ORPHAN DRUGS IN THE UNITED STATES:

An Examination of Patents and Orphan Drug Exclusivity

A NORD® Commissioned Report with Avalere®

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EXECUTIVE SUMMARY

Overview

- In the United States, rare diseases are those that affect patient populations of fewer than 200,000 per disease.
- Today, 30 million Americans live with around 7,000 different rare diseases. There remains an unmet need for patients with rare diseases, as only about 5% of rare diseases have an FDA-approved treatment.
- The Orphan Drug Act (1983) incentivizes drug development in the rare disease space by offering grants, tax credits for clinical trial costs, waiving fees, and providing a 7-year regulatory exclusivity period to incentivize sponsors to develop "orphan drugs" for rare diseases.
- The Hatch-Waxman Act, also known as the Drug Price Competition and Patent Term Restoration Act (1984), inaugurated the modern generic industry by providing an Abbreviated New Drug Application (ANDA) pathway and a 5-year new chemical entity exclusivity period to reference listed drug sponsors, as well as restoring patent time lost during FDA review for both drugs and biologics.
- The Biologics Price Competition and Innovation Act (2010) introduced the biosimilars pathway to the biological product space, and a 12-year Reference Product exclusivity period to originator sponsors, but no further changes were made for patent restoration. The Purple Book Continuity Act of 2020, once implemented by FDA, will provide the public with a complete picture of the intellectual property landscape for a given biological product.
- Patents grant inventors a right to exclude others from making or using their invention for 20 years from the date of filing under the America Invents Act (2011). In certain circumstances (i.e., under a patent settlement agreement), generics or biosimilars may be marketed before this period expires

Findings

- With 552 drugs and biologics on the market having an orphan designation, 394 products enjoyed some form of patent or orphan exclusivity protection. Of the remaining 158 products, which had no protection as of December 1, 2020, generics are on the market for 81 products (51%).
- Four hundred forty-five (75%) of orphan products have one orphan indication and are not approved for anything else. As sponsors and clinicians learn more about drugs and biological pathways, they may discover that a treatment has clinical efficacy for conditions not initially studied, or for which they otherwise lacked substantial evidence at launch. Thirty-seven (7%) orphan products were first approved to treat a prevalent/common condition and later earned orphan indication(s); 154 were first approved to treat a rare disease and later earned one or more additional orphan indications; still only 64 (10%) orphan products have three or more orphan indications.
- For 125 of the 552 orphan products, the patent life exceeds the term of orphan drug exclusivity. In only 61 of the 552 products, does the orphan drug exclusivity exceed the patent life.

BACKGROUND

Untreated Rare Diseases Prompt the Passage of the Orphan Drug Act

About 7,000 rare diseases affect approximately 30 million Americans, and only about 5% of rare diseases have treatments approved by the FDA.[1] A rare disease is defined in statute as one which affects fewer than 200,000 Americans.[2] Prior to 1983, patients with rare diseases had few treatment options, or none at all. Given the costs involved for the research and development necessary to meet the safety and efficacy standards for FDA approval,[3] industry efforts were overwhelmingly focused on prevalent diseases. Drugs for the small patient populations in rare diseases were deemed to be too risky and likely to have resulted in a commercial loss.[4]

The Orphan Drug Act (ODA) of 1983[5] was enacted to provide treatment options for rare diseases by stimulating the development of so-called "orphan drugs."[6] Before ODA, industry focused on recouping its substantial investment into drug development: to maximize revenue, they would frequently look to candidates which could treat the largest numbers of patients at an accessible price and, thus, generate a viable return on investment.

In the 97th Congress, the leadership of Congressman Henry Waxman helped pass the ODA, which provides drug sponsors with a series of incentives for developing drugs for rare diseases or conditions.[7] ODA empowers the FDA, through the Office of Orphan Products Development (OOPD),[8] to designate drugs for rare diseases as "orphan" if they: (1) affect less than 200,000 Americans, or (2) are for diseases that affect more than 200,000 Americans, but only if there is no reasonable expectation that the sponsor would recover its research and development costs.[9]

Once a drug is designated as an orphan, the sponsor is entitled to several benefits under ODA. To help offset the cost of research and development, ODA provides for tax credits equal to 25% of development costs; in addition, it provides for clinical research subsidies and grants for drug development.[10] Most significantly, when the drug (or subsequent indication, if the product is already FDA-approved) is approved, ODA provides the sponsor with seven years of market exclusivity, during which the FDA will not approve[11] or license[12] another application for a generic drug or biosimilar for the same indication. Further, FDA waives user fees required for orphan drug application examination, which would otherwise be required under the Prescription

