Orphan drug incentives in the pharmacogenomic context: policy responses in the USA and Canada

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INTRODUCTION

The US Orphan Drug Act1 is a policy response to diseases that have been orphaned under ordinary market conditions, and thus remain unmet medical needs. They create special, streamlined regulatory pathways and incentives such as grant funding, tax credits, and market exclusivity in order to encourage drug researchers and firms to develop interventions that address these unmet medical needs.

As with any system of incentives, concerns have been raised about ‘noise’ in the system from the start of the orphan drug regime.2 The worry is that firms will take advantage of the increased knowledge they have (relative to regulators) about the safety and efficacy of a drug and its potential impact on one or more forms of disease in order to secure multiple orphan drug designations and approvals, extracting greater revenues over time. This is known as ‘salami slicing’.3 The classic example is Epogen, an orphan drug approved in 1989 to treat anemia linked to end-stage renal disease but subsequently widely prescribed for all kinds of anemia, quickly becoming a blockbuster drug.4

Several commentators have suggested that the shift toward ‘pharmacogenomics’ in drug research and development (R&D) portends more salami slicing.5 The claim is that findings from genomics and related fields of research will make it easier for industry

1 Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).
2 David Loughnot, Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses, 31 AM. J. L. & MED. 365, 380 (2005); Matthew Herder, When Everyone Is an Orphan: Against Adopting a U.S.-Sty ded Orphan Drug Policy in Canada, 20 ACCOUNT RES. 227, 269 (2013).
3 Loughnot, Id. at 371.
4 Id. at 370, 371.
5 Herder, supra note 2 at 244, 245.
players to manufacture new orphan diseases with all the market-based benefits that that category enjoys.

Shannon Gibson and Barbara von Tigerstrom\(^6\) unpack this concern against new regulations\(^7\) developed by the US Food and Drug Administration (FDA). The authors argue convincingly that the FDA’s 2013 regulations offer an improved means to curb pharmacogenomics-related salami slicing by pharmaceutical firms. The wording of the new regulations appears more alive to tactics that companies might utilize during the research process, such as narrowly defining clinical trial eligibility criteria based on a genetic biomarker in order to ‘enrich’ the study population and secure an orphan drug designation.\(^8\) By requiring companies to ‘show not just that the drug is more effective or less likely to cause adverse effects within the subset population, but also that the difference between the subset and the larger group is sufficient to prevent the drug from being a viable treatment option for patients in the larger group’,\(^9\) the FDA’s new regulations impose evidentiary requirements that may significantly limit companies’ ability to engage in salami slicing.

However, Gibson and von Tigerstrom’s analysis fails to respond to a prior, more fundamental question; namely, is the Orphan Drug Act the best means to respond to rare, unmet medical needs? Using two kinds of evidence—the first a survey of all US orphan drug designations and approvals since 2010 by therapeutic class, and the second a case study of one particular orphan drug known commercially as Ravicti—I suggest that it is time to entertain other policy responses to rare, unmet medical needs.

RARE DISEASE RESOURCE ALLOCATION: A QUICK SURVEY

Current estimates put the total number of rare diseases in the 6000–8000 range.\(^10\) The public justification for orphan drug laws is that, taken together, rare diseases are of comparable public health importance as much more prevalent diseases, including HIV/AIDS and common forms of cancer.\(^11\) In numeric terms, the Orphan Drug Act appears to be servicing this broad spectrum of rare diseases. The percentage of clinical trials targeting rare diseases has substantially increased;\(^12\) according to the FDA’s website, >500 orphan drugs have been approved since 1983, and a growing proportion of drugs that enter the market each year are orphan drugs.\(^13\)

However, a careful review of the available evidence reveals that orphan drug laws have not stimulated research into rare diseases generally. According to a 2010 study by Wellman-Labadie and Zhou, only one therapeutic class (oncology) has demonstrated product growth since 1983 ‘and this growth appears to be the major contributor to the

