The Benefits and Costs of
Promoting the Development of New Orphan Drugs

Nicholas Bagley (lead author)
Draft, February 12, 2017

It is commonly believed that the patent system affords manufacturers inadequate incentives to invest in the development of drugs for rare diseases. Several countries—most significantly, the United States, Japan, and the EU—have therefore adopted laws to encourage manufacturers to bring "orphan drugs" to market. Although the details of the laws differ, they generally subsidize the development of orphan drugs and grant a fixed period of post-approval market exclusivity.

Today, orphan drugs account for nearly half of new drugs approved for sale in the United States. In one sense, this is a mark of success: the pharmaceutical industry no longer neglects orphan diseases. But the high prices for orphan drugs have attracted concern in many quarters, and questions have been raised about the costs and benefits of orphan drug legislation. The time is ripe to evaluate the tradeoffs associated with policies that foster the development of orphan drugs.

I. The Expanding Orphan Drug Market.

The United States enacted the first orphan drug law in 1983, followed by Japan in 1993 and the EU in 2000 (see Table). The laws offer special incentives to manufacturers to develop drugs to treat rare diseases, with rarity defined either by population size (for the U.S., fewer than 200,000 patients) or prevalence (for the EU, fewer than 5 in 10,000). A number of other countries—including Australia, Korea, and Hong Kong—have adopted similar legislation, but orphan drug laws do not exist in Africa, South America, and most of Asia (Gammie et al. 2015).

These laws typically extend a fixed period of market exclusivity to orphan drugs, running from the time of approval and concurrently with any patents. The EU and Japan offer 10 years of market exclusivity; the U.S. offers 7 years. Most orphan drug laws also provide substantial tax advantages for R&D into orphan drugs. In the U.S., for example, a manufacturer can receive a credit worth half its development costs. Orphan drug laws also reduce the time and expense of securing regulatory approval: both Japan and the U.S., for example, offer fast-track approvals for orphan drugs.

The adoption of orphan drug legislation has coincided with a large increase in the number of orphan drugs. In the decade preceding 1983, just 10 drugs were approved to treat orphan conditions in the U.S. In the decade spanning 2006 to 2015, 266 orphan drugs were approved. Similar increases in the pace of approvals have been seen in the EU and Japan, with

most of the growth driven by the development of new cancer drugs (Figure 1; Daniel et al. 2016).

Some of these drugs are breakthroughs. Half of all orphan drugs approved in the U.S. are first in their class, a rate much higher than for non-orphans (Miller & Lanthier 2015). Ivacaftor (Kalydeco), for example, offers life-changing relief for those suffering from certain subtypes of cystic fibrosis. And imiglucerase (Cerezyme) and eliglustat (Cerdelga) treat variants of Gaucher's disease, a debilitating condition that occurs when an enzyme responsible for fat metabolism malfunctions.

Orphan drugs cost less to develop than non-orphans. On average, they enroll 34% as many patients in clinical trials and are approved about three months earlier, and at a higher rate, than non-orphans (EvaluatePharma 2015; Thomas et al. 2016). Studies of neurology and oncology drugs indicate that orphan drugs are often approved on the strength of lower-quality clinical trials than conventional therapies (Mitsumoto et al. 2009; Kesselheim, Myers, & Avorn 2011). Tax credits further reduce the costs of developing orphan medications.

With the accelerating pace of new drug approvals, the global market for orphan drugs is growing at 12% each year, roughly twice as fast as the drug market in general. Sales of orphan drugs topped $100 billion in 2015; one estimate suggests that sales of orphan drugs will amount to 20% of worldwide prescription drug spending in 2020 (EvaluatePharma 2015), although other research suggests a more moderate rate of growth (Divino et al. 2016).

II. The High Prices of Orphan Drugs

The accepted wisdom is, without orphan drug laws, market incentives are inadequate to tempt drug manufacturers to develop drugs that could only be sold to a restricted patient population. Evidence to back up this accepted wisdom, however, is elusive.

What drives investment is not simply the size of the patient population. It is the size of the *market*, which is a function of the price of the drug and the number of units sold. Even if drug manufacturers cannot sell as many orphan drugs, sufficient incentives may remain if they can charge large amounts for the drugs they do sell.

Experience suggests that they can. In the U.S., the median price of an orphan drug in 2015 was nearly $100,000 USD per year, almost twenty times the median price of non-orphans (EvaluatePharma 2015). Some drugs cost much more. Eculizumab (Soliris), for example, is used to treat an extremely rare blood disease and costs about $440,000 each year. Prices for orphan drugs are somewhat lower in the EU and the rest of the world but are still high relative to conventional drugs (Gammie 2015).