1 National Institutes of Health (NIH), Rare Disease Day at NIH (last updated 10 December 2020).
2 21 U.S.C. §360bb(a)(2) (2020); interestingly, Europe defines it somewhat differently, as being prevalent in 5 persons in 10,000, or less; *see* Official Journal of the European Communities, *Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan medicinal products*, at Art. 3.1(a).
3 21 U.S.C. §355(b)(1) (2020).
4 *See, e.g.*, Department of Health and Human Services, Office of Inspector General, *The Orphan Drug Act – Implementation and Impact* (2001), at 1.
5 Public Law 97-414 (1983), 96 Stat. 2049, codified at 21 U.S.C. §§ 360aa-360ee (2020).
6 Public Law 97-414 (1983), at §1(b)(3); throughout the paper, we refer to drugs and biological products with orphan indications by the collective term "orphan drugs."
7 21 U.S.C. §360bb(a)(1) (2020).
8 *See generally* FDA, Office of Orphan Products Development (2019).
9 21 U.S.C. §360bb(a)(2) (2020) (The second route of designation has been done only rarely with only 3 such designations as of December 2019; *see* IQVIA Institute for Human Data Science, Orphan Drugs in the United States – Rare Disease Innovation and Cost Trends through 2019 (2020), at 3).
10 *See, e.g.*, 21 U.S.C. §3600ee (2020).
11 A drug under Section 505(b) of the Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. §355).
12 A biologic under Section 262(a) of the Public Health Service (PHS) Act (42 U.S.C. §262).

Drug User Fee Act (PDUFA).[13] Significantly, however, ODA does not change the Food, Drug, and Cosmetic (FD&C) Act and Public Health Service (PHS) Act requirements of safety and efficacy (in the case of small-molecule drugs) or safety, purity, and potency (in the case of biological products).

Prior to 1983, only 38 orphan drugs had been approved by FDA.[14] By 2002, there were over 230 orphan approvals;[15] by 2014, the number of indications reached 468, covering 373 drug products; [16] and, at the end of 2019, orphan indications reached 838 for 564 distinct drugs.[17] ODA has been and continues to be a success, and has inspired similar legislation in other countries.[18] In 1993, Japan adopted similar measures, conferring 10 years' regulatory exclusivity to orphan drugs; in 1997, Australia followed suit with a 5-year exclusivity regulation; and the European Union looked to ODA as the model for their 2000 regulation which, like Japan, conferred 10 years' exclusivity.[19] America led the way in this effort, the highly regulated markets of the world followed suit, and now, generations of those living with rare diseases have hope that they will not be forgotten in the quest for cures and treatments for their ailments.

The Hatch-Waxman Act Ushers in the Modern Generics Industry

Another success for American patients came in the form of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly called the Hatch-Waxman Act.[20] The Hatch-Waxman Act amended the FD&C Act by creating "abbreviated pathways for the approval of drug products"[21] through the submission of an Abbreviated new drug application (ANDA).[22]

The Hatch-Waxman Act provides a pathway for generic drug sponsors to produce therapeutically equivalent, meaning both chemically identical (pharmaceutically equivalent)[23] and clinically equivalent (bioequivalent), copies of an originator reference listed drug (RLD)[24] by codifying the ANDA application process and mitigating the need for unnecessary and consequently unethical human clinical trials.[25] Prior to this, FDA only applied ANDA as policy and then only to drugs approved before 1962.[26] The Hatch-Waxman Act provided originator sponsors with a 5- year term of regulatory new chemical entity exclusivity from the date of approval, imposing a moratorium on FDA approving any ANDA for that time.[27] The Hatch-Waxman Act further requires generic companies

