



## **House Orphan Drug Proposal: A Windfall for Pharma, False 'Cure' for Patients**

Provision in Proposed 21<sup>st</sup> Century Cures Act Could Cost the Public \$12 Billion

### **Acknowledgments**

This report was written by Sammy Almashat and Sarah Sorscher of Public Citizen's Health Research Group and Steven Knievel of Public Citizen's Access to Medicines Division.

### **About Public Citizen**

Public Citizen is a national non-profit organization with more than 400,000 members and supporters. We represent consumer interests through lobbying, litigation, administrative advocacy, research, and public education on a broad range of issues including consumer rights in the marketplace, product safety, financial regulation, worker safety, safe and affordable health care, campaign finance reform and government ethics, fair trade, climate change, and corporate and government accountability.



## Introduction

In July 2015, the House of Representatives passed the 21<sup>st</sup> Century Cures Act, a bill purported to provide “help and hope for patients through biomedical innovation.”<sup>1</sup> Yet in many ways the “cure” presented by the bill is a false one. Many of the provisions purportedly aimed at accelerating the pace of “life saving and life improving”<sup>2</sup> drugs and medical devices serve to effectively water down Food and Drug Administration (FDA) approval standards for these products, meaning the new cures approved for patients may not actually be safe and effective and may fail to truly advance care for patients.<sup>3</sup> New false cures would be costly: A new analysis published in the *British Medical Journal* illustrated how the premature approval of just a single ineffective new Alzheimer’s drug could result in \$7 billion in wasteful health care spending over four years.<sup>4</sup>

Ineffective and unsafe treatments are not the only costly problem with the 21<sup>st</sup> Century Cures Act. This report focuses on a particular provision of the bill that will allow pharmaceutical companies to charge high prices for brand-name drugs for longer periods, in exchange for repurposing existing drugs to treat rare, or “orphan,” diseases.<sup>5</sup> This new incentive will be costly: We estimate that this provision alone could cost U.S. taxpayers and patients up to \$12 billion over 10 years.

Such a gift to the pharmaceutical industry is hardly necessary at a time when investment in orphan drugs is already soaring. Moreover, the new law would exacerbate current patterns of orphan drug development, which already results in the approval of far too many non-innovative, poorly tested drugs and would open the door to gaming and abuse of the system. And worse, it involves depriving patients with more common diseases of cheaper generic medicines for an additional six months. This provision, like many in the 21<sup>st</sup> Century Cures Act, is bad policy for medical innovation in this country, offering a false cure to American patients.

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<sup>1</sup> U.S. House of Representatives. Committee on Energy and Commerce. The 21<sup>st</sup> Century Cures Act (HR 6). Summary.

<http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/114/Cures2015FACTSHEET.pdf>. Accessed December 4, 2015.

<sup>2</sup> *Ibid.*

<sup>3</sup> The bill also provides a boost in biomedical research funding to the National Institutes of Health, but that influx of money is temporary, expiring after five years and doing little to restore the yearslong decline in federal funding for public research. For data on declining, inflation-adjusted NIH funding since FY2003, see: Johnson JA. Brief history of NIH funding: Fact sheet. Congressional Research Service. December 23, 2013.

<https://www.fas.org/sgp/crs/misc/R43341.pdf>. Accessed December 2, 2015.

<sup>4</sup> Zuckerman DM, Jury NJ, Silcox CE. 21<sup>st</sup> Century Cures Act and similar policy efforts: At what cost? *BMJ*. 2015;351:h6122.

<sup>5</sup> See 114th Congress H.R.6, Sec. 2151: Extension of Exclusivity Periods for a Drug Approved for a New Indication for a Rare Disease or Condition. Federal regulations define an orphan drug as one that is intended to treat a condition affecting fewer than 200,000 persons in the U.S., or which is not expected to recoup research and development costs within seven years following approval by the Food and Drug Administration. 21 CFR 316.20(b) and 21 CFR 316.21(c).

## Part I: The True Cost of the Proposed Expanded Monopoly

The 21<sup>st</sup> Century Cures Act that passed the U.S. House of Representatives in July would encourage drug manufacturers to repurpose old drugs for new orphan uses by providing each manufacturer that wins approval for a new orphan indication on an existing FDA-approved drug with an additional six months of monopoly protections for *all indications* on that drug. For example, if an existing high-blood-pressure treatment were approved for a rare disease or condition, six months of monopoly protection would be added to the patent and regulatory exclusivity terms for the original high-blood-pressure indication.<sup>6</sup> In other words, cheaper generic versions of drugs would be inaccessible to patients with much more common, non-orphan diseases, for an additional six months. This section explores the direct financial cost of that provision on health care payers and the public.

### *Cost estimates from the Congressional Budget Office and Public Citizen*

The Congressional Budget Office (CBO) has estimated that adding six months of exclusivity to drugs with new orphan indications would cost Medicare, Medicaid, and other federal health programs \$869 million over the 2016-2025 period.<sup>7</sup> Public Citizen estimates that over the same period, 2016-2025, the cost to both public and private payers for a new six-month exclusivity term for products receiving an orphan drug indication would at least approach \$3.9 billion, and could easily reach \$11.6 billion.

In making our estimate, we used the CBO's assumption that only about 15 percent of the aggregate sales of brand-name drugs previously approved by the FDA and expected to first experience generic competition before 2025 would benefit from a six-month delay in generic competition under the proposed new provision.<sup>8</sup> However, unlike the CBO, which, per its mandate, looked at the costs to federal health programs alone, we also included costs to patients and private insurance companies in addition to direct costs to the government. We did this by considering recent annual U.S. sales for the 50 best-selling pharmaceutical products, a total that includes all costs to the U.S. public.<sup>9</sup> (See Appendix 1: Cost estimate for currently approved drugs.)