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\(^6\) Shannon Gibson & Barbara von Tigerstrom, Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the US and Canada, 2 J. L. & BIOSCI. 263, 291 (2015).
\(^7\) Orphan Drug Regulations (Final Rule), 78 Fed. Reg. 35,117, 35,120-1 (June 12, 2013).
\(^8\) Gibson & von Tigerstrom, supra note 6, at 271, 272.
\(^9\) Id. at 272.
\(^10\) Lucio Luzzatto et al., Rare Diseases and Effective Treatments: Are We Delivering?, 385 THE LANCET 750, 752 (2015); Wim Pinxten et al., A Fair Share for the Orphans: Ethical Guidelines for a Fair Distribution of Resources Within the Bounds of the 10-Year-Old European Orphan Drug Regulation, 38 J. MED. ETHICS 148, 153 (2012).
\(^11\) Who We Are, Global Genes, http://globalgenes.org/who-we-are-2/ (last accessed Nov. 24, 2015).
\(^12\) Wesley Yin, Market Incentives and Pharmaceutical Innovation, 27 J. HEALTH ECON. 1060, 1077 (2008).
\(^13\) Kurt Karst, FDA Law Blog: The 2014 Numbers Are In: FDA’s Orphan Drug Program Shatters Records, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records.html (last accessed Nov. 24, 2015).
yearly increase in orphan drug designations. There are many forms of rare cancer, but it is not known whether they account for a disproportionate share of the health burdens within the full spectrum of the ~7000 rare diseases.

Following Wellman-Labadie and Zhou, I examined whether this pattern still holds for 2010–14. As Figs 1 and 2 below show, a disproportionate focus on oncology orphan products remains. Oncology-related orphan drug designations account, on average, for 38.2% of all orphan drug designations between 2010 and 2014. Likewise, oncology-related orphan drug approvals account, on average, for 37.2% of all orphan drug approvals from 2010 to 2014.

This decided focus on oncology-related orphan drugs is telling of biopharmaceutical firms’ underlying business model. Far more firms profess an interest in rare diseases nowadays, yet their R&D efforts tend to focus narrowly on oncology. Off-label use of drugs is particularly common in oncology. Industry’s forecast of the potential market returns associated with oncology orphan products are likely greater than treatments for other rare diseases, and their resources are allocated accordingly.

On the whole, then, the observed spike in orphan drugs reaching the market after the enactment of the US Orphan Drug Act is misleading; the incentives offered by the legislation are not effective in steering R&D efforts toward rare, unmet medical needs beyond oncology. Not all orphan drugs are oncology related, but products outside of that therapeutic class offer a worrisome window onto firms’ business models as well.

Figure 1. FDA orphan drug designations targeting oncology and nononcology forms of rare diseases, 2010–14.
RAVICTI: A SHORT CASE STUDY

Urea cycle disorders (UCDs) precipitate increased blood ammonia levels leading to brain damage and death, and occur in approximately 1 in 45,000 persons in the USA. Owing to pioneering work by academic researchers dating back to the 1970s, however, a succession of closely related treatments for UCDs have come on the market between 1987 and 2013. Ravicti is the latest drug in this chain of products. Its chemical composition differs only slightly from its precursor product, and its regulatory approval turned on one phase 3 clinical trial, 28 days in duration, involving 44 patients, which was designed to demonstrate Ravicti’s ‘non-inferiority’ to the existing therapy Buphenyl. The FDA described the trial as ‘essentially a bioequivalence trial between Ravicti and the currently marketed sodium phenylbutyrate product’. The drug’s ‘bench to market cost’ was reportedly ‘10% of that of a typical drug’. Yet, Ravicti’s manufacturer, Hyperion Therapeutics, which entered the scene long after most of the clinical evidence base and precursor products were developed, has set Ravicti’s price at US$ 250,000–290,000 per patient per year.

16 Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 203284Orig1s000 Summary Review (2013), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000SumR.pdf (last accessed Nov. 26, 2015) [hereinafter Ravicti FDA Review].
17 Mark L. Batshaw, Robert B. MacArthur & Mendel Tuchman, Alternative Pathway Therapy for Urea Cycle Disorders: Twenty Years Later, 138 J. PEDIATR. S46, S55 (2001).
18 Malini Guha, Urea Cycle Disorder Drug Approved, 31 NAT. BIOTECH. 274, 274 (2013).
19 Ravicti FDA Review, supra note 16, at 14.
20 Batshaw ML, Groft SC & Krischer JP, Research into Rare Diseases of Childhood, 311 JAMA 1729, 1730 (2014).
21 Guha, supra note 18, at 274.
To assess the value of Ravicti, its stated price, and what the story suggests about orphan drug policy, it is worth mining the details of Ravicti’s development. The story begins with a ‘serendipitous’ discovery by Saul Brusilow of Johns Hopkins University, which precipitated a series of promising studies published through the 1970s and early 1980s.22 By 1981, Brusilow et al. obtained a patent on a ‘process for controlling waste nitrogen accumulation diseases in humans’,23 which was assigned to Johns Hopkins.