13 21 U.S.C. §379h(a)(1)(F) (2020), "unless the human drug application includes an indication for other than a rare disease or condition."
14 EvaluatePharma, *Orphan Drug Report* 2014, at 3.
15 Swann J., FDA, *The Story Behind the Orphan Drug Act* (2018).
16 EvaluatePharma, *Orphan Drug Report* 2014, at 3.
17 IQVIA, Orphan Drugs in the United States 2020, at 4.
18 *See, e.g.*, Department of Health and Human Services, Office of Inspector General, *The Orphan Drug Act – Implementation and Impact* (2001), at 13.
19 Institute of Medicine of the National Academies, *Rare Diseases and Orphan Products* (2010), at 30.
20 Public Law 98-417 (1984), 98 Stat. 1585, codified at 21 U.S.C. §§ 355, 360cc (named for Senator Orrin Hatch (R-UT) and Congressman Henry Waxman (D-CA)).
21 *See, e.g.*, FDA, *Implementation of the Biologics Price Competition and Innovation Act of 2009* (last visited 11 December 2020).
22 *See* 21 U.S.C. §355(j) (2020); often referred to as FD&C Section 505(j).
23 21 U.S.C. §355(j)(8)(B) (2020).
24 *See, e.g.*, FDA, Drugs@FDA Glossary of Terms, (last accessed 11 December 2020).
25 Congressional Record, Proceedings and Debates of the 98th Congress, H.R. 3605 (19 July 1983) (Henry A. Waxman: "The generic manufacturer need not conduct human clinical trials. Such retesting is unnecessary and wasteful because FDA has already determined that the drug is safe and effective. In fact, such retesting may be unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.").
26 *Id*.
27 21 U.S.C. §355(c)(3)(E)(ii) (2020).

to submit how their small molecule drug relates to patents to the RLD, which are submitted by the RLD sponsor and listed in the Orange Book, a repository database of new drug applications (NDAs) and related data.[28] And the first generic to market sometimes[29] enjoys a 180-day exclusivity period,[30] during which time the FDA will not approve a subsequent generic. According to an FDA study, subsequent entrants rapidly infuse robust competition into the market, driving down the cost of prescription drugs – up to a 95% price reduction when there are 6 or more competitors.[31]

The Affordable Care Act Creates the Biosimilar Pathway through BPCIA

The Hatch-Waxman Act laid the groundwork for another landmark in healthcare legislation, this time in the biological product space. A biological product[32] is inherently more complex than a small-molecule, chemical drug, and is regulated under the PHS Act, further subsuming the safety and efficacy requirements of the FD&C Act. By 2007, Americans spent $286.5 billion on all prescription drugs, and 14% of that, or $40.3 billion, was spent on biologics.[33] Title VII of the Patient Protection and Affordable Care Act (ACA) of 2010, the Biologics Price Competition and Innovation Act (BPCIA), created an abbreviated pathway for biologic products which are biosimilar, or clinically equivalent, to a reference product.[34] The BPCIA sought to encourage access and affordability for biologics in the same way Hatch-Waxman had done for generics by encouraging competition amongst drug manufacturers[35] through an abbreviated development and approval pathway for products demonstrated to be "biosimilar"[36] to or "interchangeable"[37] with an FDA-approved reference biologic product.[38]

The BPCIA requires biosimilar sponsors to demonstrate that there are no clinically meaningful differences in safety, purity, and potency between the biosimilar and the reference product, through generating and submitting preclinical and clinical data from at least one human study, albeit these studies are waivable at FDA's discretion.[39] FDA further requires biosimilar sponsors to

28 *See generally* FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (last visited 11 December 2020); *see* 21 U.S.C. §355(j)(2)(A)(vii) (2020) (where there are active patents listed in the Orange Book for an RLD, a generic sponsor typically will submit either a paragraph (III) declaration [that the generic sponsor will not market or sell the drug in interstate commerce until the patents have expired], or a paragraph (IV) declaration [that the generic sponsor believes such patent is invalid or would not be infringed by the generic drug, which may lead to patent litigation]).

29 If such generic ANDA contains a paragraph (IV) certification: *see Id*.

30 21 U.S.C. §355(j)(5)(B)(iv) (2020).

31 Conrad R and Lutter R, FDA, Report, *Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices* (2019), at 3.

32 42 U.S.C. §262(i)(1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. (2020).

33 Federal Trade Commission, Report, *Emerging Healthcare Issues: Follow-on Biologic Drug Competition* (2009), at 3.

34 42 U.S.C. §262(k); often referred to as PHS Act Section 351(k).

35 *See, e.g.*, Darrow J, Health Affairs Blog, *Biosimilar Approvals and the BPCIA: Too Soon to Give Up* (19 July 2019).

36 42 U.S.C. §262(i)(2) (2020) ("that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.").

37 42 U.S.C. §262(i)(3) (2020) ("in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." further subject to state law). As of the time of this writing, there are no FDA approved interchangeable products; for the sake of brevity, we do not discuss interchangeable products further. *See* McCamish M, et al., 97 Clin. Pharmacol. Ther., 215-17 *Toward interchangeable biologics* (2015).