Yet we believe that the \$3.9 billion estimate is conservative, representing a low-end estimate of the total costs of this provision. If the bill is successful in providing an incentive for companies to seek more orphan indications for drugs that are already FDA-approved, this would lead to a

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<sup>6</sup> The new six months of monopoly protection for all indications would be in addition to the seven years of monopoly protection for a new orphan use of a previously approved drug granted under current law. 21 U.S.C. §360cc.

<sup>7</sup> Congressional Budget Office Cost Estimate: H.R. 6, 21<sup>st</sup> Century Cures Act. As ordered reported by the House Committee on Energy and Commerce on May 21, 2015. <https://www.cbo.gov/sites/default/files/114th-congress-2015-2016/costestimate/hr65.pdf>. Accessed December 3, 2015.

<sup>8</sup> Congressional Budget Office Cost Estimate: H.R. 6, 21<sup>st</sup> Century Cures Act. As ordered reported by the House Committee on Energy and Commerce on May 21, 2015. <https://www.cbo.gov/sites/default/files/114th-congress-2015-2016/costestimate/hr65.pdf>. Accessed December 4, 2015.

<sup>9</sup> Brown T. 100 Best-Selling, Most prescribed branded drugs through March. Medscape Medical News. May 6, 2015. <http://www.medscape.com/viewarticle/844317>. Accessed December 3, 2015.

considerable increase in the rate at which companies apply for and successfully achieve FDA approval for orphan indications.

Furthermore, companies likely would focus their efforts on their most lucrative products, leading to a rush to develop orphan indications for blockbuster drugs. This has been the experience with pediatric exclusivity, which similarly offers a six-month extension of exclusivity for all indications in exchange for a study of the drug in pediatric patients.<sup>10</sup> Much of the investment fueled by this incentive has focused on blockbuster drugs. A 2013 report by McKinsey & Co. found that, since the policy's inception in 1997, the extra six months of pediatric exclusivity had generated \$71 billion in additional sales for the 145 drugs for which financial data were available.<sup>11</sup> This means that the average sales of drugs receiving this exclusivity have been at blockbuster levels, generating nearly \$1 billion, on average, for each drug per year.<sup>12</sup> The report concluded that the benefits of the pediatric exclusivity have “skew[ed] heavily toward blockbuster treatments,” with 80 percent of the added sales received by the top 35 percent best-selling drugs.<sup>13</sup>

While the pediatric exclusivity extension differs in certain ways from the proposed orphan exclusivity extension,<sup>14</sup> the reward of a six-month delay in generic competition would be expected to stimulate a similar level of interest in new orphan drug development — and a similar concentration of development resources toward a company's best-selling drugs.

Public Citizen estimates that each additional blockbuster drug approved for a new orphan indication would result in an additional \$768 million in costs to the public. This estimate was

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<sup>10</sup> Food and Drug Administration. Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric “Rule,” and Their Interaction.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm>. Accessed December 4, 2015.

<sup>11</sup> Aumock N, Smith J, Townsend S. Do Incentives Drive Pediatric Research? McKinsey & Co., McKinsey Center for Government. October 2013.

[http://www.mckinsey.com/~media/mckinsey/dotcom/client\\_service/public%20sector/regulatory%20excellence/do\\_incentives\\_drive\\_pediatric\\_research.ashx](http://www.mckinsey.com/~media/mckinsey/dotcom/client_service/public%20sector/regulatory%20excellence/do_incentives_drive_pediatric_research.ashx). Accessed December 4, 2015.

<sup>12</sup> This estimate was derived by dividing \$71 billion by 145 drugs to obtain average 6-months sales per drug, then multiplying by two to obtain average annual sales per drug.

<sup>13</sup> Aumock N, Smith J, Townsend S. Do Incentives Drive Pediatric Research? McKinsey & Co., McKinsey Center for Government. October 2013.

[http://www.mckinsey.com/~media/mckinsey/dotcom/client\\_service/public%20sector/regulatory%20excellence/do\\_incentives\\_drive\\_pediatric\\_research.ashx](http://www.mckinsey.com/~media/mckinsey/dotcom/client_service/public%20sector/regulatory%20excellence/do_incentives_drive_pediatric_research.ashx). Accessed December 4, 2015.

<sup>14</sup> There are at least two key differences between pediatric exclusivity and the proposed orphan exclusivity extension. First, companies must receive a written request from the FDA before proceeding with a pediatric study for the purposes of exclusivity (although companies can encourage the FDA to issue such a request). In addition, pediatric exclusivity is granted to a company regardless of the outcome of the study, while orphan exclusivity is granted only if the study is sufficient to support an FDA approval for the orphan indication (although the standards for orphan drug approval are considerably lower than those for non-orphan drug approvals — see Part 3). Source: Food and Drug Administration. Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric “Rule,” and Their Interaction. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm>. Accessed December 4, 2015.

made using the average sales of all blockbuster drugs during the April 2014 to March 2015 time period (see Appendix 1: Cost estimate for future blockbuster approvals).<sup>15</sup>

Even an average of one additional blockbuster drug for which a new orphan indication is approved each year over the next 10 years as a result of this provision<sup>16</sup> would increase costs to the public by \$7.7 billion. Added onto the conservative estimate of \$3.9 billion from currently approved drugs expected to achieve new orphan approvals, this additional amount would mean the bill would increase total drug costs by \$11.6 billion over 10 years.

## Part 2: No Need for Further Incentives

Another striking aspect of the current House proposal for a six-month exclusivity extension for new orphan drug approvals is its timing, as there has never been a more active time for orphan drug development. Even without the 21<sup>st</sup> Century Cures Act, pharmaceutical companies already receive many incentives to develop orphan drugs. These incentives have generated booming investment in the orphan drug industry.

Thanks to the Orphan Drug Act (ODA), passed by Congress in 1983,<sup>17</sup> makers of orphan drugs benefit from a tax credit covering half of clinical trial costs for their product, a seven-year exclusive marketing term that provides a monopoly on drug sales for the orphan indication, and special grants to fund orphan drug research.<sup>18</sup>

The decision to pass the ODA was based on the belief that pharmaceutical companies would otherwise fail to develop orphan drugs because these treatments generate relatively small sales and consequently fail to turn high profits after accounting for resources spent on research.<sup>19</sup> Yet now, more than three decades after the passage of the ODA, the landscape of orphan drug development has changed dramatically.

