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Orphan Drug Approval Takeaways From Recent FDA Data

By **Omar Robles and Katherine Jones** (January 14, 2022, 4:02 PM EST)

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Several members of Congress have touted the Fairness in Orphan Drug Exclusivity Act, passed by the U.S. House of Representatives in May,[1] as a bill that closes a loophole in the Orphan Drug Act, or ODA.[2]

According to Rep. Madeleine Dean, D-Penn., the bill's primary author, the legislation would, among other things, "boost competition in the marketplace and drive down the cost of new medicines."[3]

Frank Pallone Jr., D-N.J., and Anna Eshoo, D-Calif., the Energy and Commerce Committee chair and Health Subcommittee chair, respectively, stated that the bill will close "a loophole that has been used to unfairly block generic drugs from coming to market."[4]

However, it is unknown to what extent, if at all, generic drugs have been delayed or deterred from the marketplace by the regulatory process created by the ODA. In this article, we start to explore this allegation using publicly available records of small-molecule approved orphan drugs.

The ODA has provided for the granting of a special status, commonly referred to as "orphan designation" or "orphan status," that qualifies sponsors of a drug for certain benefits from the federal government.[5] The ODA is often credited by researchers and policymakers alike for increasing the number of approved drugs for the treatment of rare diseases.[6] Since 1983, the U.S. Food and Drug Administration has awarded over 2,000 designations and approved hundreds of orphan-designated drugs.[7]

A drug may receive initial marketing approval from the FDA with or without an orphan designation. A drug that already has marketing approval without an orphan designation may subsequently receive marketing approval for an orphan designation — hereafter referred to as orphan drug approval. Moreover, a drug may receive marketing approval for multiple orphan designations.

Generally, new drugs that receive marketing approval are granted distinct exclusivities in the marketplace.[8] In the case of small-molecule drugs — hereafter simply referred to as drugs — competition from a generic version of a new drug is typically delayed until certain patents covering the new drug expire, are declared invalid, or until there is mutual agreement of the patentee and the

generic manufacturer.[9]

Upon marketing approval, an orphan drug is awarded seven years of exclusivity — referred to as orphan drug exclusivity or ODE — from "the same drug … for the same use or indication" unless the subsequent drug is "clinically superior to all previously approved same drugs for the same use or indication," according to recent FDA guidance on orphan drug regulations.[10]

Consequently, the ODE has the potential to delay generic competition if it extends the new drug's exclusivity beyond the generic's entry date but for the orphan drug approval.

For the purposes of our analysis, we limit the data to drugs that received marketing approval for at least one orphan designation between 1990 and September 2021. Moreover, since a drug may receive multiple marketing approvals for distinct orphan designations, our analysis in this article focuses on the first orphan approved designation.

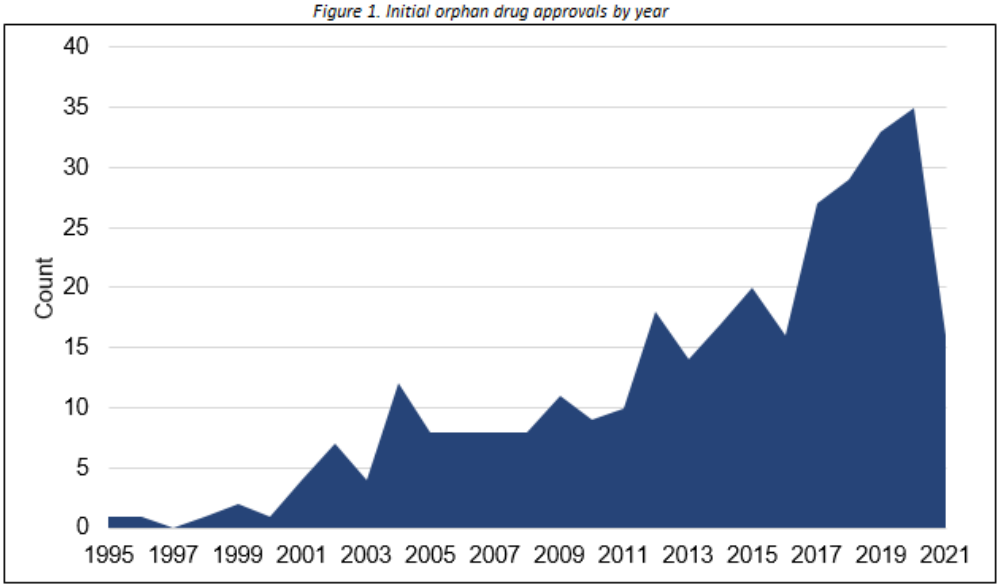
Our analysis is based on a dataset downloaded from an FDA searchable database on orphan drug approvals.[11] The dataset includes, among other things, information on a drug's orphan designation date, marketing approval date, orphan designation status — limited to designated or approved for our purposes — and orphan designation.