38 42 U.S.C. §262(i)(4) (2020) ("means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)").

39 *See* 42 U.S.C. §262(k)(2)(A)(i)(I) (2020); *see also* 42 U.S.C. §262(k)(2)(A)(ii) (2020).

include in their applications, a demonstration that their products utilize the same mechanism of action, same conditions of use, same route of administration, dosage, strength as the reference product, manufactured in a facility that meets standards to ensure safety, purity, and potency.[40] In the same spirit as the Hatch-Waxman new chemical entity exclusivity, the BPCIA also affords reference biologic sponsors an exclusivity period (12 years) during which FDA will not approve a biosimilar application.[41] Significantly, the BPCIA provides a mechanism for patent information exchange in those situations when a biosimilar sponsor would potentially seek licensure for a product, and the sale in interstate commerce could infringe on the intellectual property (IP) of the reference sponsor[42] – the so-called "patent dance."[43] While discretionary for the biosimilar applicant,[44] this provides a litigative way forward in both the rare and prevalent disease contexts, as intellectual property rights have become a crucial inflection point for biosimilar launch and successful commercialization. Some of the same trends have begun to take shape in the generic drug space, too, as small molecule drug sponsors begin to file subsequent patents on their active moieties, further confounding generic entry.

Intellectual Property

Codified in the US Constitution,[45] and in the Patent Statute at Title 35, US Code, as amended by the Leahy-Smith America Invents Act (AIA, 2011),[46] a patent secures for an inventor a 20-year right to exclude others from using the inventor's new and useful,[47] novel,[48] non-obvious[49] invention, running from the date of filing and effective on the date of approval.[50] This is distinct from regulatory exclusivity discussed above. A patent holder's right to exclude is the right of the inventor – here, ultimately, the reference product sponsor – to prevent others from making or using, or introducing into commerce, their invention, while the regulatory exclusivity is explicitly binding on FDA. An application for a generic or biosimilar (or indication therin) cannot be approved by FDA until the exclusivity has expired. These terms run parallel with one another in practice, but the expiration of one has no bearing on the expiration of another.

For the purposes of generic drug sponsors, the path is clearly laid out for them: a generic sponsor consults the Orange Book for their active moiety and associated NDA of interest, and sees the regulatory exclusivity *and* patent exclusivity expiration dates, as well as all patents the reference sponsor asserts would protect their

40 *See* 42 U.S.C. §262(k)(2)(A)(i)(II)-(V) (2020) (the FDA's interpretation of "strength" [at IV] has come under recent scrutiny, with Boehringer Ingelheim's Citizen Petition of 2 December 2020 challenging the prevailing interpretation).
41 *See* 42 U.S.C. §262(k)(7)(A) (2020). *See also* §262(k)(7)(B), which establishes a separate 4-year exclusivity period, during which a biosimilar sponsor cannot even submit an application for FDA review.
42 *See, e.g.*, Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664 (US 2017) (Justice Clarence Thomas provides a masterful procedural explanation of §262(l) at 1670-72).
43 *See, e.g.*, Winston & Strawn LLP, *What Is the Patent Dance?* (last visited 11 December 2020).
44 *See* Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664, at 1669 (US 2017) ("We conclude that an applicant may provide notice before obtaining a license.").
45 U.S. Const., art. I, § 8, cl. 8 (An enumerated power to Congress, "To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries.")
46 Pub Law 112-29 (2011), 125 Stat. 284.
47 35 U.S.C. §101 (2020).
48 35 U.S.C. §102 (2020).
49 35 U.S.C. §103 (2020).
50 35 U.S.C. §154(a)(2) (2020).

product from use and sale by others. The generic sponsor must wait for the regulatory exclusivity to expire before obtaining FDA approval per se. But with patents, what often happens is the generic sponsor will either wait patiently to launch,[51] or assert the patent(s) is (are) invalid, unenforceable, or would not be infringed – being fully prepared to litigate the matter in court, if necessary.[52] For biologics, on the other hand, it is a it is a complex and different situation. Until the recent enactment of the Consolidated Appropriations Act of 2021 on December 21, 2020, the Purple Book,[53] a searchable database of approved biologics and approved biosimilars, provided far less information, limited to the reference product label, approval date, date of first licensure, biologics license application (BLA) number, applicant (sponsor) name, and versions of the product.[54] There was nothing about when exclusivity would expire and, more significantly, nothing about when the patents expire, or even which patents the reference sponsor would assert against the biosimilar sponsor in any putative litigation.[55] In the future, and with the passage of the Purple Book Continuity Act of 2020,[56] additional information on the patents protecting biologics will be readily available. FDA will be required to codify in the Purple Book all regulatory exclusivities for biological products, as well as publish biological product patents disclosed in the course of the PHS Act Section 351(l) patent dance. This law still must be implemented by the FDA and there are questions remaining about timelines, what the submission process looks like, and whether patents disclosed through the patent dance will provide the public with a complete picture of the intellectual property landscape for a given biological product. Nevertheless, this is a significant legislative step forward towards greater transparency in the biologics space.