For each of the past two years, according to the FDA Law Blog, records were set on all three measures of orphan drug development: 1) company requests for orphan drug designations; 2) FDA granting of orphan drug designations; and 3) FDA granting of orphan drug product approvals (see Appendix 2).<sup>20</sup> Orphan drugs also have grown to represent a sizable portion of all

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<sup>15</sup> This refers only to a speculative pool of blockbuster drugs granted orphan drug approvals, for which orphan drug approvals *would not otherwise have been sought* in the absence of the new six-month exclusivity extension.

<sup>16</sup> This is a plausible scenario, as the median time between orphan designation and orphan drug approval has historically been approximately four years. See, e.g., Braun MM, Farag-El-Massah S, Xu K, Coté TR. Emergence of orphan drugs in the United States: A quantitative assessment of the first 25 years. *Nat Rev Drug Discov*. 2010;9(7):519-522.

<sup>17</sup> Department of Health and Human Services, Office of Inspector General. The Orphan Drug Act: Implementation and impact. May 2001. <http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf>. Accessed December 4, 2015.

<sup>18</sup> Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for orphan drug research and development in the United States. *Orphanet J Rare Dis*. 2008;3:33. <http://www.ojrd.com/content/3/1/33>. Accessed December 3, 2015.

<sup>19</sup> Food and Drug Administration. Orphan Drug Act. <http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAAct/OrphanDrugAct/default.htm>. Accessed December 4, 2015.

<sup>20</sup> Karst KR. The 2014 numbers are in: FDA's orphan drug program shatters records. FDA Law Blog. February 15, 2015. [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records.html). Accessed December 4, 2015.

biomedical research activity: As of 2009, orphan drugs constituted roughly one-third of all FDA drug approvals<sup>21</sup> and, from 2005 to 2014, made up one-fifth of all new indications for previously approved drugs.<sup>22</sup>

Why the uptick in orphan development? A 2014 report by the industry consulting group EvaluatePharma explains:<sup>23</sup>

“The reason is clear. The industry has rushed to develop orphan drugs in recent years because they cost their developers less to put through clinical trials, and command higher prices when they do launch. Trial sizes are naturally smaller than for diseases with large populations, and the lack of alternative treatments give orphan agents an advantage when up for regulatory review. Tax incentives reduce development costs further. And when orphan drugs do reach the market, on average their cost per patient is six times that of non-orphan drugs, a clear indication of their pricing power.”

The report then presents data demonstrating that the average return on investment for orphan drugs is nearly double that for non-orphan drugs: \$14.90 vs. \$7.90 for every dollar invested in Phase III trials, respectively.<sup>24</sup> This is due partly to lower Phase III trial costs for orphan versus non-orphan drugs (with most products costing \$97 million vs. \$143 million or more to develop, respectively), which, in turn, are due mainly to smaller trials (with most products requiring 538 vs. 1,491 subjects or more, respectively).<sup>25</sup> Of note, these data on the costs of orphan drug Phase III trials do not account for the 50 percent tax credit on orphan drug research and development costs granted to companies conducting trials on rare diseases.<sup>26</sup>

Higher prices are the other major driver of the greater returns for orphan drugs. In 2014, most orphan drugs cost patients at least \$98,534 per year; the corresponding annual cost of a non-orphan drug was \$5,153.<sup>27</sup> In some cases, the price of orphan drugs has been astronomical, provoking political pushback from governments. Eculizumab (Soliris) has been called the world’s most expensive drug,<sup>28</sup> priced at \$669,000 per patient per year in the U.S.<sup>29,30</sup> It was

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<sup>21</sup> Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. Washington (DC): National Academies Press (US); 2009. 3, The Food and Drug Administration’s Orphan Drug Program. <http://www.ncbi.nlm.nih.gov/books/NBK50974/>. Accessed December 4, 2015.

<sup>22</sup> Wang B, Kesselheim AS. Characteristics of efficacy evidence supporting approval of supplemental indications for prescription drugs in United States, 2005-14: Systematic review. *BMJ*. 2015;351:h4679.

<http://www.bmj.com/cgi/pmidlookup?view=long&pmid=26400844>. Accessed December 3, 2015.

<sup>23</sup> EvaluatePharma. Orphan Drug Report 2014. October 2014.

<http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf>. Accessed December 4, 2015.

<sup>24</sup> *Ibid.*

<sup>25</sup> *Ibid.* Numbers represent median values.

<sup>26</sup> 26 CFR 1.28-1 — Credit for clinical testing expenses for certain drugs for rare diseases or conditions.

<https://www.law.cornell.edu/cfr/text/26/1.28-1>. Accessed December 4, 2015.

<sup>27</sup> EvaluatePharma. Orphan Drug Report 2014. October 2014.

<http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf>. Accessed December 4, 2015.

<sup>28</sup> Herper M. The World's Most Expensive Drugs, *Forbes*. February 22, 2010.

<http://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html>. Accessed December 3, 2015.



initially approved in 2007 for the orphan disease paroxysmal nocturnal hemoglobinuria<sup>31</sup> and subsequently received another orphan approval in 2011.<sup>32</sup>

Given the low development costs and high prices of orphan drugs, EvaluatePharma concluded in its report, “Looking ahead, there does not appear to be much to slow down the sector’s rush into orphan indications.”<sup>33</sup> By any measure, the current orphan drug approval system is hardly in need of a stimulus, especially not one that entails depriving patients with more common diseases of cheaper generic medicines for an additional six months.