We cross-referenced the list of orphan drugs against the FDA's publications, commonly referred to as the Orange Book and the Purple Book,[12] which list all FDA-approved small-molecule drugs and FDA-licensed large-molecule drugs, to determine an orphan drug's molecule size.[13][14]

Analysis

First, we find that the number of drugs receiving initial orphan drug approvals has increased steadily over time. Figure 1 shows that fewer than five initial orphan drug approvals occurred each year between 1995 and 2000, but 25–35 new orphan drug approvals have occurred each year since 2017.

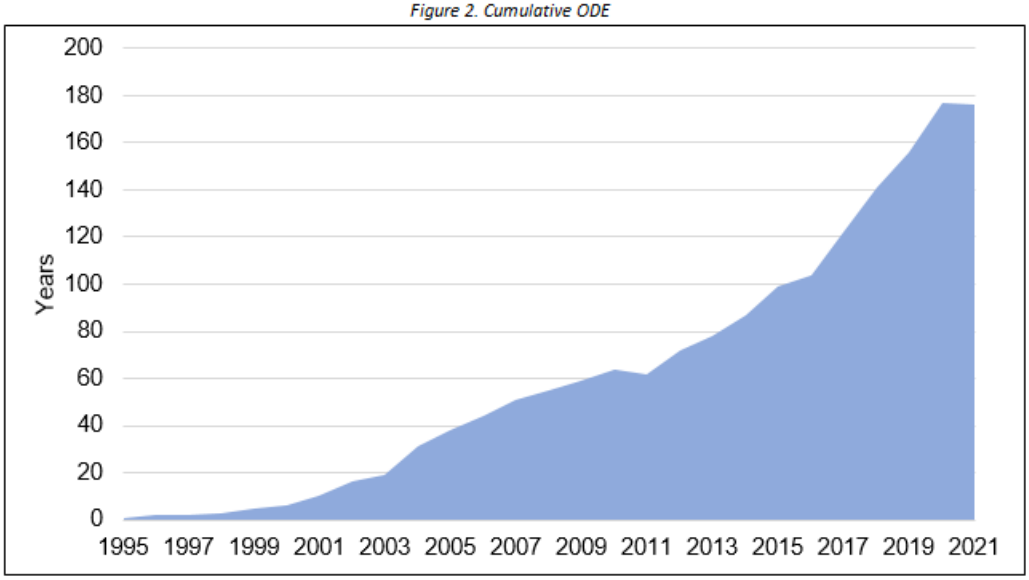
Figure 1. Initial orphan drug approvals by year



Notes: [1] Excludes 1 drug with orphan drug approval before 1995. [2] Based on year of initial orphan drug approval.

Since each new orphan drug approval is accompanied by seven years of ODE, the number of orphan drugs with ODE at a given time has similarly increased, as shown in Figure 2. Indeed, as of September 2021, at least 170 orphan drugs maintain ODE — all drugs approved since 2014. The relevance of this analysis is underscored by the growth of orphan drugs' prevalence over time.