On the strength of these findings and patent rights, Brusilow et al. worked with the support of a private company to develop the first treatment for UCDs, Ucephan (a sodium phenylacetate-sodium benzoate combination product). The FDA classified Ucephan as a new molecular entity, reviewed it on a priority basis, and designated it as an orphan drug, which the sponsoring company, Braun Medical (later Immunex Corp., located in Irvine, CA), began marketing in 1987 when it was approved by the FDA.

In 1997, Ucephan was ‘discontinued for reasons other than safety’ (ie business reasons), likely because it was not well tolerated by patients due to its strong odor. Brusilow worked to develop an alternative formulation, which would result in Buphenyl (Ucephan converted to more palatable tablet and powder formulations of sodium phenylbutyrate). However, Brusilow struggled to entice commercial sponsors to bring the therapy to market.24 Ucyclyd Pharma, a start-up company initially based in Maryland, which Brusilow, Batshaw, and others advised, stepped in to fill the void. Thereafter, Buphenyl was designated as an orphan product in 1993 by the FDA, and approved in 1996 as an adjunctive therapy for the chronic management of patients with UCDs. In 1999, Ucyclyd was acquired by Medicis Pharmaceutical Corp. of Scottsdale, AZ, which continued to market Buphenyl as an oral maintenance therapy for UCDs. That same year, Brusilow entered a license agreement with Ucyclyd/Medicis in respect of his patent rights and associated products.25

Despite Buphenyl’s improvements over Ucephan, side effects (eg exacerbation of peptic ulcers) continued to be observed. The oral route of administration for both products, moreover, presented challenges given that patients with UCD in hyperammonemic crisis suffer from extensive vomiting and seizures.26 Ucyclyd/Medicis thus sought to further improve its treatment for UCDs, creating an intravenous formulation called Ammonul. The FDA, in turn, granted Ammonul orphan drug status, again reviewed it in expedited fashion, and approved it for sale in 2005.

At some point, however, Brusilow grew frustrated with Ucyclyd/Medicis’ performance. According to documentation provided to the US Securities Exchange Commission, the two parties settled the dispute on August 21, 2007, with Ucyclyd/Medicis agreeing to pay Brusilow an undisclosed percentage of net sales on the products encompassed in the 1999 license agreement.27 The settlement was likely essential to

22 Batshaw et al., supra note 17, at S46.
23 US Patent No. 4,284,647 (filed Mar. 31, 1980).
24 Mark Guidera, ‘Orphan Drug’ Finds a Home Process: Developing a Drug is Only Half the Battle in Treating Rare Diseases. The Other Half is Finding a Company to Market the Drug and Seek FDA Approval. BALTIMORE SUN (1996), http://articles.baltimoresun.com/1996-10-13/business/1996287173_1_ urea-cycle-disorder-orphan-drug-drug-companies (last accessed May 16, 2013).
25 US Patent No 5,968,979 (filed Jan. 13, 1998).
26 Batshaw et al, supra note 17, at S51.
27 Hyperion-Ucyclyd/Medicis Collaboration Agreement (2007), http://agreements.realdealdocs.com/ Collaboration-Agreement/COLLABORATION-AGREEMENT-1774950/ (last accessed Nov. 24, 2015).
finalizing a research collaboration agreement between Ucyclyd/Medicis and Hyperion, dated August 23, 2007, for the development of further products for UCDs.\footnote{Id.}

Between 2007 and 2009, Hyperion sponsored a series of small phase 1 (in collaboration with Ucyclyd) and phase 2 trials, investigating its product, Ravicti, in patients with UCDs. In early 2009, Hyperion representatives met with the FDA to discuss its findings and begin to work out a ‘special protocol assessment’ (SPA) agreement for a phase 3 study. Ravicti received an orphan drug designation on April 27, 2009. By June 2009, the SPA was concluded and the ensuing phase 3 trial was limited to 44 adult patients, spanned 28 days, and designed to show Ravicti’s noninferiority to Byphenyl.