### Part 3: Drawbacks of the Current Orphan Drug Approval System

One of the worst aspects of the new incentive proposed in the 21<sup>st</sup> Century Cures Act is that it encourages exactly the wrong type of drug development, resulting in new approvals that are not truly innovative, are poorly tested, and are open to gaming and abuse. Rather than add yet another — and unnecessary — incentive for drugmakers to develop orphan products, Congress should instead address the underlying deficiencies of the current system.

#### *Many orphan drugs are not newly developed compounds*

To find real breakthrough cures for orphan diseases, truly innovative research and development is needed. Yet many drugs developed under the current orphan drug incentive are not truly innovative at all. A 2010 Institute of Medicine (IOM) review found that, of the 101 orphan drugs approved from 2000 to 2009, only about a third were new molecular entities, while the remaining two-thirds were either drugs that had been previously approved in the U.S. or elsewhere or were closely related to such drugs.<sup>34</sup>

Adding a new six-month exclusivity period for existing drugs with new, orphan indications will further encourage this trend, by offering additional incentives to companies to spend money on developing new uses of and minor changes to existing blockbusters, rather than identifying more innovative new treatments.

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<sup>29</sup> Palmer E. Alexion sues Canada over Soliris price cut attempt as drug cost debate explodes on center stage. FiercePharma. September 25, 2015. <http://www.fiercepharma.com/story/alexion-sues-canada-over-soliris-price-cut-attempt-drug-cost-debate-explode/2015-09-25>. Accessed December 4, 2015.

<sup>30</sup> *Ibid.* The drug’s price in Canada (\$700,000 in Canadian dollars, equivalent to about \$524,000 U.S. dollars, per exchange rate on December 3, 2015) prompted the Canadian Patented Medicine Prices Review Board to attempt to force the drug’s maker, Alexion, to lower the price, to which Alexion responded by filing suit in U.S. federal court to stop the Canadian government from taking any action.

<sup>31</sup> Food and Drug Administration. FDA-approved label, eculizumab (Soliris), revised March 2007. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/125166lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/125166lbl.pdf). Accessed December 4, 2015.

<sup>32</sup> Food and Drug Administration. Orphan Drug Designations and Approvals. Eculizumab (Soliris). [https://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD\\_Results\\_2.cfm?Index\\_Number=173203](https://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD_Results_2.cfm?Index_Number=173203). Accessed December 4, 2015.

<sup>33</sup> EvaluatePharma. Orphan Drug Report 2014. October 2014. <http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf>. Accessed December 4, 2015.

<sup>34</sup> IOM (Institute of Medicine). 2010. *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington, DC: The National Academies Press. Appendix B: Kesselheim AS. Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs. <http://www.ncbi.nlm.nih.gov/books/NBK56187/>. Accessed December 4, 2015.



*Lower standards to demonstrate safety and efficacy*

There often is much less evidence to support FDA approval of drugs for rare diseases than there is for other drugs. This leads to effectively lower approval standards, and higher chances that some orphan drugs may have risks that outweigh potential benefits of use.

Some of the problems with lack of evidence are due to the fact that orphan diseases are relatively rare and finding eligible patients for clinical trials can be difficult, leading to smaller clinical trials that gather less information about a drug's risks or benefits. For example, a trial on a drug for Pompe disease, which affects just 70 newborns worldwide each year, was able to enroll only 50 subjects.<sup>35</sup>

Yet even for orphan diseases with patient populations much closer to the 200,000-patient threshold, clinical trials still have often been extremely small. For example, despite an estimated 100,000 U.S. patients with a condition known as non-24-hour sleep-wake disorder, just 104 totally blind subjects with the disease were enrolled in the pivotal clinical trials that formed the basis for FDA approval of the orphan drug tasimelteon (Hetlioz).<sup>36,37</sup> A study of all novel drugs and biological products<sup>38</sup> approved from 2005 to 2012 found that the median number of subjects enrolled in the pivotal efficacy trials supporting approval of new orphan drugs was 150, compared to a median of 480 subjects enrolled in trials for all other new drugs.<sup>39</sup> When approvals of new orphan uses are considered in addition to approvals of new orphan drugs, the orphan pivotal trials are even smaller: Among 30 such orphan approvals from 2007 to 2009, half were based on efficacy trials enrolling 75 or fewer subjects, with three-quarters enrolling 158 or fewer subjects, according to a 2010 report by the IOM.<sup>40</sup>

Furthermore, studies that support orphan drug approvals often are not randomized, controlled trials, the gold standard for medical research, which are generally required for non-orphan drugs

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<sup>35</sup> BBK Worldwide. Rare Diseases: Phase I/II Study // Pompe Disease.

[http://www.bbkworldwide.com/experience/pdfs/BBKWorldwide\\_RareDiseases.pdf](http://www.bbkworldwide.com/experience/pdfs/BBKWorldwide_RareDiseases.pdf). Accessed December 4, 2015.

<sup>36</sup> Food and Drug Administration. FDA news release: FDA approves Hetlioz: First treatment for non-24 hour sleep-wake disorder. January 31, 2014. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm384092.htm>. Accessed December 3, 2015.

<sup>37</sup> There were other problematic aspects of tasimelteon's approval, including a) numerous changes to the pivotal clinical trials' primary endpoints, and b) the drug's approval for use in non-totally-blind patients, despite the fact that it was studied specifically for use in totally blind patients with non-24-hour sleep-wake disorder. See, respectively: Public Citizen. Testimony to the FDA Peripheral and Central Nervous Systems Drugs Advisory Committee on Tasimelteon for the Treatment of Blind Persons with Non-24 Hour Sleep Disorder. November 14, 2013. <http://www.citizen.org/documents/2170.pdf>; and Public Citizen. Petition to FDA Concerning the Inappropriately Expanded Approval of the Sleep Drug Tasimelteon (Hetlioz). June 11, 2015. <http://www.citizen.org/documents/2265.pdf>. Both accessed December 4, 2015.

<sup>38</sup> In other words, active ingredients never before approved.

<sup>39</sup> Downing NS, Aminawung JA, Shah ND, et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA*. 2014;311(4):368-377.

