 2018).

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. 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—ie design costs). An empirical investigation into the pharmaceutical R&D potential in Canada would further inform this issue, and would be of assistance to policymakers trying to estimate how much incentives would cost (at least for an incentive such as a tax credit). Furthermore, as discussed above, motivating companies to launch their orphan drugs in Canada should be the first and foremost objective of any Canadian orphan drug policy. Given that there are questions about Canada's innovative potential (or lack thereof), promoting R&D in the orphan drug field should be pursued only as a secondary objective.

### MARKET EXCLUSIVITY

Market exclusivity is widely considered to be the primary incentive available to orphan drug developers,<sup>101</sup> and quite possibly the most controversial.<sup>102</sup> Market exclusivity is granted once a drug is approved (ie can be sold) as a treatment for an orphan disease and functions by preventing the regulatory agency from approving another sponsor's marketing application for the same drug (US) or a similar drug (EU) as a treatment for that orphan disease.<sup>103</sup> In the US the period of protection lasts for 7 years.<sup>104</sup> The EU Regulations provide market exclusivity for 10 years though this can be shortened to 6 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.<sup>105</sup> Drug developers can obtain multiple periods of exclusivity for a single orphan drug, one for each indication for which the drug is approved as a treatment.<sup>106</sup> The 2012 draft discussion document for a proposed Canadian orphan drug framework included market exclusivity as an incentive,<sup>107</sup> and, given how popular the incentive is with the pharmaceutical industry, it is reasonable to assume that future discussions about orphan drug incentives in Canada would also include market exclusivity.

### Role of exclusivity in innovation policy

While functioning similar to a patent, market exclusivity provides some advantages over patent law, with respect to both public policy concerns and how valuable the incentive is to pharmaceutical companies. Specifically, market exclusivity involves a lesser sacrifice on the part of the public than when a patent is in effect. Additionally, it is suggested that patents, compared with market exclusivity, actually 'play a very limited role in fostering innovation'.<sup>108</sup> Market exclusivity may be a more powerful motivator for

<sup>101</sup> For example, see Office of Inspector General, *supra* note 9, at 8.

<sup>102</sup> For example, see Aaron S. Kesselheim, *Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation*, 363 N. ENGL. J. MED. 1855, 1859 (2010) [hereinafter Kesselheim, *Using Market-Exclusivity*].

<sup>103</sup> 21 C.F.R. § 316.31(a); EC Regulation 141/2000, *supra* note 30, at 8(1).

<sup>104</sup> *Id.*

<sup>105</sup> EC Regulation 141/2000, *supra* note 30, at 8(2).

<sup>106</sup> Sponsors can obtain additional orphan drug designations for the same drug: 21 C.F.R. § 316.23(b).

<sup>107</sup> *Health Canada Draft Orphan Drug Framework*, *supra* note 3, at 25.

<sup>108</sup> Shamnad Basheer, *The Invention of an Investment Incentive for Pharmaceutical Innovation*, 15 J. WORLD INTELL. PROP. 305, 315 (2012) [hereinafter Basheer, *An Investment Incentive*].

pharmaceutical companies because of the certainty and predictability associated with obtaining market exclusivity, as well as the length and strength of the protection conferred by the incentive relative to patent law.

Both patent protection and market exclusivity create a ‘give-and-take’ relationship between the inventor/drug developer and all other members of the public because potential competitors are prevented from marketing the protected product and the general public is denied the ability to purchase the product from another company. However, the scope of protection (ie the rights given up by the public) provided via market exclusivity is arguably narrower than a patent.<sup>109</sup> Granting patent protection requires a significant degree of ‘give’ on the part of society because patentees can exclude all others from making, using, or selling the invention.<sup>110</sup> This total exclusivity over a patented invention is considered by some to be overly generous.<sup>111</sup> Market exclusivity, on the other hand, is far narrower in scope.<sup>112</sup> The protection that a drug developer gets via market exclusivity is limited to the specific orphan indication for which market approval was granted; other drug developers are free to get market approval for the protected drug for a different disease (barring any applicable patent protection), or (more commonly) to market a drug that is sufficiently different (ie not the ‘same’ in the US, or ‘similar’ in the EU) as a treatment for that orphan disease.<sup>113</sup> The narrower scope of market exclusivity means that society does not ‘give up’ as much as it does when a patent is in effect.

Furthermore, both the ODA and the European Regulations allow for exclusivity to be ‘broken’ in favor of a ‘clinically superior’ version of the protected drug, even if the second drug is essentially the same (US)/similar (EU).<sup>114</sup> This ability to break exclusivity protection is intended to ‘ensure that orphan drug exclusivity approval does not preclude significant improvements in treating rare diseases’.<sup>115</sup> From a public policy perspective, this aspect of how market exclusivity operates ensures that patients will not be denied the benefit of medical advances because exclusivity is in effect, and therefore is a potentially meaningful advantage over patent law.

Market exclusivity may also be a more powerful incentive than patent law.<sup>116</sup> For one thing, in some ways it is easier to obtain market exclusivity than it is to secure a patent

<sup>109</sup> Kesselheim, *Using Market-Exclusivity*, *supra* note 102, at 1857.

<sup>110</sup> Canada Patent Act, R.S.C., c. P-4, s 42.

<sup>111</sup> For example, see Benjamin J. Kormos, *Giving Frankenstein a Soul: Imposing Patentee Obligations*, 21 INTELL. PROP. J. 309, 330 (2009).

<sup>112</sup> Kesselheim, *Using Market-Exclusivity*, *supra* note 102, at 1857. There is some debate regarding relative breadth of protection. For example, see Peter S. Arno, Karen Bonuck & Michael Davis, *Rare Diseases, Drug Development, and AIDS: The Impact of the Orphan Drug Act*, 73 MILBANK Q. 231, 235 (1995) 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’ (ie 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 89, 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.

<sup>113</sup> 21 C.F.R. § 316.31(a); EC Regulation 141/2000, *supra* note 30, at 8(1).

<sup>114</sup> 21 C.F.R. § 316.25(a)(3); EC Regulation 141/2000, *supra* note 30, at 8(3)(c).

<sup>115</sup> US Food & Drug Administration, *Designating an Orphan Product: Drug and Biological Products Frequently Asked Questions (FAQ)*, <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm> (accessed Mar. 26, 2018).

<sup>116</sup> Cynthia Luchetti, *Market Exclusivity Strategies for Pharmaceuticals*, 23 PHARM. MED. 77, 83 (2009).

because of the strict requirements of patent law. To qualify for patent protection an invention must be both novel and inventive,<sup>117</sup> and it has been said that patent regimes insufficiently protect investments in pharmaceutical development because of these requirements.<sup>118</sup> Important medical advances might not be patentable because they are not sufficiently novel.<sup>119</sup> Patent protection does not encourage such developments and may therefore be insufficient to encourage companies to invest in developing an orphan drug.

Market exclusivity does not become effective until market authorization is granted and the drug may be sold, and therefore the incentive can last longer than a patent, at least during the period when a company can profit from its investment.<sup>120</sup> Patent protection, on the other hand, must typically be secured well before the development process can be completed and may have expired or be close to its expiration by the time the drug is approved for the market.<sup>121</sup> Even if there is the opportunity for companies to have their patent extended, this is neither guaranteed nor free of charge.<sup>122</sup> Finally, market exclusivity offers a strong degree of protection because enforcing market exclusivity is taken care of by the regulators of medicinal products. In the US, for example, the FDA protects a product's exclusivity by not granting market approval for the same drug to treat the same orphan disease.<sup>123</sup> Pharmaceutical companies can therefore confidently rely on exclusivity protection because sales of unauthorized medical treatments are rare, and will be quickly dealt with by the drug regulator in the unlikely event that a competitor does attempt to market an unauthorized drug.<sup>124</sup>

### Impact of Exclusivity on Orphan Drugs

While it appears to have had a significant impact on the orphan drug market, exclusivity protection is also frequently associated in the literature with high prices for orphan drugs.<sup>125</sup> Orphan drugs are generally more expensive than non-orphan drugs,<sup>126</sup> and as a result patients have faced challenges when trying to access these products. Market exclusivity allegedly encourages high prices because the incentive in effect creates a

<sup>117</sup> Patent Act, *supra* note 110, s 2.