PURPOSE OF THIS STUDY

Congressional action has done much to benefit persons living with rare diseases. The ODA incentivizes innovation in the rare disease space, furthering the advancement of science and medicine, and bringing hope to millions of Americans who might otherwise go without safe and effective treatment. Through the Hatch-Waxman Act and BPCIA, Congress helped facilitate the commercialization of therapeutically equivalent alternatives to branded drugs and biological products with a market-based mechanism – competition drives down costs and promotes innovation. Both offer the potential for a big win for patients in terms of more affordable and accessible medicines. This, too, has helped persons living with rare diseases as more are able to access affordable drugs and biological products to treat or manage their conditions.[57]

51 *Supra* note 27.
52 *Id*.
53 *See generally*, FDA, *Purple Book Database of Licensed Biological Products* (last updated 3 December 2020).
54 *E.g.*, dosage form, route of administration, strength, presentation, etc.
55 Hence the creation of the option of the "patent dance" as described above.
56 As part of H.R. 1520 – Further Extension of Continuing Appropriations Act, 2021; Public Law No. 116-246 (2020).
57 *See* NORD, Rare Disease Day: Frequently Asked Questions (2019) ("Of the 7,000 known rare diseases, approximately 95 percent have no treatment").

The National Organization for Rare Disorders (NORD®) commissioned Avalere to compile data surrounding the present-day impact of the Orphan Drug Act and the role of market protections it provides in the form of orphan drug exclusivity (ODE), as well as the impact of corresponding patent protection. Avalere is a leading healthcare consulting firm specializing in strategy, policy and data analysis for life sciences, health plans and providers.

This report also assesses the data regarding the biosimilars and generic drugs associated with such orphan drugs. This report comprehensively assesses the FDA's Orphan Drug Database,[58] Drugs@FDA,[59] the Orange Book, the Purple Book, as well as publicly available patent information. It presents a snapshot in time of all designated orphan drugs and biologics, their orphan indications and exclusivities, all active patents related to RLDs, and an estimate of IP protection for reference biological products. For a more thorough description of our methodology, see the Appendix.

The findings note both the promise realized and the promise yet to be fulfilled in both the orphan drug context and the generic/biosimilar contexts.

DATA AND DISCUSSION

On Orphan Indications

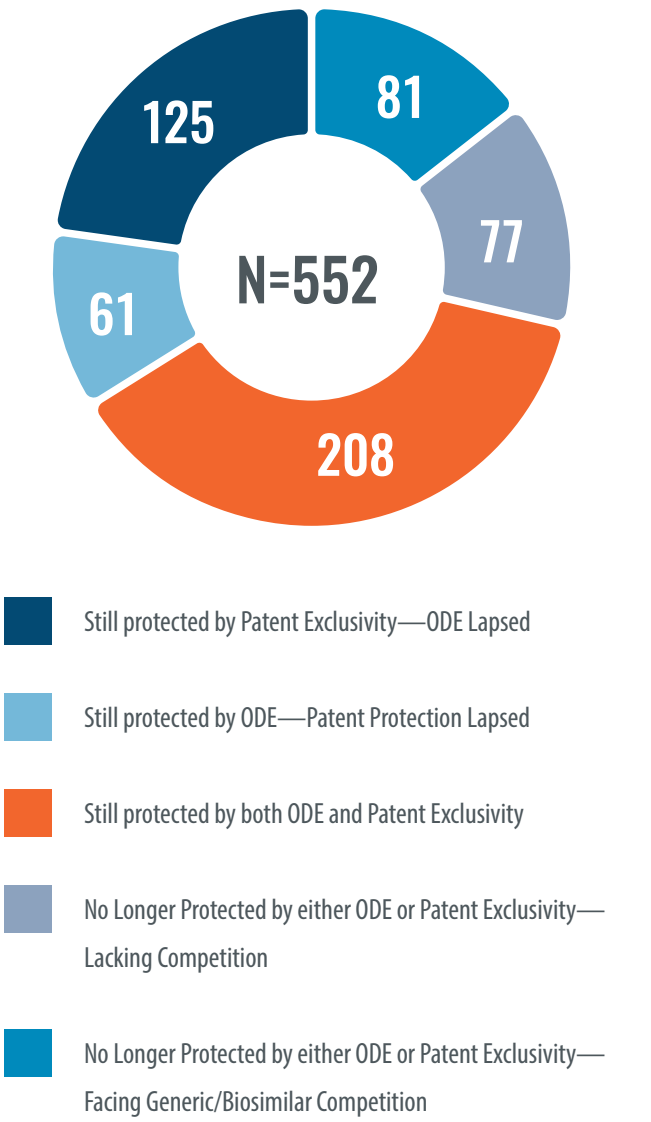
As of July 8, 2020, this study found 599 drug and biological products which have at least one orphan designation, which are or have been FDA-approved at some point in time; of those, 47 have been discontinued, be it for safety and efficacy reasons, or commercial reasons. Among those 599, 413 were small-molecule drugs with associated NDAs, and 186 were biological products having BLAs.