Hyperion formally submitted a new drug application for Ravicti to the FDA on December 23, 2011. It was reviewed by the FDA on a standard (rather than fast-track) basis as a ‘new ester, new salt, or other noncovalent derivative’ of an existing (rather than new) chemical entity, intended for patients with treatment options already available. On March 22, 2012, Hyperion and Ucyclyd/Medicis (now owned by Valeant Pharmaceuticals International, Inc., headquartered in Montréal, QC) entered into an amended research agreement, granting Hyperion the option to acquire in the first half of 2013 ‘worldwide rights’ to Buphenyl.\footnote{Hyperion Therapeutics Acquires Worldwide Rights to BUPHENYL, GlobeNewswire News Room (2013), \url{http://globenewswire.com/news-release/2013/06/03/551549/10034885/en/Hyperion-Therapeutics-Acquires-Worldwide-Rights-to-BUPHENYL.html} (last accessed Nov. 26, 2015).}

The option proved well timed: On February 1, 2013, the FDA approved Ravicti for the treatment of UCDs in patients aged two years or older. On June 3, 2013, Hyperion exercised its option to acquire Buphenyl pursuant to its agreement with Valeant. Hyperion’s CEO emphasized that ‘Ravicti remains the cornerstone of our commercial plan’.\footnote{Guha, supra note 18, at 274.} Although Ravicti was not approved for children younger than two, it remains to be seen whether Buphenyl will stay on the market. Hyperion plans to deploy sales representatives to educate physicians about Ravicti, anticipating that most patients with UCD will transition over to the newly approved therapy in time.\footnote{Gregory M. Enns et al., Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders, 356 N. ENGL. J. MED. 2282, 2292 (2007).}

Ravicti’s backstory surfaces shortcomings with the US Orphan Drug Act. First, given the array of actors and intermingled forms of market exclusivity involved in this story, it is a stretch to suggest that the incentives contained in the Orphan Drug Act were the primary stimulus for the development of UCD therapies. Instead, it appears that the orphan drug law enticed Hyperion to develop Ravicti, a version of Buphenyl seemingly modified just enough to overcome regulations that preclude the FDA from granting orphan drug status to the ‘same drug’ for the same indication, but priced substantially above its precursors.

Second, an entity’s R&D performance may have little bearing on orphan drug pricing. The bulk of the clinical evidence surrounding benzoate-phenylacetate products for patients with UCD was generated before Hyperion entered into the field.\footnote{Id.} Hyperion is responsible for the sole randomized, controlled study, but it was short in duration, small in size, and designed only to show Ravicti’s noninferiority to Buphenyl. (See Table 1 for a summary of completed clinical trials sponsored by Hyperion.) Ravicti was touted as having significant benefits in terms of patient compliance, but according to regulatory
Table 1. Completed Hyperion-sponsored trials registered on ClinicalTrials.gov for UCDs with supplementary information from the FDA’s reviews of Ravicti, in chronological order.

| ClinicalTrials.gov identifier (other ID) | Trial phase (endpoint classification) | Design | Participants (discrepancies with FDA summaries) | Intervention timeframe | Study timeframe |
|----------------------------------------|---------------------------------------|--------|-----------------------------------------------|------------------------|----------------|
| NCT00977600 (UP-1204-001)              | 1 (Safety/efficacy)                    | Randomized, open-label, cross-over | n = 24, ≥ 18 yr (none) | 24 h | Mar 05–Jul 05 |
| NCT00986895 (UP-1204-002)              | 1 (Safety)                            | Nonrandomized, open-label         | n = 32, ≥ 18 yr (none) | 7 days | Sept 06–Jun 07 |
| NCT00551200 (UP-1204-003)              | 2 (Safety)                            | Nonrandomized, open-label, fixed-sequence, dose-escalation (followed by 12 mos. safety monitoring) | n = 14, ≥ 18 yr (n = 10) | 28 days (with 12 mos. safety monitoring) | Oct 07–Jul 08 |
| NCT00947544 (HPN-100-005)              | 2 (Safety/efficacy)                    | Nonrandomized, open-label, fixed-sequence, cross-over | n = 17, 6–17 yr (n = 11) | 14 days (with 12 mos. safety monitoring) | Mar 10–Aug 11 |
| NCT00992459 (HPN-100-006)              | 3 (Safety/efficacy)                    | Randomized, double-blind, cross-over | n = 46, ≥ 18 yr (n = 44) | 28 days | Oct 09–Sep 10 |
Table 1. Continued.