<sup>118</sup> 'The novelty and non-obviousness requirements... [have] 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'. Shannad Basheer, *Alternative Incentives for Pharmaceutical Innovation*, 27 INTELL. PROP. J. 13, 18 (2014).

<sup>119</sup> For example, see Ashish Kumar Kakkar & Neha Dahiya, *The Evolving Drug Development Landscape: From Blockbusters to Niche Busters in the Orphan Drug Space*, 75 DRUG DEV. RES. 231, 232 (2014).

<sup>120</sup> Haffner, Whitley & Moses, *supra* note 71, at 821.

<sup>121</sup> For example, see Maxwell R. Morgan, *Regulation of Innovation under Follow-on Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism*, 11 COL. SCI. & TECH. L. REV. 93, 105 (2010).

<sup>122</sup> *Id.* at 106.

<sup>123</sup> For example, see Dov Greenbaum, *Incentivizing Pharmacogenomic Drug Development: How the FDA can Overcome Early Missteps in Regulating Personalized Medicine*, 40 RUTGERS L. J. 97, 124–25 (2008).

<sup>124</sup> *Id.*

<sup>125</sup> For example, see Cote & Keating, *supra* note 78, at 1190. But see David C. Babaian, *Adopting Pharmacogenomics and Parenting Repurposed Molecules under the Orphan Drug Act: A Cost Dilemma?*, 13 J. MARSHALL REV. INTELL. PROP. L. 667, 712 (2014): 'the ODA is not responsible for the exorbitant expense of new orphan drugs...Concurrent market exclusivity provides qualitative protection over patent rights but often does not itself enable monopoly pricing'.

<sup>126</sup> For example, see Basheer, *An Investment Incentive*, *supra* note 108, at 324.

monopoly within which companies can charge whatever it likes.<sup>127</sup> Nevertheless, other factors play a role in pricing decisions and the extent to which high prices for orphan drugs are actually caused by market exclusivity is uncertain. Rare disorders naturally create a small market, which can lead to the appearance of a monopoly simply because small markets are less likely to attract competitors.<sup>128</sup> At least one member of the pharmaceutical industry argues that what looks like a monopoly may in fact be 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 product and enter the market.<sup>129</sup> One study indicates that orphan drugs protected by market exclusivity do not dissuade alternative treatments from being developed and marketed as treatments for a given orphan disease.<sup>130</sup>

Even so, any connection between market exclusivity and high prices works against the objective of promoting access to orphan drugs. There is 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’.<sup>131</sup> As market exclusivity is a valuable and powerful incentive, it should be used in Canada, but in a manner that, at least, attempts to discourage excessively high prices for orphan drugs. One limitation of using market exclusivity is that the decisions of health care payers (ie to reimburse or not reimburse) will ultimately determine whether access to orphan drugs is improved. Furthermore, drug companies hesitate to apply for Health Canada approval if their orphan drug is unlikely to be covered by health care plans. Orphan drugs are often authorized for market based on studies involving a limited number of participants where surrogate endpoints (as opposed to measures of disease progression as typically used in clinical trials for non-orphan diseases) are used to demonstrate efficacy.<sup>132</sup> With weaker evidence of effectiveness, combined with the high prices of many orphan drugs, health care payers could refuse to reimburse patients for orphan drugs.<sup>133</sup> Improvements probably could be made to how coverage decisions for orphan drugs are approached.<sup>134</sup> While this topic is beyond the scope of this article, coverage decisions that are sensitive to rare disease drugs would be an important factor in whether or not market exclusivity has a significant impact on Canadian patients.

### Introducing Market Exclusivity in Canada

It is possible that the problems associated with high prices for orphan drugs will be mitigated in the Canadian context because, unlike the US, Canada has a price control mechanism (administered by the Patented Medicine Prices Review Board (PMPRB)) that is intended to prevent companies from charging excessively high prices for

<sup>127</sup> *Id.*

<sup>128</sup> Babaian, *supra* note 125, at 712.

<sup>129</sup> Tambuyzer, *supra* note 5, at 924.

<sup>130</sup> Anne E.M. Brabers et al., *Does Market Exclusivity Hinder the Development of Follow-on Orphan Medicinal Products in Europe?*, 6 ORPHANET J. RARE DIS. 59, 9 (2011).

<sup>131</sup> Kesselheim, *Using Market-Exclusivity*, *supra* note 102, at 1856.

<sup>132</sup> Kesselheim, Myers & Avorn, *supra* note 16, at 2324.

<sup>133</sup> Conor M. W. Douglas et al., *Why Orphan Drug Coverage Reimbursement Decision-Making Needs Patient and Public Involvement*, 119 HEALTH POL’Y 588, 590 (2015).

<sup>134</sup> *Id.* See also Pierpaolo Mincarone et al., *Reimbursed Price of Orphan Drugs: Current Strategies and Potential Improvements*, 20 PUB. HEALTH GENOMICS 1, 4–6 (2017).



pharmaceuticals.<sup>135</sup> In reality, it is fairly unlikely that this measure ensure affordable access given that Canada actually pays a lot for drug products relative to other countries.<sup>136</sup> Health Canada has recently solicited comments on proposed amendments to the Regulations that govern how the PMPRB operates, because of concerns that the regulations are outdated and Canadians are not being adequately protected from excessive prices as a result.<sup>137</sup> Given that the ability of the board to function as intended is currently questionable, this mechanism cannot be relied on to control the prices of orphan drugs.

Drug pricing issues are complicated, and a number of factors likely work in conjunction to inform these decisions, making it difficult to identify unreasonable prices.<sup>138</sup> The costs of orphan drug development combined with a smaller market probably also ‘encourage’ high prices, not *entirely* the market exclusivity period itself. Notwithstanding the available incentives, it can still be financially risky to successfully develop safe and effective treatments for a very limited patient population, though the additional costs will not be present in all cases.<sup>139</sup> Unfortunately, for policymakers, orphan drugs are not a homogenous group and in all likelihood market protection will be necessary to make some orphan drugs profitable and quite unnecessary for other orphan drugs. Health Canada should therefore have the ability to terminate market exclusivity once a drug becomes ‘sufficiently profitable’ to the point that market exclusivity is no longer needed to protect a company’s investment, as provided for in the EU Regulations.<sup>140</sup> The strength of the EU Regulation is questionable though, particularly because it has never been applied. The EU Regulations do not elaborate on the term ‘sufficiently profitable’ and in order to be an effective provision, the term should be given meaningful clarification.<sup>141</sup> 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. Clearly defining what it means for a drug to be sufficiently profitable would assist Health Canada by providing a brightline test that can be used to determine whether the provision should be applied.

Determinations of profitability should also consider other indications that a drug is an approved treatment for, when it is appropriate to do so.<sup>142</sup> Not ‘adding up’ profitability from multiple indications when assessing the profitability of an orphan drug assumes that a developer is incurring roughly equivalent additional costs and risks for each indication that a drug is approved for. This assumption was probably reasonable when the US and EU orphan drug policies were originally enacted. Adding up multiple indications is appropriate if subsequent approvals have been essentially ‘built off’ the

<sup>135</sup> Patent Act, *supra* note 110, 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).

<sup>136</sup> Health Canada, *Consulting on Proposed Amendments to the Patented Medicines Regulations*, <https://www.canada.ca/en/health-canada/programs/consultation-regulations-patented-medicine.html> (accessed Mar. 26, 2018).