With 552 drugs and biologics on the market having an orphan designation, we found that 394 products enjoyed some form of patent or orphan exclusivity protection. Of the remaining 158 products which had no protection as of December 1, 2020, generics are on the market for 81 products. That is not to say that products that enjoy patent or regulatory exclusivity protections do not have generics per se, but that some products have subsequent orphan indications for which a generic must "carve out" its label to comply with Hatch-Waxman or BPCIA. This means that a generic or biosimilar label must have as its FDA-approved label fewer than the complete number of indications for which the RLD or reference biologic is approved, if the specific indication or indications of the RLD or reference biologic remain protected by some form of exclusivity.[60] In other words, the generic can come to market so long as it doesn't include or "carves out" the protected

58 *See generally*, FDA, *Orphan Drug Product designation database* (last visited 11 December 2020).
59 FDA, *Drugs@FDA* (last visited 16 December 2020).
60 *See* 21 USC §355(j)(2)(A)(viii) ("if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.") (2021); *see also* 21 CFR §314.94(a)(8)(iv) ("[…] Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include […] omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.") (2021).

orphan indication from its label, resulting in what others have called a "skinny label,"[61] a label for which the generic or biosimilar is not indicated – as a regulatory matter – for a particular disorder or patient population; when the particular exclusivity for the RLD or reference biologic expires, the generic or biosimilar sponsor may subsequently expand its label to include the no longer protected indication. Similarly, patent protection does not foreclose generics per se either, as generic or biosimilar manufacturers may, for example, enter a licensing agreement with the innovator company to develop and market a generic, but offer the innovator sponsor contractual consideration for the licensure of the patent(s) until the patent expires. See **Figure 1** for more details.

Figure 1. Patent and Orphan Exclusivity Status of Orphan Designated Drugs



Among the products not discontinued for safety or efficacy reasons, 186 of the active moieties have commercially approved generics or biosimilars: 179 drug products and seven biological products, respectively.[62]

61 *See, e.g.*, Zheng L, Biosimilar Development, *What Is Skinny Labeling – And Will It Work For Biosimilars?* (2019).

62 *See, e.g.*, Christl LA, Woodcock J, and Kozlowski S, *Biosimilars: The US Regulatory Framework*, 68 Annu. Rev. Med. 243-54 (2017); *see also* Leber MB, *Optimizing Use and Addressing Challenges to Uptake of Biosimilars*, 24 Am. J. Manag. Care -S0 (2018); *see also* Woollett G and Jackson J, Avalere Health, *Use of Step Through Policies for Competitive Biologics Among Commercial US Insurers* (2018); *see also* Pyenson B and Woollett G, Biocentury, *Is personalized medicine doomed worldwide if biosimilars fail in the US?* (2019).