<sup>40</sup> IOM (Institute of Medicine). 2010. *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington, DC: The National Academies Press. Appendix B: Kesselheim AS. Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs. <http://www.ncbi.nlm.nih.gov/books/NBK56187/>. Accessed December 4, 2015.

to definitively assess efficacy.<sup>41</sup> The IOM report analyzed the 30 drugs approved for orphan designations from 2007 to 2009 for which full FDA medical officer reviews of the drugs' clinical trial data were available. Of the 55 trials pivotal to the approval decisions of these drugs, one third (18 trials) did not include a prospective control group.<sup>42</sup> A 2009 review of studies of FDA-approved drugs for neurological diseases also found striking differences in the quality of orphan review versus review of other drugs. Only about a third of orphan drugs approved for neurological diseases had been tested in two or more double-blind, randomized controlled trials.<sup>43</sup> By contrast, all drugs approved for non-orphan neurological diseases during the same period had two such trials.

These lower standards of evidence mean many drugs approved to treat orphan indications will have undetected risks and more uncertain effectiveness compared with non-orphan treatments.

*'Orphan' drugs used in much broader populations*

A new study by researchers at Johns Hopkins has documented how an increasing number drug companies are gaming the system by taking advantage of incentives available for orphan drugs to reap blockbuster profits.<sup>44, 45</sup> Currently, seven out of the top 10 projected worldwide bestselling drugs in 2015 have an FDA-approved orphan indication.<sup>46</sup> While much of this profit is due to the high prices of these drugs, many orphan drugs are used in surprisingly large population of patients, well above the 200,000 threshold set by the Orphan Drug Act.

Current federal regulations are meant to prevent this type of abuse in various ways, including by only allowing orphan drug designations for distinct subsets of more common diseases if the drug cannot be used in a broader population of patients with the same disease.<sup>47</sup> This is intended to prevent a company from artificially dividing common diseases into smaller "orphan subsets," a practice sometimes referred to as salami slicing.

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<sup>41</sup> Food and Drug Administration. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf>. Accessed December 4, 2015.

<sup>42</sup> IOM (Institute of Medicine). 2010. *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington, DC: The National Academies Press. Appendix B: Kesselheim AS. Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs.

<http://www.ncbi.nlm.nih.gov/books/NBK56187/>. Accessed December 4, 2015.

<sup>43</sup> Mitumoto J, Dorsey ER, Beck CA, et al. Pivotal studies of orphan drugs approved for neurological diseases. *Ann Neurol*. 2009;66(2):184-190.

<sup>44</sup> Gusovsky D. How a blockbuster drug can become a subsidized 'orphan.' CNBC. December 2, 2015.

<http://www.cnbc.com/2015/12/01/an-obscure-fda-rule-adding-to-drug-company-profits.html>. Accessed December 3, 2015.

<sup>45</sup> Daniel MG, Pawlik TM, Fader AN, et al. The Orphan Drug Act: Restoring the mission to rare diseases. *Am J Clin Oncol*. November 17, 2015. [Epub ahead of print]

<sup>46</sup> *Ibid*.

<sup>47</sup> An orphan designation may be granted for a subset of a larger population only if "due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug 21 CFR 316.20(b)(6). <http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=91b7be5e87481538e33a4c0a76ba7183&rgn=div8&view=text&node=21:5.0.1.1.6.3.1.1&idno=21>. Accessed December 4, 2015.

Yet the Johns Hopkins researchers describe how supposedly “orphan” cancer treatments have ultimately treated populations far larger than the 200,000-patient threshold enacted in the Orphan Drug Act.<sup>48</sup> This has been done through, among other means, multiple sequential approvals for rare cancers. The Johns Hopkins researchers also noted that an increasing number of cancer drugs are being developed to treat only patients with both genetic- and organ-based subtypes of common cancers, thus allowing cancer drugs to account for an ever-increasing proportion of orphan approvals.

In addition to cancer drugs, pediatric subgroups of common adult diseases are a second source of potential abuse, as these drugs generally qualify for orphan status even if they are also safe and effective in a much broader population of adults. Orphan designations therefore can be granted to drugs for any disease with fewer than 200,000 pediatric patients.<sup>49</sup> Given that, for any chronic health condition, there are almost invariably fewer than 200,000 pediatric patients,<sup>50</sup> this exception makes orphan designations possible for a wide range of drugs that treat common diseases.<sup>51</sup>

Certain drugs approved after receiving an “orphan” designation are simply not true orphans at all. Levodopa-carbidopa (Rytary) was granted an orphan drug approval in 2015.<sup>52</sup> While initially

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<sup>48</sup> Daniel MG, Pawlik TM, Fader AN, et al. The Orphan Drug Act: Restoring the mission to rare diseases. *Am J Clin Oncol*. November 17, 2015. [Epub ahead of print]

<sup>49</sup> Personal communication, on October 20, 2015, with Debra Lewis and Henry Startznan, officials in the Food and Drug Administration’s Office of Orphan Products Development.

<sup>50</sup> The total population of children in the U.S. is 74 million. (Source: [Childstats.gov](http://www.childstats.gov). POP1 Child Population: Number of Children (in millions) Ages 0-17 in the United States by Age.

<http://www.childstats.gov/americaschildren/tables/pop1.asp>. See 2015 figure) To reach the 200,000 patient threshold, the prevalence of a condition would have to be above 0.3 percent among children. Only a few very common conditions exceed this 0.3 percent threshold. Rezaee ME, Pollock M. Multiple chronic conditions among outpatient pediatric patients, southeastern Michigan, 2008-2013. *Prev Chronic Dis*. 2015;12:E18.