<sup>137</sup> *Id.*

<sup>138</sup> Eline Picavet et al., *Shining a Light in the Black Box of Orphan Drug Pricing*, 9 ORPHANET J. RARE DIS. 62, 3 (2014) [hereinafter Picavet et al., *Shining a Light*].

<sup>139</sup> For example, see Oo & Rusch, *supra* note 6, at 257.

<sup>140</sup> EC Regulation 141/2000, *supra* note 30, at 8(2).

<sup>141</sup> Picavet, Cassiman & Simoens, *supra* note 76, at 7

<sup>142</sup> Panos Kanavos & Elena Nicod, *What Is Wrong with Orphan Drug Policies? Suggestions for Ways Forward*, 15 VALUE HEALTH 1182, 1183 (2012).

first approval, where the additional clinical testing needed to acquire the subsequent approvals required relatively less risk and cost. For example, conducting clinical trials for a drug to treat biomarker-defined disease subsets of a disease can be quicker and cheaper than testing a drug for multiple (largely unrelated) diseases.<sup>143</sup> Where drug X is approved to treat diseases A(1), A(2), and so on, with each distinct orphan disease being a biomarker-defined subset of disease A, it would be logical to add up the associated costs and profits in order to determine whether terminating the exclusivity period for drug X is warranted.

A significant limitation of this recommendation is the lack of transparency that surrounds the pricing of orphan drugs.<sup>144</sup> 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 identify when an orphan drug has become sufficiently profitable and terminate market exclusivity accordingly. 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, if the drug's sponsor agrees to certain post-marketing conditions (a common condition is that the drug company supply evidence that the drug actually does provide a clinical benefit).<sup>145</sup> Law and Lexchin both found that it is not unusual for conditions to remain unfulfilled for many years, seemingly without any action taken by Health Canada to enforce the conditions.<sup>146</sup> That being said, under the NOC/c policy, conditions are enforced by withdrawing market approval for the drug in question. Law notes that withdrawing a drug from the market entirely is a drastic, 'all-or-nothing' measure that Health Canada may be (reasonably) hesitant to take.<sup>147</sup> Terminating market exclusivity would be a less drastic course of action, and the onus of providing information could be placed on the drug company (by automatically terminating market exclusivity after a specified length of time if the company fails to provide evidence that the drug is not sufficiently profitable). Admittedly, 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.

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<sup>143</sup> Kesselheim, Treasure & Joffe, *supra* note 79, at 7.

<sup>144</sup> 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. For example, see Jonathan C. P. Roos, Hanna I. Hyry & Timothy M. Cox, *Orphan Drug Pricing May Warrant a Competition Law Investigation* 341 *BMJ*. 1084 (2010); Picavet et al., *Shining a Light*, *supra* note 138.

<sup>145</sup> Health Canada, Health Products and Food Branch, *Guidance Document: Notice of Compliance with conditions (NOC/c)*, 2016, at 2–3, [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/pdf/prodpharma/applic-demanded/guide-ld/compli-conform/noccg\\_accd-eng.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demanded/guide-ld/compli-conform/noccg_accd-eng.pdf) (accessed Mar. 26, 2018).

<sup>146</sup> Michael R. Law, *The Characteristics and Fulfillment of Conditional Prescription Drug Approvals in Canada*, 116 *HEALTH POL'Y* 154, 160 (2014); Joel Lexchin, *Notice of Compliance with Conditions: A Policy in Limbo*, 2 *HEALTH POL'Y* 114, 119 (2007).

<sup>147</sup> *Id.* at 160.

## PRIORITY REVIEW VOUCHERS

The second orphan drug incentive assessed in this article is a PRV, which is, literally, a voucher for priority review. Vouchers are being used only in the US, where the first voucher program was implemented in 2012 to encourage the development of treatments for neglected tropical diseases.<sup>148</sup> Additional streams of the original voucher program have subsequently been implemented for RPDs,<sup>149</sup> and medical countermeasures.<sup>150</sup> A detailed evaluation of all three voucher programs be completed by the Government Accountability Office (GAO) and submitted by January 31, 2020.<sup>151</sup> A PRV entitles a drug sponsor to have a NDA subject to priority review by the FDA, as opposed to standard review.<sup>152</sup> In order to receive a voucher, drug developers must obtain market approval for an eligible drug (ie a drug to treat a neglected tropical disease, a disease RPD, or function as a medical countermeasure against a material threat) with the FDA.<sup>153</sup> The drug must also qualify for priority review in order to be eligible for a voucher.<sup>154</sup> Priority review is typically reserved for drugs that are expected to provide a significant benefit over existing treatments.<sup>155</sup> Redeeming a voucher allows a drug developer to circumvent this criterion. Priority review can allow a sponsor to market, and profit from, their product within an accelerated timeframe (provided that they are successful in obtaining market authorization). The FDA typically takes about 10 months to complete a standard review<sup>156</sup> while the agency's goal is to complete a priority review within 6 months.<sup>157</sup>

In order to redeem a voucher a drug's sponsor must pay an additional priority review user fee, the amount of which is based on the difference between the average cost incurred by the FDA in the previous year to perform a standard review and the average cost to perform a priority review.<sup>158</sup> Priority review user fees have ranged from \$2325,000 in 2014 up to \$5280,000 in 2012.<sup>159</sup> The priority review user fee for 2018 is \$2830,579.<sup>160</sup> Drug sponsors must also give the FDA 90 days notice of their intention

<sup>148</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1102, 121 Stat 823, 972 (2007) (codified as amended at 21 U.S.C. § 360n).

<sup>149</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 360ff, 126 Stat 993, 1094 (2012) (codified as amended at 21 U.S.C. § 360ff).

<sup>150</sup> 21<sup>st</sup> Century Cures Act, Pub. L. No. 114-255, § 3086, 130 Stat 1033, 1144 (2016) (to be codified at 21 U.S.C. § 360bbb-4a) [hereinafter 21<sup>st</sup> Century Cures Act].

<sup>151</sup> *Id.*, § 3014.

<sup>152</sup> 21 U.S.C. §360ff(a)(2).

<sup>153</sup> 21<sup>st</sup> Century Cures Act, *supra* note 150, § 3086.

<sup>154</sup> 21 U.S.C. § 360n(4)(A)(ii); § 360ff(a)(4)(C).

<sup>155</sup> Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, § 103(1)(b), 106 Stat. 4491, 4491 (codified as amended at 21 U.S.C. § 379g) [hereinafter PDUFA]; US Food & Drug Administration, *Priority Review*, <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm> (accessed Mar. 26, 2018).

<sup>156</sup> US Food & Drug Administration, *Priority Review*, *supra* note 155.

<sup>157</sup> PDUFA, *supra* note 155, § 103(1)(b).

<sup>158</sup> 21 U.S.C. § 360ff(c). This fee is in addition to the PDUFA user fee that is typically required for NDAs.

<sup>159</sup> For example, see Gaffney, Mezher & Brennan, *supra* note 25.