Because they can command high prices, drug manufacturers see them as a business opportunity (Meekings et al. 2012), and the pursuit of new orphan drugs has led to a flurry of acquisitions in the industry (Loftus et al. 2015). In 2014, at least 8 orphan drugs had annual, worldwide sales exceeding $1 billion (Table 2); Roche reported $6.9 billion in 2014 sales of the highest-grossing orphan drug, rituximab (Rituxan) (Roche 2015). High prices for orphan drugs burden governments that provide health insurance as well as patients who must sometimes pay a portion of their drug costs out of pocket. In the developing world, access to orphan drugs is foreclosed to all but the wealthy.

Why do orphan drugs command such high prices? As with conventional drugs, many orphan drugs are patented. The $300,000-per-year drug ivacaftor (Kalydeco), for example, is unlikely to face generic competition until 2027. For those drugs that are unpatented or have weak patents, orphan drug exclusivity can also serve to protect a brand-name drug from generic competition.

Even with exclusive marketing rights, however, manufacturers can set high prices only because patients, governments, and private insurers are willing to pay them. In many developed countries, demand for orphan drugs is inelastic, meaning that it is relatively insensitive to changes in price. Three features of orphan drugs contribute to that inelasticity.

First, orphan drugs are often developed for conditions for which there are few effective treatment options. Especially for first-in-class drugs, payers may be unable to substitute cheaper therapies.

Second, the relatively small number of afflicted patients means that the cost of any one drug may not severely strain a health system. The less common the disease, the less intensive the scrutiny will be of manufacturers' pricing practices. That dynamic may partly explain the strong correlation between a drug's price and the size of the affected population (EvaluatePharma 2015).

Third, those afflicted with an orphan disease are sympathetic and supported by well-organized patient-advocacy organizations, including the National Organization for Rare Disorders in the U.S. and EURORDIS in the EU. It may be politically untenable for a payer to refuse coverage for a promising new therapy on cost grounds.

In short, the combination of patents and price inelasticity enables drug manufacturers to aggressively price orphan drugs in the developed world. Market incentives are thus likely adequate to foster the development of many orphan drugs. To be sure, *fewer* orphan drugs would be developed in the absence of special legislation. But researchers have struggled to discern the magnitude of that response and disentangle it from the response to changes in market conditions (Kesselheim 2011). At a minimum, the relative importance of the orphan drug laws has waned as the prices for orphan drugs have climbed.

III. The Costs of Orphan Drug Legislation.

What are the costs of orphan drug laws? The laws' financial incentives function as a hidden tax. That is most obvious with respect to R&D tax credits, which reduce tax revenue and require spending cuts or higher taxes in other domains. The tax credits are substantial: in the U.S., they will cost roughly $1.75 billion in foregone revenue in 2016 (U.S. Treasury 2016).

The 7- and 10-year periods of regulatory exclusivity also function as a tax, one shared between patients, governments, and the privately insured. For drugs with patents that extend beyond the window of regulatory exclusivity, the size of that tax is likely small. For drugs that lack patents or have weak patents, however, orphan drug legislation can impose large costs.

Consider 3,4-diaminopryne (3,4-DAP), which has been used for thirty years off-label to treat two rare neuromuscular diseases. Two drug companies have recently put 3,4-DAP through clinical trials for those diseases and, after securing orphan drug approval in the EU, increased the price from $1,600 to $60,000 per year. The companies are likely to seek approval in the U.S., prompting a group of more than 50 physicians to express their concerns about the possibility of an "exorbitant pricing strategy" (Burns et al. 2016).

The practice of securing orphan drug approval for old drugs is common (Murphy et al. 2012; Döring 2016). But repurposing old drugs is not what the orphan drug laws aimed to accomplish. Although there is social value in encouraging clinical trials into new drug uses, it would be more efficient to publicly fund those trials than to grant an extended period of market exclusivity.

In addition, drug manufacturers may seek orphan-drug approval for a narrow indication in the expectation that the drug will be prescribed more extensively off-label. A 2012 study concluded that the unapproved use of orphan drugs is common (Kesselheim et al. 2012). The lidocaine patch, for example, was approved to treat an orphan condition—painful hypersensitivity and chronic pain in postherpetic neuralgia—but was prescribed 82.3% of the time for different uses.