<sup>51</sup> Another concern for pediatric drugs is that drugmakers already receive a six-month extension of the market monopoly for a drug for conducting a study in pediatric subjects in fulfillment of a written request from the FDA. (Food and Drug Administration. Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric “Rule,” and Their Interaction.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm>. Accessed December 4, 2015.) Should the provision on orphan approvals in the House version of the 21st Century Cures Act pass, drugs approved for common diseases that achieve a pediatric orphan designation and approval could potentially be granted an additional six months, essentially double-dipping to receive two large payouts for the price of one approval. However, it is as yet unclear whether the new six-month exclusivity provision would apply to approvals of orphan drugs for pediatric indications. (Personal communication, on October 20, 2015, with Debra Lewis and Henry Startznan, officials in the Food and Drug Administration’s Office of Orphan Products Development, who indicated that their policy was based on that followed for Humanitarian Use Device (HUD) designations for rare diseases: Food and Drug Administration. Guidance for Industry and Food and Drug Administration Staff: Humanitarian Use Device (HUD) Designations. January 24, 2013.

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336515.pdf>. Accessed December 3, 2015.)

<sup>52</sup> Food and Drug Administration. Letter of approval, levodopa-carbidopa (Rytary). January 2015.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2015/203312Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/203312Orig1s000ltr.pdf). Accessed December 3, 2015.

designated as an orphan drug intended to treat only advanced Parkinson's disease,<sup>53</sup> the drug was eventually approved for all patients with Parkinson's,<sup>54</sup> a disease that affects up to 1 million people in the U.S.<sup>55</sup> A second drug, droxidopa (Northera), was granted an orphan designation<sup>56</sup> and subsequently approved to treat low blood pressure upon standing when caused by several nervous system disorders, including in Parkinson's disease patients and several other patient populations.<sup>57</sup> However, up to one-half of the estimated 1 million American patients with Parkinson's disease and 10-30 percent of people 65 years of age and older display symptoms consistent with droxidopa's approved orphan use,<sup>58</sup> meaning that the drug can potentially be used in an enormous population.<sup>59,60</sup>

A third drug, tasimelteon, was granted an orphan drug designation<sup>61</sup> and, in 2014, approved for the treatment of non-24-hour sleep-wake disorder.<sup>62</sup> The FDA ended up expanding the drug's

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<sup>53</sup> Food and Drug Administration. Orphan Drug Designations and Approvals. Levodopa and carbidopa (Rytary). [http://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD\\_Results\\_2.cfm?Index\\_Number=129499](http://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD_Results_2.cfm?Index_Number=129499). Accessed December 4, 2015.

<sup>54</sup> Food and Drug Administration. Letter of approval, levodopa-carbidopa (Rytary). January 2015. [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2015/203312Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2015/203312Orig1s000ltr.pdf). Accessed December 3, 2015.

<sup>55</sup> Impax. Press release: Impax Pharmaceuticals announce FDA approval of RYTARY™ (Carbidopa and Levodopa) extended-release capsules for the treatment of Parkinson's disease. January 8, 2015.

<http://investors.impaxlabs.com/Media-Center/Press-Releases/Press-Release-Details/2015/Impax-Pharmaceuticals-Announce-FDA-Approval-of-RYTARY-Carbidopa-and-Levodopa-Extended-Release-Capsules-for-the-Treatment-of-Parkinsons-disease/default.aspx>. Accessed December 3, 2015.

<sup>56</sup> Food and Drug Administration. Orphan Drug Designations and Approvals. Droxidopa (Northera). [http://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD\\_Results\\_2.cfm?Index\\_Number=229506](http://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD_Results_2.cfm?Index_Number=229506). Accessed December 4, 2015.

<sup>57</sup> Food and Drug Administration. Letter of approval, droxidopa (Northera). February 2014. [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2014/203202Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/203202Orig1s000ltr.pdf). Accessed December 3, 2015.

<sup>58</sup> Low PA. Prevalence of orthostatic hypotension. *Clin Auton Res*. 2008;18 Suppl 1:8-13.

<sup>59</sup> Some of these patients will display symptoms of low blood pressure that are not caused by Parkinson's disease or other neurological conditions listed in the labeling, and use of the drug in these patients would therefore be off-label. For example, a number of elderly patients may have drug-induced orthostatic hypotension symptoms, which is not covered in the label. Nevertheless, distinguishing between drug-induced and neurogenic causes of orthostatic hypotension can often be difficult, making such off-label use highly likely.

<sup>60</sup> Notably, both the FDA's medical reviewer and the director of the agency's Division of Cardiovascular and Renal Products opposed droxidopa's approval, with the latter noting that "the evidence supporting any effect is poor, and the nominal effect seen is not clinically relevant." In a comment revealing the often lower standards required for orphan drug approvals, the division director went on to note: "If one were to decide that the evidence of effectiveness needs not be good in the setting of an orphan disease and that [it] does not matter if the effects of treatment will be overwhelmed by waxing and waning of disease symptoms, the product should then be approved... with labeling that describes the observed effect size and durability." Apparently, the agency did indeed decide that the evidence for the drug's effectiveness needed "not be good" to warrant an orphan drug approval. (Food and Drug Administration, Division of Cardio-Renal Drug Products. Divisional Memo by Dr. Norman Stockbridge, on NDA 203202 Droxidopa (Northera) for symptomatic treatment of neurogenic orthostatic hypotension. [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2014/203202Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203202Orig1s000MedR.pdf). Accessed December 4, 2015.)