<sup>160</sup> Fee for Using a Rare Pediatric Disease Priority Review Voucher in Fiscal Year 2018, 82 Fed. Reg. 45,291, 45,292 (Sept. 28, 2017). The FDA has indicated that the user fee will be the same for vouchers awarded for NTDs; see United States Food and Drug Administration, *Tropical Disease Priority Review Vouchers: Guidance for Industry*, Oct. 2016, at 9, <https://www.fda.gov/downloads/Drugs/Guidances/UCM080599.pdf> (accessed Mar. 26, 2018) [hereinafter *FDA Tropical Disease PRVs*].

to redeem a PRV, in order to give the agency sufficient time to organize its resources and plan its review strategy.<sup>161</sup>

A company that has been awarded a voucher may either use the voucher themselves or transfer (ie sell) it to another company.<sup>162</sup> Allowing transfers is a crucial feature of the program because some companies will not have a potential ‘blockbuster’ drug in development (or any other drug for that matter) and therefore must sell a voucher in order to receive a benefit from being awarded a voucher. As of March 2018, 18 PRVs have been awarded, 13 for RPDs and 5 for tropical diseases.<sup>163</sup> Since then, at least seven vouchers have been sold, at prices ranging from \$67 million up to \$350 million.<sup>164</sup> Several companies appear to have benefited from redeeming 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 6 months earlier may have earned the company an additional \$1 billion.<sup>165</sup>

### Potential issues with the voucher program

While a formal assessment of the effectiveness of the RPD voucher program was mandated and completed by the GAO in 2016, the assessment found that it was too early to determine what the consequences and impact of the program are,<sup>166</sup> a conclusion that largely mirrors the academic literature on the subject. Given that it often takes over a decade to complete the drug development process and that the RPD voucher program had only existed for 3 years, it is hardly surprising that vouchers had been awarded for products that were already being developed.<sup>167</sup> Nevertheless, several authors have unequivocally argued against the use of vouchers as an incentive, citing the potential for serious and unintended consequences of the program.<sup>168</sup>

To begin with, there are concerns that vouchers will compromise the safety of drugs for which a PRV is redeemed. FDA officials have in fact questioned the wisdom of subjecting potential ‘blockbuster drugs’ to priority review because ‘there is a different benefit-risk balance to be considered’<sup>169</sup> when reviewing drugs that are expected to be widely used, making it inappropriate to approve such drugs within an accelerated

<sup>161</sup> 21 U.S.C. § 360ff(b)(4); Lesley Hamming, *The Promise of Priority Review Vouchers as a Legislative Tool to Encourage Drugs for Neglected Diseases*, 11 DUKE L. & TECH. REV. 390, 408 (2013).

<sup>162</sup> 21 U.S.C. § 360ff(b)(2)(a) 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’.

<sup>163</sup> For example, see Gaffney, Mezher & Brennan, *supra* note 25.

<sup>164</sup> The selling price of a voucher appears to have peaked in August 2015 at \$350 million, while the three vouchers that were sold in 2017 went for \$125–130 million. *Id.*

<sup>165</sup> Kevin Khachatryan, *Incentivizing Drug Development: Novel Reforms of Pharmaceutical Innovation*, 18 COL. SCI. & TECH. L. REV. 139, 148 (2016).

<sup>166</sup> The original PRV program for tropical diseases did not require a formal assessment of its efficacy.

<sup>167</sup> United States Government Accountability Office, *Rare Diseases: Too Early to Gauge Effectiveness of FDA’s Pediatric Voucher Program*, Mar. 2016, at 9, <https://www.gao.gov/assets/680/675544.pdf> (accessed Mar. 26, 2018) [hereinafter *GAO Pediatric Voucher Program Report*].

<sup>168</sup> For example, see Aaron S. Kesselheim, *Priority Review Vouchers: An Inefficient and Dangerous Way to Promote Neglected-Disease Drug Development*, 85 CLIN. PHARMACOL. & THER. 573 (2009) [hereinafter *Kesselheim, Inefficient and Dangerous*].

<sup>169</sup> *GAO Pediatric Voucher Program Report*, *supra* note 167, at 14. See also The Weinberg Group, *FDA Insider Shares Thoughts on Priority Review Vouchers*, Oct. 12, 2015, <https://weinberggroup.com/fda-news/fda-priority-review-program-thoughts/> (accessed Mar. 26, 2018).

timeframe. Blockbuster drugs are drugs that make over \$1 billion in sales within 5 years of being on the market.<sup>170</sup> 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 (should) take longer to review.<sup>171</sup> Pressure to review a NDA for these types of drugs within a limited, 6-month timeframe may therefore generate legitimate questions about the safety of ‘vouchered’ drugs.

At this moment, there is insufficient evidence to determine whether or not vouchers will actually risk the safety of ‘vouchered’ drugs. On the one hand, NDAs that were approved by the FDA between November 21, 1997 and December 31, 2009 according to its priority review process 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.<sup>172</sup> Priority reviewed drugs were not, however, more likely to be associated with safety-related withdrawals or restricted indications.<sup>173</sup> 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’<sup>174</sup>; 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.<sup>175</sup> While the priority review process itself may not create an additional safety risk, there may be some cause for concern about granting priority review status to drugs that would not otherwise merit an accelerated review.

On the other hand, faster review by the FDA does not mean that the safety and efficacy standards for approval are lowered.<sup>176</sup> Furthermore, redeeming a voucher does not guarantee either a shorter review time or that FDA will grant market approval.<sup>177</sup> Novartis was the first company to redeem a voucher, and rather than granting approval, the FDA requested that more data be submitted in support of the NDA.<sup>178</sup> This example suggests that the agency is not necessarily going to compromise on its safety standards when conducting priority reviews of vouchered drugs.<sup>179</sup> Therefore, it currently 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.

<sup>170</sup> Ridley, Grabowski & Moe, *supra* note 26, at 314.

<sup>171</sup> The Weinberg Group, *supra* note 169.

<sup>172</sup> Andreas Schick et al., *Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals*, 40 DRUG SAF. 497, 501–02 (2017).

<sup>173</sup> *Id.* 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.’

<sup>174</sup> *Id.* at 502.

<sup>175</sup> The Weinberg Group, *supra* note 169.

<sup>176</sup> Ridley, Grabowski & Moe, *supra* note 26, at 321–22.

<sup>177</sup> The FDA has made it clear that the agency does not guarantee that the review of vouchered drugs will be completed within 6 months, only that its targeted review time will be 6 months. *FDA Tropical Disease PRVs*, *supra* note 160, at 9.

<sup>178</sup> For example, see *First Priority Review Voucher Wasted*, 10 NAT. REV. DRUG DISC. 721 (2011).

<sup>179</sup> For example, see Hamming, *supra* note 161, at 405.

A second question about vouchers is whether or not the redemption of vouchers will overload the FDA and slow the review of drugs that actually merit priority status.<sup>180</sup> Some academics argue that the special user fee and 90-day notice cannot alleviate the added workload because they ‘will not change the institutional hiring and organizational parameters that ultimately shape FDA’s review capabilities’.<sup>181</sup> According to the Director of FDA’s Office of New Drugs, these measures are insufficient because the agency will not have enough time to hire and train the additional staff members, nor, in any event, would it be reasonable to hire additional reviewers only to let them go after the priority review is completed.<sup>182</sup> The FDA’s workload-related complaints about the voucher program have yet to be corroborated by evidence, and one study 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’.<sup>183</sup> 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.<sup>184</sup> As with the potential safety concerns discussed above, increases to FDA workload are a potential concern that warrants ongoing attention and monitoring, but at this stage it is too early to consider this to be an inevitable consequence of PRV programs.

Finally, whether directly involving the FDA ‘as an integral component of the economic incentive’<sup>185</sup> is an appropriate use of a government function is certainly open to debate. In this respect voucher programs have been criticized in the grounds that they interfere with the FDA’s ability to set its own priorities with respect to reviewing drugs.<sup>186</sup> 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 (eg pediatric exclusivity) be used.<sup>187</sup> The 2016 GAO report on the RPD voucher program includes statements from the FDA 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’.<sup>188</sup> 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.

<sup>180</sup> Anne M. Readal, *Finding a Cure: Incentivizing Partnerships Between Disease Advocacy Groups and Academic Commercial Researchers*, 26 J. L. & HEALTH 285, 306 (2013).

<sup>181</sup> Sana Mostaghim & Aaron S. Kesselheim, *Suitability of Expanding the Priority Review Voucher into Rare Disease Drug Development*, 4 EXPERT OPIN. ORPHAN DRUGS 1001, 1002 (2016).

<sup>182</sup> The Weinberg Group, *supra* note 169.

<sup>183</sup> Chris Bialas et al., *Analyzing the FDA Priority Review Voucher Program’s Stimulation of Research and Public Health Impact*, 3 TECH. TRANSFER & ENTREPRENEURSHIP 131, 134, 137 (2016).