| ClinicalTrials.gov identifier (other ID) | Trial phase (endpoint classification) | Design | Participants (discrepancies with FDA summaries) | Intervention timeframe | Study timeframe |
|----------------------------------------|--------------------------------------|--------|-----------------------------------------------|------------------------|----------------|
| NCT00947297 (HPN-100-007)             | 3 (Safety)                           | Nonrandomized, open-label extension of HPN-100-006 | n = 60, ≥ 6 yr, ≥ 18 yr (n = 60, 40 of which in HPN-100-006) | 12 mos.               | Nov 09–Sep 11 |
| NCT01135680 (HPN-100-010)             | 1 (Safety)                           | Randomized, double-blind, cross-over, TQT study | n = 72, ≥ 18 yr (none) | 24 h                  | May 10 – ?    |
| NCT01347073 (HPN-100-012)             | 2 (Safety/efficacy)                  | Nonrandomized, open-label, cross-over (followed by 12 mos. safety monitoring) | n = 23, <6 yr (n = 15 for 10 days, n = 22 for 12 mos.) | 10 days (with 12 mos. safety monitoring) | Jul 11–Mar 13 |
| Not found on ClinicalTrials.gov (HPN-100-011) | 2 (Safety)                           | Uncontrolled extension for patients completing HPN-100-005 + HPN-100-007 | (n = 67, 6–17 yr (n = 24), ≥18 yr (n = 43) | ?                     | ?             |

Notes: (1) Trials with ‘Other IDs’ beginning with the prefix ‘UP’ were initiated by or otherwise involved Ucycld Pharma, whereas trials with the ‘HPN’ prefix were initiated and sponsored by Hyperion (and may or may not have involved Ucycld). (2) Fields in which a question mark (‘?’) appears indicate that no information was found using the ClinicalTrials.gov website or from the FDA’s published review material. (3) NCT00992459 (HPN-100-006) is highlighted (in red text) because FDA reviews and secondary sources indicate that Ravicti’s approval turned on this particular phase 3 trial.
documents no data to support that claim were submitted by Hyperion. Thus, Ravicti’s price point of US$ 250,000–290,000 is less a reflection of the clinical evidence Hyperion helped generate, and more a carefully calculated judgment by Hyperion about the premium it can charge for its product compared to previous treatments taking into account the low risk that competitors will enter the UCD market.

Ideally, Ravicti will facilitate UCD patients’ compliance with the therapy. But it is not a therapy for a population without treatment options, and the benefits of improved patient compliance assume that Ravicti will be readily available to persons with UCDs, a significant assumption given the drug’s hike in price compared to Buphenyl (priced at roughly US$ 45,000 for children and US$ 115,000 for adults). It is especially puzzling that Ravicti’s approval was based on a noninferiority trial design given that, ‘[b]y definition, medicines aimed at unmet needs should be tested for their superiority over available treatments, if any, or placebo’.

CONCLUSION

The underlying point from the above survey and case study is that the Orphan Drug Act defers to the decision making of drug manufacturers about which diseases to target, how to develop them, and when a product results, what price to charge. The Orphan Drug Act has helped draw pharmaceutical firms into the orphan drug space, but industry’s discretion about which rare diseases to target and what price to charge has been preserved. The above evidence raises questions about whether the model encoded in the Orphan Drug Act is the best way to address rare, unmet medical needs. To be blunt, unless a rare disease patient has a rare form of cancer and/or belongs to a high socioeconomic class, the US approach to orphan drugs seems unlikely to improve the patient’s lot. While the new Orphan Drug Regulations promise to limit industry gaming of the boundaries of rare disease, which is important given recent progress in genomics and epigenomics, they do not respond to this prior, more fundamental problem. Ways to redesign support for R&D into rare, unmet medical needs should be explored.

32 Ravicti FDA Review, supra note 16, at 33.
33 One study based on patient self-reports, and completed after Ravicti’s approval provides some evidence of improved compliance. See Sandesh C. S. Nagamaniet al., Self-Reported Treatment-Associated Symptoms Among Patients with Urea Cycle Disorders Participating in Glycerol Phenylbutyrate Clinical Trials, 116 MOL. GENET. METABOLISM 29, 34 (2015).
34 Roberta Joppi, Vittorio Bertele’ & Silvio Garattini, Orphan Drugs, Orphan Diseases. The First Decade of Orphan Drug Legislation in the EU, 69 EUR. J. CLIN. PHARMACOL. 1009, 1024 at 1011 (2013).
35 Ana M. Valverde, Shelby D. Reed & Kevin A. Schulman, Proposed ‘Grant-And-Access’ Program With Price Caps Could Stimulate Development Of Drugs For Very Rare Diseases, 31 HEALTH AFF. 2528, 2535 (2012); Herder, supra note 2, at 250, 253ff.