As it turns out, the overwhelming majority of the 552 products which have at least one orphan indication were FDA-approved after being designated as an orphan product – only 37 products (27 drugs and 10 biologics) were approved for non-orphan indications initially and further supplemented with an orphan indication after the fact. In other words, the FDA-approved label at a product's launch included – but was not limited to – an orphan indication. For those 37 products that were not initially orphan-designated, this was the result of a subsequent label expansion by sponsors as the result of post-launch clinical testing and supplemental NDA or BLA submission (sNDA or sBLA, respectively).[63]

In addition, we note that 154 products (104 drugs and 50 biologics) were approved as orphan drugs and obtained at least one subsequent orphan indication. This is generally reasonable and expected: as sponsors and clinicians learn more about a drug, they may discover that it has clinical efficacy for conditions that were not initially studied or for which they otherwise lacked substantial evidence at launch. And this is good news for patients with rare diseases, too – for an already-existing product for a prevalent disease that undergoes a label expansion already has a well-developed safety profile and is less of a data lift for sponsors to obtain the subsequent indication. We see this from our analysis of the Orphan Drug Database; see **Table 1.**

Table 1. Many Products Have Multiple Indications, but Only About 10% Have Three or More.

# Orphan Indications	Drugs	Biologics	Total	% of Products
1 Orphan Indication	309	136	445	75%
2 Orphan Indications	67	23	90	15%
3 Orphan Indications	24	14	38	6%
4+ Orphan Indications	13	13	26	4%
Total Orphan Products	**413**	**186**	**599**	**100%**

This has a mixed output on generic and biosimilar entry; see **Table 2** for a sample representation:

Table 2. Orphan Indications and the Presence or Absence of Generics or Biosimilars

Brand name	Nonproprietary name	Drug or Biologic	# Orphan Indications	Generic or Biosimilar?
Avastin	bevacizumab	Biologic	11	Yes – Mvasi and Zirabev
Imbruvica	ibrutinib	Drug	10	No
Gleevec	imatinib	Drug	9	Yes
Revlimid	lenalidomide	Drug	9	Yes (tentative approval)
Humira	adalimumab	Biologic	7	Yes – 6 approved, launching in 2023
Ilaris	canakinumab	Biologic	6	No
Neupogen	filgrastim	Biologic	5	Yes –Zarxio and Nivestym
Velcade	bortezomib	Drug	5	Yes, but not on the market
Afinitor	everolimus	Drug	5	Yes
Arzerra	ofatumumab	Biologic	4	No
Botox	botulinum toxin type A	Biologic	4	No

63 *See* 21 U.S.C. §355(c)(3)(E)(iv) (2020) (This raises yet another exclusivity provision of Hatch-Waxman, the so-called "other" or "change" exclusivity, during which FDA would not approve "an application submitted under subsection (b) for a change approved in the supplement effective before the expiration of three [3] years from the date of the approval of the supplement[.]" this leads to an important point about label expansion as a product life cycle management tool, which we discuss in the main text, but since we discuss it within the Orphan indication context, the "change" exclusivity is not particularly relevant, but worth mention); *see also* 21 U.S.C. §355(c)(5) (2020) (on supplemental applications generally); *see also* 42 U.S.C. §262(a)(2)(E) (2020) (on BLA supplementation, further referencing 21 U.S.C. §355(c)(5)).

What this does mean, however, is that as a reference product obtains new orphan indications, generic and biosimilar sponsors will remain seven years behind in terms of on-label market access for those indications, and will lack complete labels for as long as any orphan exclusivity is applicable to their reference product (meaning pharmacies must stock both the reference product and a generic or biosimilar to cover the needs of all patients). This can impede patient access, but this is arguably within the spirit of the ODA – that the innovator sponsor deserves the benefit of a natural monopoly for discovering that their product can treat a new class of patients. The basic exclusivity on the entire product (five years for drugs and 12 years for biologics) does not change as the result of an additional orphan indication – which itself is limited to that indication alone.

On Patents and Intellectual Property Protections

To date, only 29 biosimilars are approved in the US, and only one-quarter of those are for products having orphan indications.

Table 3 provides a snapshot of the numbers of products having years of patent protection, including, notably, drugs.

Table 3. Many Orphan Products Have Putative Patent Protection Far Beyond the Regulatory Expiration Period or Even a 20-Year Term of Patent

Years of patent protection, from date of product approval	Drugs with active Patent Protection	Biologics with estimated active patent protection	Percentage of all products with orphan indications
Less than 5	4	5	1.5%
5 to 10	15	9	4.0%
10 to 15	55	12	11.2%
15 to 20	93	19	18.7%
More than 20	45	85	21.7%

Notably, more than one in five products have more than 20 years of expected or estimated patent protection.

CONCLUSION

Science has evolved in recent years to provide a great deal of hope for people living with rare diseases in the US that their disease has or will have one or more safe and efficacious treatments. But there remains work to be done. There are still more than 7,000 rare diseases, and over 90% of them do not have an FDA-approved therapy. The need for the ODA remains as strong today as it did in 1983. The collective success of the ODA has become an issue for payers and providers as they consider the net cost of these available therapies.