<sup>184</sup> 21st Century Cures Act, *supra* note 150, § 3014(c)(3)(A).

<sup>185</sup> Ana Santos Rutschman, *The Priority Review Voucher Program at the FDA: From Neglected Tropical Diseases to the 21st Century Cures Act*, 26 ANN. HEALTH L. 71, 97 (2017).

<sup>186</sup> Mostaghim & Kesselheim, *supra* note 181, at 1001.

<sup>187</sup> GAO *Pediatric Voucher Program Report*, *supra* note 167, at 14.

<sup>188</sup> *Id.*

### Anticipated Utility of Voucher Programs

Concerns about the likely effectiveness of voucher programs can be roughly divided into two distinct categories: criticisms about what is (and is not) required by the eligibility criteria and uncertainty regarding the value of a voucher. To begin with, what may be the most common complaint about PRVs is that the programs do not specifically promote affordable access to qualifying drugs.<sup>189</sup> This concern is not without merit because voucher programs do not require companies to provide their qualifying drug at a reasonable price.<sup>190</sup> 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.<sup>191</sup> As such, it is questionable whether vouchers will actually have a positive impact on patient health outcomes. The original proposal for the PRV program would have required drug developers to forgo patent rights over their qualifying drug in order to be eligible for a voucher,<sup>192</sup> but this requirement did not ultimately make it into the legislation. Another suggestion is that sponsors provide some guarantee that the drugs for which vouchers are awarded will be made available at affordable prices.<sup>193</sup> Notwithstanding how unpopular these measures would likely be with the pharmaceutical industry, encouraging lower price points would support the goal of increasing patient access to treatments. On the other hand, the incentive effect of PRVS may be irreparably damaged if patent protection was lost or a price cap imposed. As such, neither of these measures is recommended. The point of 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 a company's investment. Limiting what a company could expect to receive would increase the financial disincentive associated with developing drugs for 'unprofitable' diseases, which is the exact opposite of what the voucher programs attempt to do. It is entirely possible that 'revenue-side' incentives, such as PRVs and market exclusivity, are generally not the best mechanism for promoting *affordable* access to treatments.<sup>194</sup> Innovation and access to innovative products are two distinct issues, and 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 in the future. Supply-side incentives, such as tax credits 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.

<sup>189</sup> For example, see Aaron S. Kesselheim, Lara R. Maggs & Ameet Sarpatwari, *Experience With the Priority Review Voucher Program for Drug Development*, 314 JAMA 1687, 1688 (2015).

<sup>190</sup> Khachatryan, *supra* note 165, at 168.

<sup>191</sup> Rutschman, *supra* note 185, at 86.

<sup>192</sup> Ridley, Grabowski & Moe, *supra* note 26, at 314.

<sup>193</sup> For example, see Bernard Pécoul & Manica Balasegaram, *FDA Voucher for Leishmaniasis Treatment: Can Both Patients and Companies Win?*, PLOS SPEAKING OF MEDICINE, Jan. 20, 2015, <http://blogs.plos.org/speakingofmedicine/2015/01/20/fda-voucher-leishmaniasis-treatment-can-patients-companies-win/> (accessed Mar. 26, 2018).

<sup>194</sup> '[S]uch initiatives may achieve short-term gains, but they do not consistently lead to sustained improvement and may have important unintended consequences'. Aaron S. Kesselheim, *Drug Development for Neglected Diseases – The Trouble with FDA Review Vouchers*, 359 N. ENGL. J. MED. 1981, 1982 (2008) [hereinafter Kesselheim, *Trouble with Vouchers*].

Another frequent complaint is that voucher programs allow companies to receive a potentially significant financial gain without having had to do any of the legwork or otherwise provide any additional investment to develop a qualifying drug. In order to qualify for a voucher, a drug must not have been previously approved in the US,<sup>195</sup> but there are no conditions that disqualify drugs that have already been 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’.<sup>196</sup> Clearly this can, and has, happened. To describe one prominent example, in March 2014, Knight Therapeutics was awarded a voucher for miltefosine, a leishmaniasis treatment that had already been approved and widely used in other countries for that indication.<sup>197</sup> Knight is reported to have spent roughly \$10 million dollars to purchase the rights to the drug and obtain FDA approval, and went on to sell its voucher for \$125 million.<sup>198</sup> In this instance, the voucher program was ‘effective’ only to the extent that it encouraged Knight to seek market approval in the US for miltefosine. Obtaining market approval for miltefosine in the US likely had little effect, if any, on health outcomes because patients needing leishmaniasis treatment are typically not in the US.<sup>199</sup>

Some argue that the legislation should be fixed in order to prevent companies from obtaining windfalls,<sup>200</sup> though it remains unclear how great of a problem the windfall potential truly is. While it is true that that vouchers have thus far been awarded for treatments that were already developed or being developed before the voucher programs were implemented,<sup>201</sup> this is hardly surprising. It may simply be a matter of giving the program more time because such opportunities should diminish as the programs continue and obvious sources of these types of drugs ‘dry up’.<sup>202</sup> Over time, more information will be available to help determine whether or not the voucher programs are effective at encouraging innovative drug development.

A final, and perhaps more significant, concern about the eligibility criteria is that it fails to connect the size of the reward (the voucher) with the value or utility of the drug for which a voucher is awarded.<sup>203</sup> The requirement that a drug must not contain a previously approved active ingredient<sup>204</sup> means that the voucher programs do not encourage companies to make valuable improvements to existing treatments. Drugs that make use of ‘known’ ingredients can provide a significant benefit to patients, but would be ineligible for a voucher.<sup>205</sup> 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 while an improved formula of that same drug that would greatly

<sup>195</sup> 21 U.S.C. § 360ff(a)(4)(A)(ii); § 360n(a)(4)(C); 21st Century Cures Act, *supra* note 150, § 3086(a)(4)(D).

<sup>196</sup> Cameron Graham Arnold & Thomas Pogge, *Improving the Incentives of the FDA Voucher Program for Neglected Tropical Diseases*, 21 BROWN J. WORLD AFF. 224, 231 (2015).

<sup>197</sup> Kesselheim, Maggs & Sarpatwari, *supra* note 189, at 1687.

<sup>198</sup> *Id.*

<sup>199</sup> Notable exceptions include military personnel and medical staff who travel to low income countries where tropical diseases are most prevalent: *FDA Tropical Disease PRVs*, *supra* note 160, at 2.

<sup>200</sup> For example, see Pécoul & Balasegaram, *supra* note 193.

<sup>201</sup> GAO *Pediatric Voucher Program Report*, *supra* note 167, at 9.

<sup>202</sup> Bialas et al., *supra* note 183, at 138.

<sup>203</sup> For example, see Kesselheim, *Trouble with Vouchers*, *supra* note 194, at 1981–82.

<sup>204</sup> *FDA Tropical Disease PRVs*, *supra* note 160, at 7.

<sup>205</sup> Kesselheim, *Inefficient and Dangerous*, *supra* note 168, at 574.



enhance its usefulness in lower income countries would not be rewarded.<sup>206</sup> While it is likely important to dissuade companies from making minor or otherwise meaningless alterations to existing treatments for the sole purpose of obtaining a voucher, relaxing the restrictions about known active ingredients could strengthen the connection between the reward of a voucher and the value of the qualifying drug.

There are also unanswered questions about the continuation of voucher programs that may weaken the impact of vouchers as an incentive. 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.<sup>207</sup> The original enactment of the RPD program contained a sunset clause that likely contributed to the uncertainty about obtaining a voucher<sup>208</sup>; even now, the program is set to terminate in September 2020.<sup>209</sup> While the *21<sup>st</sup> Century Cures Act* does provide an additional 2 years during which time vouchers can be awarded for treatments that were designated as RPD drugs prior to September 2020,<sup>210</sup> any potential effectiveness of the voucher program is likely impaired by the sunset clause. Drug companies are understandably unlikely to act on the basis of a program that may terminate before they can complete the drug development process and be eligible for the reward.<sup>211</sup>

Uncertainty about whether the RPD voucher program will continue 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 outweigh the disadvantages that might be incurred because of the sunset clause. Furthermore, 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.<sup>212</sup>

Vouchers also suffer from uncertainty because of the difficulty with predicting the value of a voucher. Some attempts have been made to estimate the commercial value

<sup>206</sup> Kesselheim, *Trouble with Vouchers*, *supra* note 194, at 1981–82.