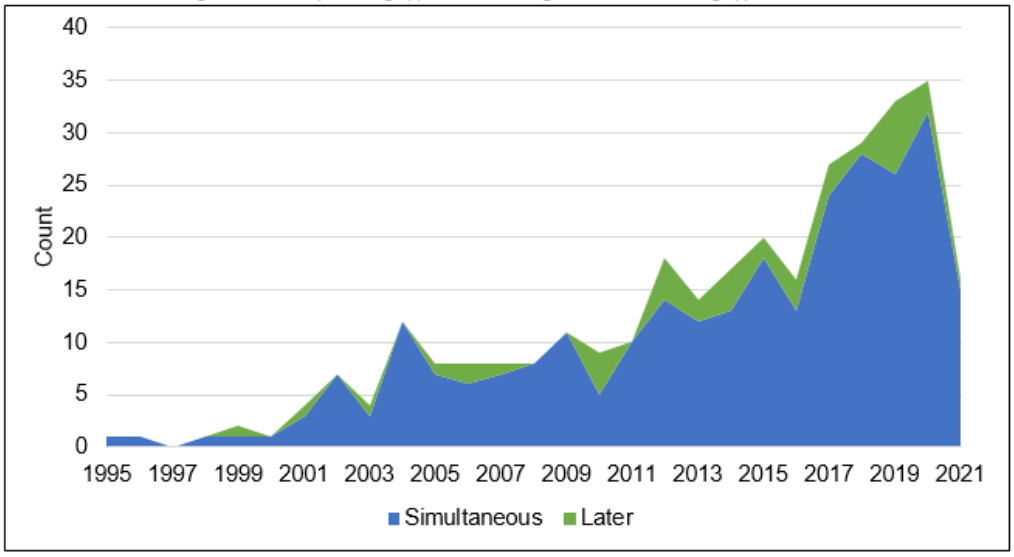
Figure 2. Cumulative ODE



Notes: [1] Excludes 1 drug with orphan drug approval before 1995. [2] Based on year of initial orphan drug approval. [3] ODE estimated as 7 years from initial orphan drug approval. Some orphan drugs may obtain additional marketing approvals for orphan designations which would increase their time with ODE.

However, among drugs receiving initial orphan drug approval, not all receive marketing approval for an orphan designation simultaneously with initial marketing approval. Drugs may receive marketing approval for an orphan designation after initial marketing approval or post-nondisclosure agreement orphan drug approval.

Figure 3. Initial orphan drug approvals coinciding with initial marketing approval



Notes: [1] Excludes 1 drug with orphan drug approval before 1995. [2] Based on year of initial orphan drug approval. [3] "Simultaneous" approvals received initial orphan drug approval on same day as initial marketing approval.

Figure 3 shows initial orphan drug approvals from Figure 1, now separated by whether the first — and only in some cases — orphan drug approval was granted on the same day as initial marketing approval or after. In 2019, approximately 21.5% of all initial orphan drug approvals were granted to drugs that had already received marketing approval.

Across all years, 87.5% of initial orphan drug approvals were granted on the same day as initial marketing approval.

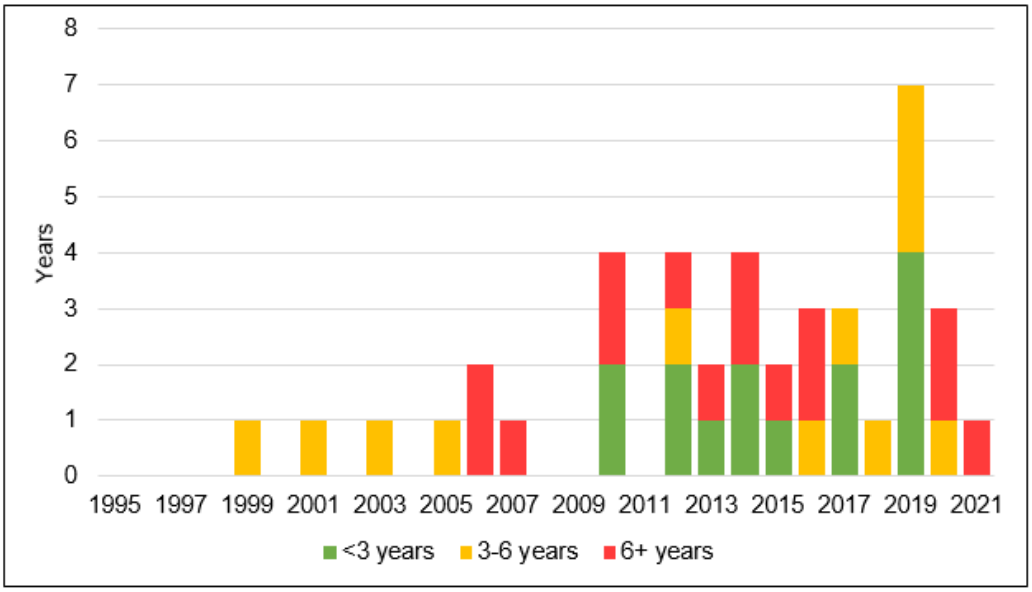
Within post-NDA orphan drug approvals, there is some variance in the time between initial marketing approval and initial orphan drug approval. Some initial orphan drug approvals may be granted soon after initial marketing approval — e.g., within the same year — while others may be approved substantially later.