<sup>61</sup> Food and Drug Administration. Orphan Drug Designations and Approvals: Tasimelteon (Hetlioz). [http://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD\\_Results\\_2.cfm?Index\\_Number=297409](http://www.accessdata.fda.gov/scripts/opdlisting/oop/OOPD_Results_2.cfm?Index_Number=297409). Accessed December 4, 2015.

approved indication to patients who are not blind, even though the relevant clinical trials were conducted only in totally blind patients with non-24-hour sleep-wake disorder.<sup>63</sup> This expansion of the indication to the nonblind increased the number of people who might qualify for the drug. Although the increase in this case may not be as large as in the previous two examples, non-24-hour sleep-wake disorder is currently not a very well defined condition and could thus potentially encompass a much larger non-totally-blind patient population in the future.<sup>64</sup>

Widespread off-label use is another way in which orphan drugs have proliferated far beyond a population of 200,000 people. The orphan approval system functions within a regulatory environment with virtually no oversight over how drugs actually are used following approval. This allows a drug approved based on minimal evidence to treat a relatively rare condition to be used off-label to treat a more common one. Off-label use of drugs in general is widespread, and orphan drugs have not been immune to this phenomenon. A study of four of the top-selling drugs in 2009, which had initially been approved as orphan drugs, found that two of the four were used mostly for off-label indications.<sup>65</sup>

The makers of some orphan drugs have been responsible for encouraging this off-label use through illegal marketing campaigns. According to *The Seattle Times*, from 2005 to 2013, there were at least 13 settlements between drugmakers and the federal government over the unlawful marketing of orphan drugs, including off-label marketing.<sup>66</sup>

## Conclusion

By any measure, the current orphan drug approval system is hardly in need of a stimulus, as companies are pursuing, and achieving, orphan drug approvals at record rates. The new 6-month orphan exclusivity provision proposed in the 21<sup>st</sup> Century Cures Act would result in higher drug prices for both orphan and non-orphan diseases: Conservatively, the provision would cost the public close to \$4 billion, but given the structure of the financial incentive, the cost could easily approach \$12 billion. The new incentive would further distort existing incentives by encouraging pharmaceutical companies to spend money repurposing old drugs, rather than investing in truly innovative new drug development. And it encourages more investment in a flawed system that effectively lowers FDA standards for approval and allows for considerable abuse. Worst of all,

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<sup>62</sup> Food and Drug Administration. Letter of approval, tasimelteon (Hetlioz). January 2014. [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2014/205677Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205677Orig1s000ltr.pdf). Accessed December 3, 2015.

<sup>63</sup> Public Citizen. Petition to FDA Concerning the Inappropriately Expanded Approval of the Sleep Drug Tasimelteon (Hetlioz). June 11, 2015. <http://www.citizen.org/hrg2265>. Accessed December 4, 2015.

<sup>64</sup> Another problem with this orphan approval is that it was granted despite the fact that the primary endpoint in the (very small) pivotal Phase III clinical trials had changed numerous times during the course of the trial and the FDA never ultimately signed off on the final primary endpoint used to support approval. Source: Public Citizen. Testimony to the FDA Peripheral and Central Nervous Systems Drugs Advisory Committee on Tasimelteon for the Treatment of Blind Persons with Non-24 Hour Sleep Disorder. November 14, 2013. <http://www.citizen.org/documents/2170.pdf>. Accessed December 4, 2015.

<sup>65</sup> Kesselheim AS, Myers JA, Solomon DH, et al. The prevalence and cost of unapproved uses of top-selling orphan drugs. *PLoS One*. 2012;7(2):e31894.

<sup>66</sup> Armstrong K, Berens JM. How a drug for few patients was turned into \$81 million in sales. *The Seattle Times*. November 16, 2013. <http://apps.seattletimes.com/reports/pharma-windfall/2013/nov/9/seattle-biotech-orphan-drug/>. Accessed December 4, 2015.

the costs of the new incentive would fall not only on taxpayers but also on the backs of patients with common, non-orphan diseases, who will be denied potentially life-saving, affordable generic medicines for six additional months.

The provision on orphan drug approvals is emblematic of the false hope offered more broadly by the 21<sup>st</sup> Century Cures legislation, which would eviscerate current FDA standards for the approval of drugs and devices, handing the pharmaceutical and device industries even greater profits at the expense of patients.



## Appendix 1. Methodology

### *Cost estimate for currently approved drugs (approximately \$4 billion)*

We began with U.S. sales for the 50 best-selling pharmaceutical products from April 2014 to March 2015.<sup>67</sup>

From these top 50, we examined likely dates of expiration of exclusivity protections for each product, relying on information gathered from the FDA Orange Book and industry press. In doing so, we accounted for, to the extent possible, several factors, including:

- 1) complexities in patent landscapes that can result in generic or biosimilar competition even before patents for an originator product listed in the FDA Orange Book expire;
- 2) current and future patent litigation brought by generic or biosimilar makers contesting originators' patents, which is especially likely for high-earning products that offer the greatest reward for a successful lawsuit; and
- 3) pay-for-delay deals in which generic or biosimilar makers agree to keep generics or biosimilars off the market in exchange for payments from originator companies.

After determining the most likely current exclusivity expiration date, we eliminated from our cost analysis any products with likely patent or exclusivity expirations that fell outside of the 2016-2025 range under consideration, leaving 32 products to consider in our calculation.

To calculate the costs of extending the monopoly period by six months, we assumed that the six months of additional exclusivity would yield sales at the same rate as reflected in the products' recent sales. For small-molecule drugs, we assumed savings lost by delaying generic competition to be 80 percent of brand-name sales for the six-month period. We assumed that savings lost by delaying competition for biological products would be only 30 percent of brand-name sales because of different rules for substitution and other challenges unique to biologic drugs that act as barriers to market entry for these treatments.