<sup>207</sup> GAO *Pediatric Voucher Program Report*, *supra* note 167, at 17.

<sup>208</sup> 21 U.S.C. § 360ff(b)(5) provides that no vouchers are to be awarded after 1 year from the day on which the third RPD voucher is awarded. The third RPD voucher was awarded in March 2015. 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*, FDA LAW BLOG, Mar. 23, 2015, <http://www.fdalawblog.net/2015/03/one-two-three-and-theyre-out-fda-issues-third-rare-pediatric-disease-priority-review-voucher-trigger/> (accessed Mar. 26, 2018). § 3013 of the 21st Century Cures Act, *supra* note 150, provides for the RPD program to continue until September 2020.

<sup>209</sup> 21st Century Cures Act, *supra* note 150, § 3013(a).

<sup>210</sup> *Id*

<sup>211</sup> Bialas et al., *supra* note 183, at 137.

<sup>212</sup> David B. Ridley, Jennifer Dent & Christopher Egerton-Warburton, *Efficacy of the Priority Review Voucher Program*, 315 JAMA 1659, 1660 (2016).

of vouchers,<sup>213</sup> and previous voucher sales can help to inform this estimate, but it remains fairly speculative.<sup>214</sup> Uncertainty about the value of a voucher has been cited by pharmaceutical companies as limiting how influential the incentive is.<sup>215</sup> 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.

Finally, in light of how expensive the drug development process is, vouchers may never be sufficiently valuable to encourage companies to invest in R&D for rare diseases.<sup>216</sup> Undoubtedly the value of PRVs alone is insufficient to trigger an orphan drug development project<sup>217</sup>; however, this does not lead to the conclusion that vouchers are altogether insufficiently valuable to have an impact. The creators of the voucher program acknowledge that vouchers are unlikely to provide a sufficiently large financial incentive on their own but nevertheless defend their utility, arguing that vouchers were never intended to operate as a stand-alone incentive.<sup>218</sup> Ridley and colleagues continue to support the utility of vouchers as a means of getting products fully through the development pipeline.<sup>219</sup> Voucher programs could also encourage drug developers to ‘salvage existing projects that were initiated for other diseases’<sup>220</sup> or otherwise ‘motivate developers to continue with existing programs’.<sup>221</sup> 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’.<sup>222</sup> 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.<sup>223</sup>

### PRVs in the Canadian Context

As in the US, Health Canada has a priority review mechanism, whereby the agency will approach a New Drug Submission (NDS) with a shortened review target in mind, 1 of 180 days instead of the standard 300 days.<sup>224</sup> The most recent performance report from the Therapeutic Products Directorate provides some insight into how well a Canadian PRV program can be expected to function. The report shows that no NDS given

<sup>213</sup> For example, see David B. Ridley & Stephane A. Regnier, *The Commercial Market for Priority Review Vouchers*, 35 HEALTH AFF. 776 (2016); Nicola Dimitri, *The Economics of Priority Review Vouchers*, 15 DRUG DISC. TODAY 887 (2010).

<sup>214</sup> Kesselheim, *Trouble with Vouchers*, *supra* note 194, at 1981.

<sup>215</sup> Andrew S. Robertson et al., *The Impact of the US Priority Review Voucher on Private-Sector Investment in Global Health Research and Development*, 6 PLOS NEG. TROP. DIS. e1750, 2 (2012).

<sup>216</sup> For example, see Rutschman, *supra* note 185, at 93.

<sup>217</sup> Robertson et al., *supra* note 215, at 2.

<sup>218</sup> Ridley, Grabowski & Moe, *supra* note 26, at 319.

<sup>219</sup> Ridley, Dent & Egerton-Warburton, *supra* note 212, at 1659.

<sup>220</sup> Ridley, Grabowski & Moe, *supra* note 26, at 321.

<sup>221</sup> *Id.* at 322.

<sup>222</sup> Ridley, Dent & Egerton-Warburton, *supra* note 212, at 1660.

<sup>223</sup> Emily Waltz, *FDA Launches Priority Vouchers for Neglected-Disease Drugs*, 26 NAT. BIOTECH. 1315 (2008).

<sup>224</sup> Health Canada, *Priority Review of Drug Submissions (Therapeutic Products)*, [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/prfs\\_tpfed-eng.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/prfs_tpfed-eng.pdf) (accessed Mar. 26, 2018).

priority status during the time period was reviewed within the targeted 180 days.<sup>225</sup> As Health Canada currently does not meet its targeted timeframe for reviewing priority drug applications, PRVs would likely introduce an additional burden that could not be met by the agency.<sup>226</sup> A voucher program would be ineffective 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 could 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.<sup>227</sup> 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.<sup>228</sup> 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. Drugs that are approved via priority review then subsequently withdrawn for safety reasons would be of greater concern. 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 standard or priority review.<sup>229</sup> 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.

In any event, the benefits to drug developers of a PRV, 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 their drug products (orphan and non-orphan) 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'.<sup>230</sup> If companies cannot be bothered to market their product in Canada at all, it is reasonable to expect that a potential priority review of an NDS by Health Canada is going to be of very little value to a drug sponsor. Given that the effectiveness of the program in the US, particularly in relation to its costs and risks, has yet to be determined, it is unlikely to be worthwhile to introduce a voucher program in Canada at this time.

<sup>225</sup> Health Canada, Therapeutic Products Directorate, *Drug Submission Performance Annual Report Fiscal Year 2015-2016*, June 8, 2016, at 18, <http://www.smart-bigger.ca/files/Therapeutic%20Products%20Annual%20Report%202016.pdf> (accessed Apr. 7, 2018).

<sup>226</sup> That being said, Health Canada is currently undertaking an initiative designed to 'make [it's regulatory system] more efficient and support timely access to therapeutic products'. Health Canada, *Improving the Regulatory Review of Drugs and Devices*, *supra* note 2.

<sup>227</sup> Joel Lexchin, *New Drugs and Safety: What Happened to New Active Substances Approved in Canada between 1995 and 2010?*, 172 ARCH. INTERN. MED. 1680, 1681 (2012).

<sup>228</sup> *Id.*

<sup>229</sup> *Id.*

<sup>230</sup> Joel Lexchin, *A Comparison of New Drug Availability in Canada and the United States and Potential Therapeutic Implications of Differences*, 79 HEALTH POL'Y 214, 219 (2006).

An alternative version of a voucher program that might warrant further consideration is a ‘fee waiver voucher’ that would be awarded to companies who apply for Health Canada approval for an eligible drug (eg an orphan drug, or a pediatric orphan drug) and could be redeemed to have the Health Canada NDS application review fee waived for a subsequent NDS of a company’s choosing. As with PRVs, the fee waiver voucher could be used for a drug that would not otherwise qualify to have the application fee waived. While the value of such a voucher would be relatively low (\$348, 606, as of April 1, 2018),<sup>231</sup> it could nevertheless be sufficient to encourage companies to market their orphan products in Canada at a timelier rate. To date, fee waiver vouchers have not been used, though the idea may be worth future discussion.