Orphan drug laws play a complex role in this dynamic. Most orphan drugs—at least the non-recycled ones—are patented. (Lidocaine, for example, was under patent during the study period.) A patent already gives a manufacturer the exclusive right to sell the drug for off-label uses. Orphan drug exclusivity, however, can function as a partial substitute for a patent for drugs with weak or lapsed patents. Although generic competitors could in principle conduct the clinical studies in order to secure approval to market the drug for unapproved uses, they are unlikely to have sufficient financial incentives to do so.

Manufacturers can also engage in a practice known colloquially as "salami slicing." Most diseases have subtypes, and manufacturers can seek to approve a drug either for the

broader disease or for those subtypes. When some of the subtypes can be characterized as orphan diseases, the manufacturer may seek approval for one subtype after another, garnering a term of market exclusivity for each new indication. As a result, a drug that is targeted at a large population can call itself an orphan.

Physicians at Johns Hopkins have recently documented how variations in cancer etiology enable manufacturers to secure approval of orphan indications. Because cancers can be characterized by organ (breast, brain, colon) or by genes that trigger them (HER2, p53, BRCA1), "almost any cancer medication can be maneuvered into an orphan disease category" (Daniel et al. 2016). Imatinib mesylate (Gleevec), for example, has received approval of 7 different orphan indications. Manufacturers can thus take advantage of disease variations to extend their exclusivity period, contributing to the high prices of orphan drugs.

IV. Discussion.

Some orphan drugs are immensely valuable, but many of the most valuable would have been developed even in the absence of orphan drug legislation. At the same time, manufacturers can receive orphan drug approval for repurposed drugs and for drugs that are sold to large numbers of people, which in turn fuels high prices for orphan drugs. Those prices strain pocketbooks in the developed world and leave patients in low- and middle-income countries with no way to access them. The costs of orphan drug laws may well outweigh their benefits; at a minimum, reform is needed.

In particular, terms of regulatory exclusivity should end when a drug is prescribed to a patient population exceeding the orphan-drug threshold—in other words, when the drug is no longer an orphan drug. EU law already allows a reduction of the exclusivity period to six years when a drug is deemed sufficiently profitable, but the authority has not been exercised. In addition, exclusivity should be available only where a manufacturer has developed a genuinely new compound, not when it has repurposed an old drug.

Manufacturers should also be required to pay back R&D subsidies once drug sales exceed any plausible estimate of development costs. In Japan, for example, manufacturers must repay R&D subsidies for drugs with annual sales that exceed 100 million yen (Wellman-Labadie 2010). The same approach should be adapted elsewhere.

It is crucial to recognize, however, that reforming orphan drug laws may not much reduce the prices of orphan drugs. Most would still be patented and the demand for the drugs would still remain high. To reduce prices, payers will have to consider the value of the drugs that they purchase. Where an orphan drug is not cost-effective—where yields only incremental health improvements at an enormous price tag—payers must be empowered to say "no." Some governments have taken steps in that direction. Sweden, for example, has declined to pay for about half of newly approved orphan drugs (Garau 2009). If a critical mass of developed

nations followed Sweden's lead, drug manufacturers would come under considerable pressure to cut their prices.

In the meantime, the high prices of orphan drugs will remain a challenge of global proportions, both for those countries that bear the burden of paying for them and those that cannot afford to.

Table 1: Orphan Drug Legislation in the U.S., Japan, and the EU

Country	Year adopted	Threshold for orphan drug status	Market exclusivity from date of approval	Financial support for R&D	Accelerated approval	Orphan drugs approved in 2014*	Total number of orphan drugs approved through February 2015*
United States	1983	Fewer than 200,000 patients in the U.S. (6 in 10,000)	7 years	Tax credits of 50% of R&D costs	Yes	40	496
Japan	1993	Fewer than 50,000 patients in Japan (4 in 10,000)	10 years	Reimbursement of up to 50% of R&D costs, plus 6% tax credit	Yes	30	236
EU	2000	Fewer than 5 in 10,000	10 years	Varies across member states	Yes	17	87

Source: Murakami M. & Narukawa M., Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan. Drug Discovery 21:4, 544-549 (2016).