### *Cost estimate for future blockbuster approvals (approximately \$8 billion)*

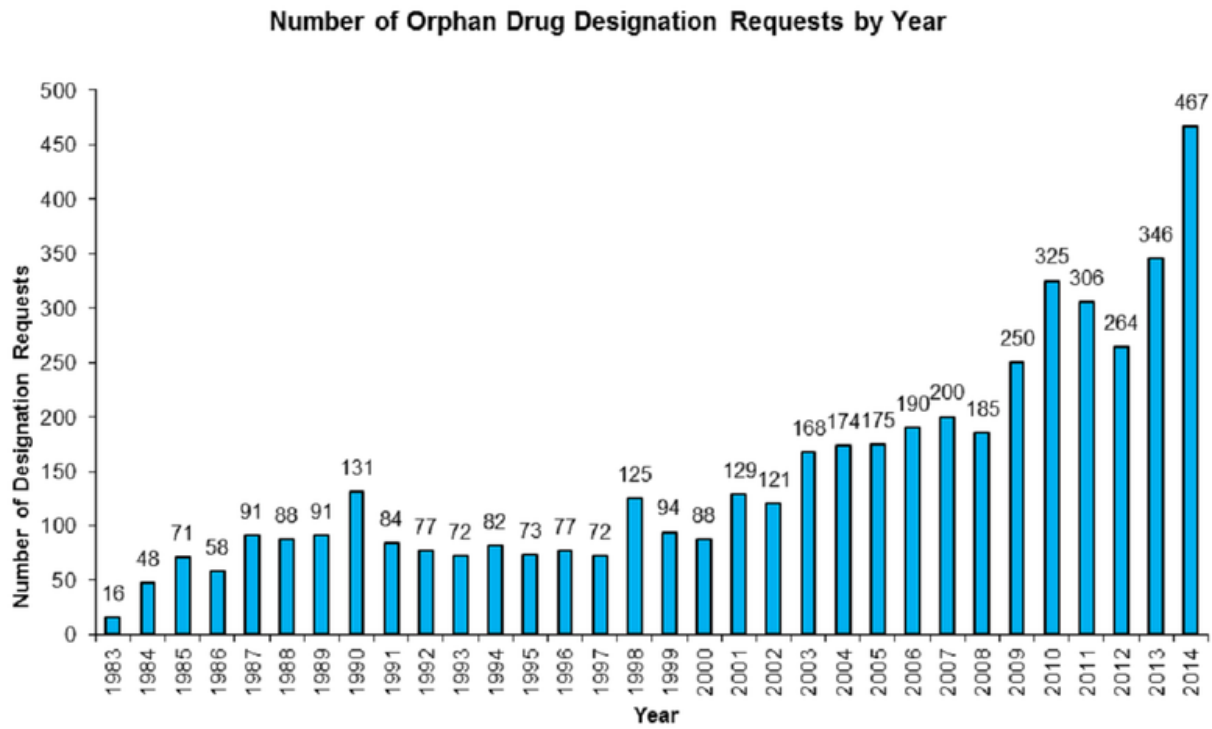
We estimated that the cost of the provision would amount to \$768 million for each additional blockbuster drug approved for an orphan indication. This represents a mean of the six months' savings predicted from generic and biosimilar competition for the 66 drugs that earned more than \$1 billion in the one-year period (the generally accepted definition of what constitutes a blockbuster) from April 2014 to March 2015. Thus, an average of one additional blockbuster drug for which a new orphan indication is approved each year over the next 10 years as a result of this provision would increase costs to the public by \$7.7 billion.

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<sup>67</sup> Brown T. 100 Best-Selling, Most prescribed branded drugs through March. Medscape Medical News. May 6, 2015. <http://www.medscape.com/viewarticle/844317>. Accessed December 4, 2015.

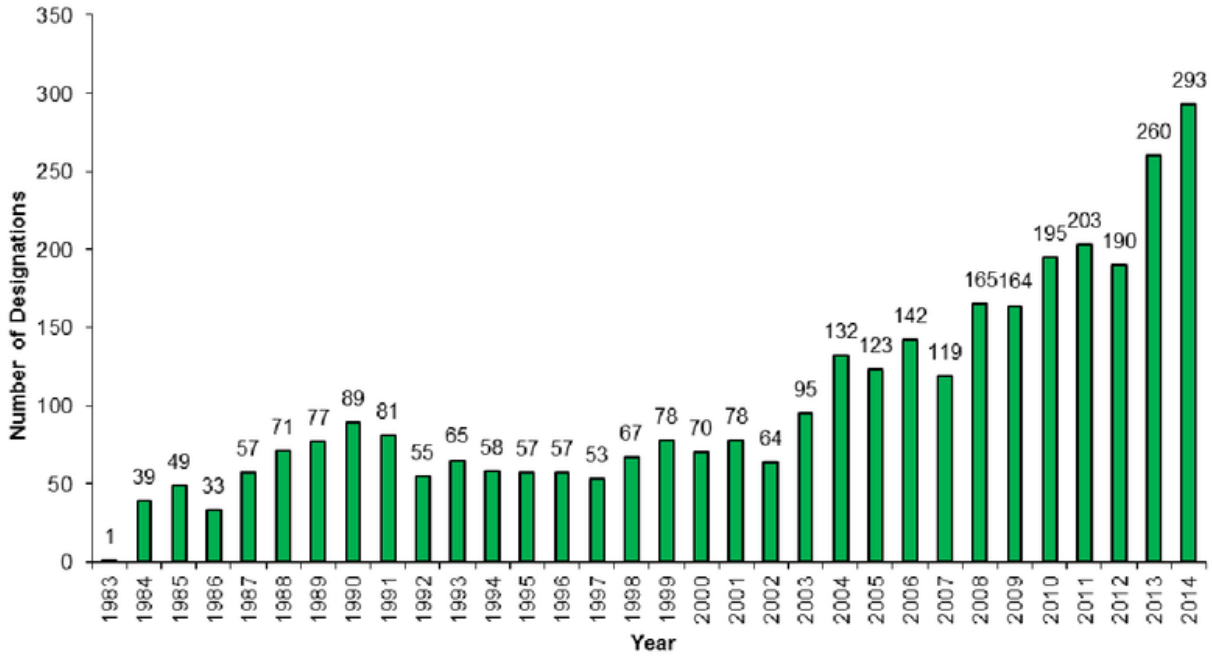


## Appendix 2. Orphan Drug Designation Requests, Designations, and Approvals Per Year (reproduced with permission from the FDA Law Blog).<sup>68</sup>



<sup>68</sup> Karst KR. The 2014 numbers are in: FDA's orphan drug program shatters records. FDA Law Blog. February 15, 2015. [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records.html). Accessed December 4, 2015.

Number of Orphan Designations by Year



Number of Approved Orphan Products by Year