### ORPHAN DRUG DEVELOPMENT TAX CREDIT

Referred to as ‘push’ or ‘supply-side’ mechanisms,<sup>232</sup> tax-based incentives for innovation operate by lowering the costs of doing R&D (as opposed to providing a reward for successful R&D projects). This has important implications for both policymakers and the pharmaceutical industry, including the timing of the incentive and the targeted behavior. 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 support the secondary objective of promoting the development of new orphan drugs. While unlikely to play any role with respect to drug launch decisions, subsidizing orphan drug development in Canada may be an appropriate supplement to market exclusivity because a majority of rare diseases still do not have any approved treatments. Providing a subsidy for orphan drug development could also motivate the Canadian pharmaceutical industry to be more innovative, and would not incur too great of an expense if the program fails to do so.

Canada already uses its tax system to subsidize R&D activity in general via the Scientific Research and Experimental Development (SR&ED) program, a federal tax program that is meant to encourage innovative activity.<sup>233</sup> 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 (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).<sup>234</sup>

The US uses its tax system to specifically promote orphan drug development, in addition to having a general R&D tax benefit and direct research grants. Implemented as part of the ODA in 1983, 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

<sup>231</sup> Health Canada, *Human Drug Submission and Application Review*, <https://www.canada.ca/en/health-canada/services/drugs-health-products/funding-fees/fees-respect-human-drugs-medical-devices/pharmaceutical-submission-application-review-funding-fees-drugs-health-products.html> (accessed Mar. 26, 2018).

<sup>232</sup> For example, see Wesley Yin, *Market Incentives and Pharmaceutical Innovation*, 27 J. HEALTH ECON. 1060, 1061 (2008).

<sup>233</sup> Department of Finance Canada & Revenue Canada, *The Federal System of Income Tax Incentives for Scientific Research and Experimental Development: Evaluation Report*, Dec. 1997, at 42, <http://publications.gc.ca/collections/Collection/F32-1-1997E.pdf> (accessed Mar. 26, 2018).

<sup>234</sup> Canada Income Tax Act, R.S.C., c. 1 (5th Supp.), s 248(1).

costs related to the development of designated orphan drugs'.<sup>235</sup> A formal assessment of the ODTC estimates that the credit is responsible for facilitating up to one third of orphan drug projects and approvals, noting that without the credit many companies could not have afforded to complete the drug development process.<sup>236</sup> That being said, the ODTC is not without its limitations. The ODTC provides a greater benefit to established drug developers (ie companies with prior drug approvals and tax liability) than to 'pre-market companies' (ie those without prior drug approvals and no expectation that they will have tax liability in the near future).<sup>237</sup> Furthermore, tax-based incentives do not affect revenue margins and, therefore, unlike market exclusivity and PRVs, cannot be expected to increase the expected return on a developer's investment.<sup>238</sup> As a result, the ODTC may be less effective at generating investment for especially rare diseases, ie diseases that have an extremely small pool of potential drug consumers and are therefore especially unlikely to be commercially viable.<sup>239</sup> 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 conduct R&D activities and complete the development process, while revenue-side incentives may be necessary to encourage companies to invest in drug development projects that would otherwise be unprofitable.<sup>240</sup>

### Issues with Subsidizing Innovation via the Tax System

As a supply-side incentive, tax benefits are available 'upfront'; in other words, companies receive the subsidy prior to product approval. For drug companies, this is an especially important aspect of tax incentives and other push mechanisms because they can rely on receiving the benefit irrespective of whether or not the R&D activities they invest in ultimately yield a marketable product. Supply-side incentives are also considered to be effective because they are available throughout the R&D process, which is precisely the time when expenses are high.<sup>241</sup> For some pharmaceutical companies supply-side incentives like tax credits may be the only way they will be able to complete (or even begin) a drug development project.

Tax incentives also tend to be more stable and permanent than direct grant programs because they are not typically subject to annual budget reviews, which may mean that tax incentives are more likely to influence behavior than a grant program that could undergo dramatic changes on a yearly basis.<sup>242</sup> Given that drug development often takes over a decade, a tax incentive that can be relied upon throughout that time facilitates planning of a project better than a direct funding program that is subject to annual review, amendments, and possible termination.

<sup>235</sup> National Organization for Rare Disorders, Biotechnology Industry Organization & Ernst & Young, *Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases*, June 2015, at 7, <https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf> (accessed Mar. 26, 2018).

<sup>236</sup> *Id.* at 20–21.

<sup>237</sup> *Id.* at 13–17.

<sup>238</sup> Yin, *supra* note 232, at 1073.

<sup>239</sup> *Id.*

<sup>240</sup> *Id.*

<sup>241</sup> *Id.*

<sup>242</sup> Barry Bozeman & Albert N. Link, *Tax Incentives for R&D: A Critical Evaluation*, 13 RES. POL'Y 21, 26 (1984).

On the other hand, unlike direct spending programs, tax-based incentives do not have a pre-determined spending limit and therefore can become incredibly expensive for the government and, in turn, taxpayers.<sup>243</sup> 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 (and taxpayers) may end up spending more in support of R&D activity than is truly justified, with little ability to curb this expenditure. In Canada, SR&ED is perceived to be very costly and efforts have been made to reduce SR&ED spending.<sup>244</sup> A targeted, orphan drug-specific tax incentive would, of course, be less expensive than SR&ED 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 positive impact on public health resulting from increases in the development of innovative treatments could justify this collective burden. Greater availability of appropriate treatments would likely promote improved health outcomes, and, in turn, result 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).

### Anticipated Effect and Impact of Tax-Based Incentives

A common issue with 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 observed with respect to both SR&ED and the ODT.<sup>245</sup> Some authors have suggested that upside-down effects are particularly problematic in the case of R&D 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 with the greatest innovative potential.<sup>246</sup> The upside-down effect can be mitigated if refundable, instead of non-refundable, tax credits are used because the value of refundable credits is not dependent on a taxpayer having tax liability.<sup>247</sup> Non-refundable credits can only be used to reduce taxes payable down to zero, while refundable credits can result in money being paid by the government to the taxpayer should they not owe any tax. The use of refundable credits for orphan drug development is cautioned against because doing so 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 expenditure associated with providing a refundable credit could be reduced by providing the credit at a lower rate (eg 35% instead of 50%).<sup>248</sup>

Smaller or otherwise less financially stable companies will also be unable to make use of tax-based incentives if they cannot afford to make the initial investment in a

<sup>243</sup> A concern also noted by Office of the Auditor General of Canada, *Report 3 Tax-Based Expenditures*, [http://www.oag-bvg.gc.ca/internet/English/parl\\_oag\\_201504\\_03\\_e\\_40349.html](http://www.oag-bvg.gc.ca/internet/English/parl_oag_201504_03_e_40349.html) (accessed Mar. 26, 2018).

<sup>244</sup> See Canada Minister of Finance, *Jobs, Growth and Long-Term Prosperity: Economic Action Plan 2012*, Mar. 29, 2012, at 70, <https://www.budget.gc.ca/2012/plan/pdf/Plan2012-eng.pdf> (accessed Mar. 26, 2018).

<sup>245</sup> For example, see Susannah Camic Tahk, *Everything is Tax: Evaluating the Structural Transformation of U.S. Policymaking*, 50 HARV. J. ON LEGIS. 67, 77 (2013).

<sup>246</sup> Bozeman & Link, *supra* note 242, at 27.

<sup>247</sup> Tahk, *supra* note 245, at 78.

<sup>248</sup> The author thanks Professor Tamara Larre for this suggestion.

development project that would be needed to receive the subsidy.<sup>249</sup> R&D tax incentives seem to primarily assist firms that are not operating under significant financial constraints.<sup>250</sup> Therefore, basing an orphan drug incentive in the tax system can operate 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,<sup>251</sup> though companies could face similar difficulty in obtaining assistance in this manner because of uncertainty around a project's feasibility.