Table 2

Worldwide Top 20 Selling Orphan Drugs in 2020

Source: EvaluatePharma® 30 September 2015

Rank	Product	Generic Name	Company	Phase (Current)	Pharmacological Class	WW Product Sales ($m) 2014	2020	CAGR
1.	**Revlimid**	lenalidomide	Celgene	Marketed	Immunomodulator	4,980	**10,058**	+12%
2.	**Opdivo**	nivolumab	Bristol-Myers Squibb	Marketed	Anti-programmed death-1 (PD-1) MAb	6	**8,192**	+233%
3.	**Soliris**	eculizumab	Alexion Pharmaceuticals	Marketed	Anti-complement factor C5 MAb	2,234	**5,414**	+16%
4.	**Keytruda**	pembrolizumab	Merck & Co	Marketed	Anti-programmed death-1 (PD-1) MAb	55	**5,297**	+114%
5.	**Rituxan**	rituximab	Roche	Marketed	Anti-CD20 MAb	7,547	**5,117**	-6%
6.	**Orkambi**	lumacaftor; ivacaftor	Vertex Pharmaceuticals	Marketed	Cystic fibrosis transmembrane conductance regulator (CFTR) corrector	-	**5,051**	n/a
7.	**Imbruvica**	ibrutinib	AbbVie	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	-	**2,982**	n/a
8.	**Imbruvica**	ibrutinib	Johnson & Johnson	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	55	**2,712**	+91%
9.	**Esbriet**	Pirfenidone	Roche	Marketed	Tumour necrosis factor alpha (TNFα) & transforming growth factor-beta (TGF-β) inhibitor	48	**2,492**	+93%
10.	**Tasigna**	nilotinib hydrochloride monohydrate	Novartis	Marketed	BCR-ABL tyrosine kinase inhibitor	1,529	**2,331**	+7%
11.	**Pomalyst**	pomalidomide	Celgene	Marketed	Immunomodulator	680	**2,060**	+20%
12.	**Alimta**	pemetrexed disodium	Eli Lilly	Marketed	Thymidylate synthase inhibitor	2,792	**2,019**	-5%
13.	**Gazyva**	obinutuzumab	Roche	Marketed	Anti-CD20 MAb	54	**1,932**	+82%
14.	**Advate**	factor VIII (procoagulant)	Baxalta	Marketed	Factor VIII	2,348	**1,918**	-3%
15.	**Kyprolis**	carfilzomib	Amgen	Marketed	Proteasome inhibitor	331	**1,857**	+33%
16.	**Obeticholic acid**	obeticholic acid	Intercept Pharmaceuticals	Filed	Farnesoid X receptor (FXR) agonist	-	**1,827**	n/a
17.	**Yervoy**	ipilimumab	Bristol-Myers Squibb	Marketed	Anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) MAb	1,308	**1,723**	+5%
18.	**Ofev***	nintedanib	Boehringer Ingelheim	Marketed	Tyrosine kinase inhibitor	5	**1,674**	+164%
19.	**Cyramza**	ramucirumab	Eli Lilly	Marketed	Anti-VEGF-2 MAb	76	**1,655**	+67%
20.	**Sprycel**	dasatinib	Bristol-Myers Squibb	Marketed	Tyrosine kinase inhibitor	1,493	**1,646**	+2%
	Other					**71,487**	**109,870**	+7%
	Total					**97,026**	**177,827**	+10.6%

Note: * Forecast based on a single broker model.

Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Worldwide sales represent sales for all indications.