The Hatch-Waxman Act and BPCIA have enabled a robust generic and emerging biosimilar industry to introduce competition and drive down healthcare dollars spent on drugs and biologics, offering affordable – but no less safe and efficacious – alternatives, increasing access for all, including persons living with rare diseases. The patent statute gives inventors the right to exclude others from making use of their invention, "[t]o promote the progress of science and useful arts,"[64] and incentivizes innovation. Regulatory exclusivity and intellectual property protections are crucial to giving inventors and life science innovator companies legal incentives to invest the massive amount of time, effort, and capital required to bring a drug to market – estimated to be around $1 billion.[65] It is possible to drive both innovation and access for persons living with rare diseases: innovation to bring new treatments and cures to people who can only be treated off-label with what physicians have already available, or worse, no treatment at all; also it is important to maximize access, which can readily be achieved with a robust generic/biosimilar market, so long as Congress clears the way for competition after a reasonable time.

64 US Const., art. I, § 8, cl. 8.
65 *See, e.g.*, Terry M, BioSpace, *The Median Cost of Bringing a Drug to Market is $985 Million, According to New Study* (4 March 2020).

APPENDIX

Selected Glossary

Rare disease – A disease affecting fewer than 200,000 Americans; in the Orphan Drug Act, also includes diseases affecting greater than 200,000 Americans, if there is no reasonable expectation that the sponsor would recover its research and development costs.

Orphan drugs – Drugs designated as being indicated for rare diseases; eligible for beneficial incentives under the Orphan Drug Act.

Reference product – An original drug or biological product for which a new drug application and biologics license application forms the basis of a generic drug or biosimilar.

Carve-outs or **skinny labeling** – Generic or biosimilar sponsor obtaining an FDA approved label which lacks indications or presentations which are exclusive to the reference product.

Methodology

An **Orphan Drug Exclusivity and Patent Database** was generated by using multiple publicly available databases to extract orphan drug exclusivity and patent information between January 1, 1983, and July 8, 2020. The databases included:

1. FDA, Orphan Drug Designations and Approvals Database;
2. Drugs@FDA;
3. FDA Orange Book (small molecule drugs);
4. FDA Purple Book (biological products); and
5. FDA Approval Letters (as needed).

The information from sources 1-4 were downloaded in their entirety, and aligned into a single, unified and harmonized Excel spreadsheet. Products without an approved orphan indication were discarded; orphan indications which were not associated with an approved product were likewise discarded. Entries were manually curated to align all relevant data, including:

1. Proprietary and nonproprietary names;
2. NDA or BLA designation and number;
3. Orphan indication designations and descriptions (as applied for and FDA-approved);
4. Approval date for each orphan indication;
5. Approval date of the associated NDA or BLA;
6. Calculated orphan exclusivity end date;
7. Sponsor name;
8. All patents for small molecule drugs and a biologic patent exclusivity estimation, as described below, which includes:
    a. Patent number
    b. Expiration date
9. Whether a generic or biosimilar has been approved for such active moiety; and
10. Whether such generic or biosimilar described in (9) is on the market.

Biologic Patent Exclusivity was estimated by — for each biological product having an orphan indication — querying publicly available patent databases (including the United States Patent and Trademark Office [USPTO], Google Patents) for patent titles, abstracts, and claims containing the nonproprietary name of the biological product (as represented by the United States Adopted Name [USAN], the FDA's proper name sometimes containing a 4-letter suffix). Third-party databases (i.e., Drug Patent Watch) were supplementarily consulted for active patent protections. Where feasible, biological product sponsors' public disclosures were reviewed (including Securities and Exchange Commission reports, investor reports, company websites), and patents listed were referenced, focusing on the most recently issued patent. Where feasible, patents assigned to the sponsor or a readily known collaborator of the sponsor were preferentially selected, as this improved the chances that the sponsor would assert this patent in a hypothetical infringement allegation.

Once a reasonably relevant patent was identified, the term of a patent was estimated by using the USPTO Patent Term Calculator.[66] Terminal disclaimers were noted, but the estimated term of a patent was not otherwise adjusted, to provide the most generously interpreted estimation of the duration of protection.

66 United States Patent and Trademark Office, *Patent Term Calculator* (last updated 4 April 2018).

MISSION STATEMENT

NORD, a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 330 patient organization members, is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services.

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