One final issue about a tax credit for orphan drug development remains to be considered and that is whether a tax agency represents the optimal policy means to provide an orphan drug subsidy. A tax-based incentive for orphan drug development would fail to take advantage of Health Canada's existing expertise in that subject matter, and therefore it is possible that an orphan drug subsidy should be administered by Health Canada as a direct funding program rather than the CRA.<sup>252</sup> On the other hand, as the CRA already administers SR&ED, a tax credit for orphan drug development could reasonably be added to the agency's tasks with relatively little additional burden. Drug developers in Canada already use the SR&ED program,<sup>253</sup> and there would be minimal additional compliance costs for them to claim an orphan drug tax credit. Having an orphan drug subsidy in the tax system would also provide the advantages associated with yearly filing. Specifically, annual filing of taxes can increase awareness, and therefore take-up, of the program,<sup>254</sup> and offers companies a convenient way to apply for the subsidy.<sup>255</sup> Furthermore, allocating significant amounts to directly fund orphan drug projects 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.<sup>256</sup> Assuming that some subsidization of orphan drug development is necessary, a tax-based program that could be introduced without

<sup>249</sup> M. Beatriz Corchuelo & Ester Martínez-Ros, *Who Benefits from R&D Tax Policy?*, 45 CUADERNOS DE ECONOMÍA Y DIRECCIÓN DE LA EMPRESA 145, 577 (2010).

<sup>250</sup> *Id.* at 590.

<sup>251</sup> In its report on government spending on R&D, the Expert Panel recommended that SR&ED spending be reduced in favor of allocating more resources to direct funding schemes: Industry Canada, Review of Federal Support to Research and Development - Expert Panel Report, *Innovation Canada: A Call to Action*, 2011, at 6-3-6-5, [http://publications.gc.ca/collections/collection\\_2011/ic/Iu4-149-2011-eng.pdf](http://publications.gc.ca/collections/collection_2011/ic/Iu4-149-2011-eng.pdf) (accessed Mar. 26, 2018) [hereinafter *Innovation Canada Report*].

<sup>252</sup> 'Integration theory' posits that whether a government program should be implemented as a part of the tax system depends on the extent to which the program's function complements the functions that are already performed by the tax system. David A. Weisbach & Jacob Nussim, *The Integration of Tax and Spending Programs*, 113 YALE L.J. 955, 980 (2004). 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. Jacob Nussim & Anat Sorak, *Theorizing Tax Incentives for Innovation*, 36 VA. TAX REV. 25, 75 (2017).

<sup>253</sup> For example, see Patented Medicine Prices Review Board, *supra* note 99, at 46.

<sup>254</sup> Filing tax returns provides 'automatic notification' of tax-based programs. Tahk, *supra* note 245, at 93.

<sup>255</sup> 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. For example, see Tamara Larre, *The Children's Fitness Tax Credit: Right Message, Wrong Policy Instrument*, in TAX EXPENDITURE ANALYSIS: STATE OF THE ART 12:7 (Jinyan Li & Lisa Philipps, eds, 2011).

<sup>256</sup> For example, see Sarah Jane Tribble & Sydney Lupkin, *The Orphan Drug Machine: Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies*, KAISER HEALTH NEWS, Jan. 17, 2017,

insurmountable opposition may in fact be a better policy choice than a direct funding program that would attract significant opposition.

That being said, one limitation of this paper is that the option of directly funding orphan drug development, as opposed to using the tax system, is not fully explored. Given the importance of providing some form of subsidy this possibility merits further consideration. An Independent Panel report concluded that Canada relies very heavily on SR&ED to subsidize R&D activity as opposed to direct funding schemes<sup>257</sup> and recommended that SR&ED spending be reduced in favor of more direct spending.<sup>258</sup> A separate study indicates 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.<sup>259</sup> Empirical evidence about the utility and political feasibility of directly subsidizing pharmaceutical innovation would be of assistance to future discussions about how to promote orphan drug development in Canada.

### CONCLUSION

In spite of the increased interest the pharmaceutical industry has shown in orphan drugs since the introduction of orphan drug policies in the US and EU, Canadian patients with rare diseases can still encounter difficulty in obtaining timely (and affordable) access to appropriate treatments. The additional risks (such as delayed diagnosis and treatment) and costs (of drugs accessed through the SAP) that rare disease patients often face *because their disease is rare* strengthen the argument that, for the sake of equality, incentives for orphan drugs are warranted.

As orphan drug incentives appear to have been successfully used by the EU and US to encourage the pharmaceutical industry to invest in orphan drugs (with limitations on that success, as noted above), Canada should introduce incentives designed to motivate companies to market these drugs in Canada (ie to apply for regulatory approval). Doing so will facilitate more timely access to appropriate treatment and reduce the financial burden of patients with rare diseases who currently must access treatments via the SAP. Encouraging innovative drug development remains a suitable secondary goal of a Canadian orphan drug policy, given that there continues to be many rare diseases for which no treatments have been developed. Nevertheless, it is unclear how exactly orphan drug incentives should be allocated, though there is certainly room to question whether it is appropriate to allocate government resources based solely on disease prevalence (or lack thereof). Careful drafting of how orphan disease will be defined should help to promote R&D in a more equitable and efficient manner.

This evaluation led to the conclusion that both market exclusivity and a tax credit for orphan drug development would be a good choice for policymakers in Canada. Market exclusivity may be the most powerful incentive offered through orphan drug policies and, unsurprisingly, the above analysis reached the conclusion that it should be introduced in Canada as part of an orphan drug framework. Including the ability to

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<https://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/> (accessed Mar. 26, 2018).

<sup>257</sup> *Innovation Canada Report*, *supra* note 251, at 1-2, 6-1, & 6-2.

<sup>258</sup> *Id.* at 6-4-5.

<sup>259</sup> Charles Berube & Pierre Mohnen, *Are Firms that Receive R&D Subsidies More Innovative?*, 42 CAN. J. ECON. 206, 222 (2009).



terminate the exclusivity period once an orphan drug has become sufficiently profitable is recommended in order to avoid prolonged application of the 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 biomarker-defined subsets of the original orphan condition.

While recognizing the value of having a revenue-side incentive such as market exclusivity, the importance of subsidizing orphan drug development cannot be overlooked. Therefore, an orphan drug-specific tax credit should also be introduced in Canada. Admittedly, an orphan drug tax credit in Canada can be expected to suffer from the uneven distributional effects that have been observed with the ODTTC in the US, where larger, more established firms receive a greater benefit from non-refundable tax credits because they are able to use them immediately to offset current tax liability. While refundable credits can ensure a more even distribution of the tax benefit, the credit rate would have to be reduced if refundable credits were used, in order to keep the costs of the program reasonable.

PRVs, while a unique and interesting incentive, are not recommended as part of an orphan drug framework in Canada. Generally speaking, as the costs and impact of the PRV programs in the US 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 will be further diminished by the significantly smaller pharmaceutical market here.

This article provides an analysis of the issues and utility of using market exclusivity, PRVs, and a tax credit as incentives for orphan drug development. Similar incentives have been considered to encourage innovation in other high-priority pharmaceutical fields, such as antimicrobials.<sup>260</sup> Given that there are complaints from the pharmaceutical and biotech industries that the 'current R&D incentives [are] insufficient' to address the global threat of antibiotic resistance,<sup>261</sup> the above evaluation of orphan drug incentives may be of assistance to policymakers seeking to address the market failure that exists for new antimicrobial drug products. As recommended for a Canadian orphan drug policy, the definition(s) that will determine how incentives will be allocated (ie how the appropriate behavior will be identified) require cautious drafting. Doing so will proactively seek to curb exploitation and avoid rewarding behavior that would have been undertaken in the absence of incentives. Careful consideration of who will benefit from incentives is also important; both the PRV programs and the ODTTC provide a greater benefit to larger, more established companies (ie those with potential blockbuster drugs in development, or those with tax liability). Policymakers should evaluate where the desired innovation is likely to come from and target an incentive accordingly. Finally, any new incentives should be designed to allow for a formal assessment of their utility and consequences, as the PRV programs do.

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<sup>260</sup> Seabury & Sood, *supra* note 37.

<sup>261</sup> Dall, *supra* note 34.

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