All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

Figure 1

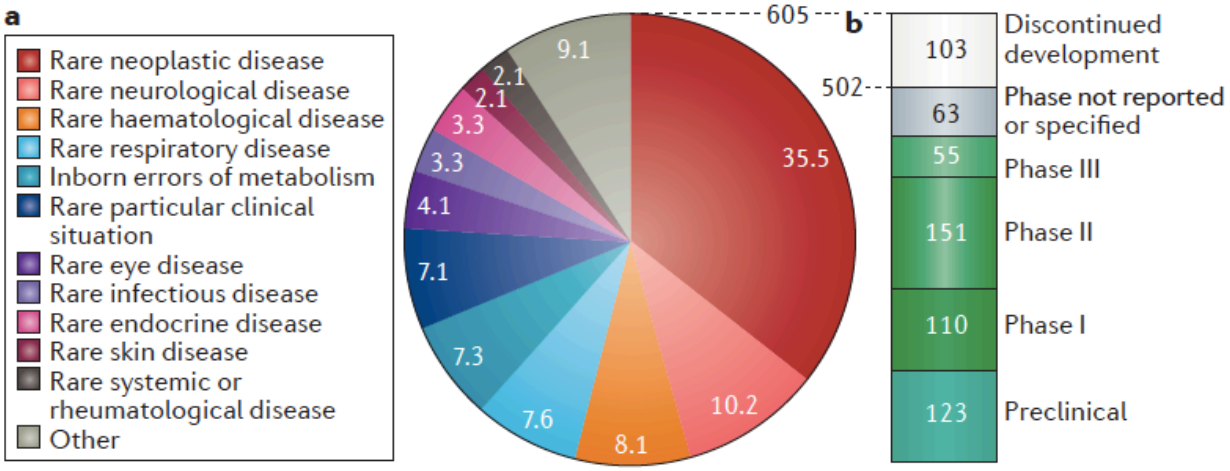

Figure 1 | **Analysis of orphan designations in the European Union.** The data are for orphan designations granted between 2002 and 2012 with annual reports filed to the European Medicines Agency in 2013 or 2014 ($n = 605$). **a** | Orphan designations granted, subdivided by therapeutic area. **b** | Orphan designations granted, subdivided by development stage.

Sources

Burns T et al. (2016). Editorial by Concerned Physicians: Unintended Effect of the Orphan Drug Act on the Potential Cost of 3,4-Diaminopyridine. Muscle & Nerve 53:165-68.

Daniel M et al. (2016). The Orphan Drug Act: Restoring the Mission to Rare Diseases. Am. J. Clin. Oncol. 39:210–213.

Döring JH, Lampert A, Hoffmann GF, Ries M (2016). Thirty Years of Orphan Drug Legislation and the Development of Drugs to Treat Rare Seizure Conditions: A Cross Sectional Analysis. PLoS ONE 11(8): e0161660.

EvaluatePharma (2015). Orphan Drug Report 2015, at http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD15.pdfDivino et al. 2016.

Gammie T, Lu CY, Babar ZU-D (2015). Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries. PLoS ONE 10(10): e0140002.

Garau M. & Mestre-Fernandez J. (2009). Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries. Office of Health Econ. Briefing, at https://www.ohe.org/publications/access-mechanisms-orphan-drugs-comparative-study-selected-european-countries.

Haffner ME, Whitley J, Moses M (2002). Two decades of orphan product development. Nat Rev Drug Discov. 1:821–825.

Kesselheim AS (2011). An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences. Milbank Quar. 89:450-502.

Kesselheim AS, Myers JA, Solomon DH, Winkelmayer WC, Levin R, et al. (2012). The Prevalence and Cost of Unapproved Uses of Top-Selling Orphan Drugs. PLoS ONE 7(2): e31894.

Kesselheim, A.S., J.A. Myers, and J. Avorn (2011). Characteristics of Clinical Trials to Support Approval of Orphan vs. Nonorphan Drugs for Cancer. JAMA 305:2320–26.

Loftus, P, J.D. Rockoff, M. Farrell. Alexion, Synageva Deal Shows Lure of Rare Disease Drugs. Wall St. J., May 6, 2015.

Meekings K, Williams CSM, Arrowsmith JE (2012). Orphan drug development: an economically viable strategy for biopharma R&D. Drug Discovery Today 17:660-64.

Miller, K., M. Lanthier (2016). Trends In Orphan New Molecular Entities, 1983–2014: Half Were First In Class, and Rare Cancers Were the Most Frequent Target. Health Affairs 35(3):464-70.

Mitsumoto, J., E.R. Dorsey, C.A. Beck, K. Kieburtz, and R.C. Griggs (2009). Pivotal Studies of Orphan Drugs Approved for Neurological Diseases. Annals of Neurology 66(2):184–90.

Murphy S et al. (2012). Unintended Effects of Orphan Product Designation for Rare Neurological Diseases. Ann. Neurol. 72(4):481-490.

Novartis Product Sales for 2015 (2016), at https://www.novartis.com/investors/financial-data/product-sales.

Roche Group, Finance Report 2014, at http://www.roche.com/dam/jcr:9d9091a6-dfcc-4d57-8017-4a4cb5fa224c/en/fb14e.pdf.

Thomas D.W., J. Burns, J. Audette, A. Caroll, C. Dow-Hygelund, M. Hay (2016), Clinical Development Success Rates 2006-15, BIO, Biomedtracker, Amplion.

U.S. Treasury (2016). Tax Expenditures 2016. https://www.treasury.gov/resource-center/tax-policy/Documents/Tax-Expenditures-FY2016.pdf.

Wellman-Labadie O, Zhou Y (2010). The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Policy 95:216-228.