Figure 4 shows how the timing of these post-NDA initial orphan drug approvals has changed over time. Earlier post-NDA orphan drug approvals predominately received initial orphan drug approval three and six years after initial marketing approval.

However, beginning in 2010, many post-NDA initial orphan drug approvals occurred sooner, within three years of initial marketing approval. There has also been an increase in initial orphan drug approvals for much older drugs since 2006 — in most years 2010 to 2021, half or more of initial orphan drug approvals have been for drugs whose initial marketing approval occurred six or more years prior.

The share of post-NDA initial orphan drug approvals corresponding to the three-to-six year window is now small, despite that time difference being more typical in earlier years.

Figure 4. Time to initial orphan drug approval after initial marketing approval



Notes: [1] Excludes 1 drug with orphan drug approval before 1995, and drugs which received initial orphan drug approval on same day as initial FDA marketing approval. [2] Based on year of initial orphan drug approval.

One complicating factor related to the ODE is that it may or may not overlap with other forms of exclusivity.

For example, when a drug that has a new chemical entity — i.e., the active moiety has not been previously approved by the FDA under Section 505(b) of the Federal Food, Drug and Cosmetic Act — is approved by the FDA, the application is referred to as a Type 1 submission. Hereafter these are referred to as Type 1 drugs.

At this point, the drug is entitled to five years of new chemical exclusivity, or NCE. This means the FDA is barred from accepting an abbreviated new drug application or Section 505(b)(2) application for a drug containing the same active moiety, regardless of whether the drug also receives ODE.[15]

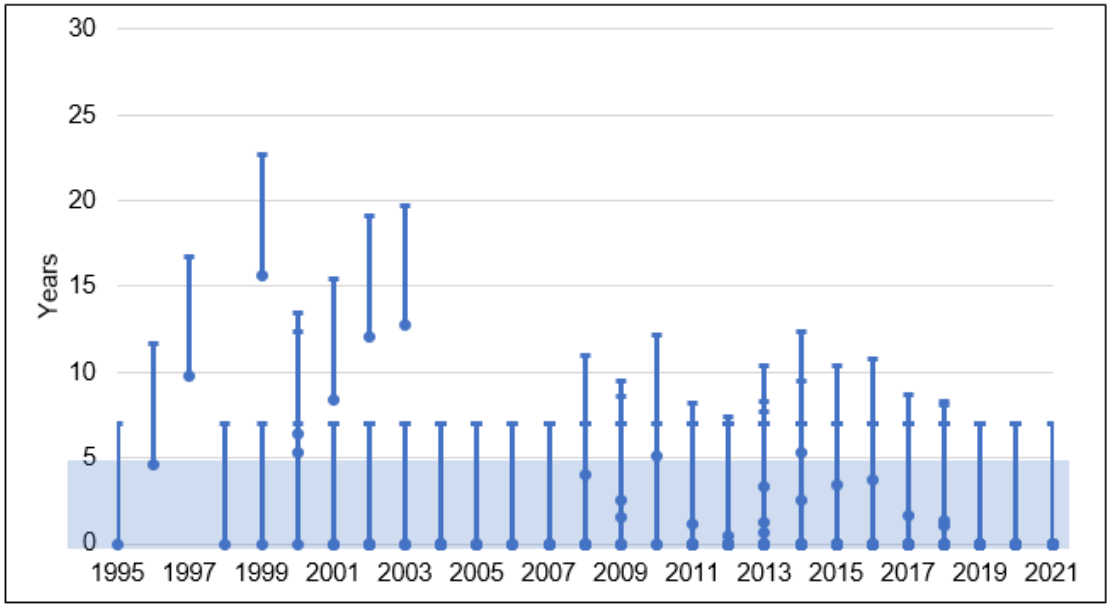
If a Type 1 drug receives initial orphan drug approval on the same day as initial marketing approval, the NCE and ODE for the drug will overlap for the first five years, with two additional years of ODE to follow. However, drugs that have a gap between their initial approval and initial orphan drug approval can receive as much as 12 years of various forms of exclusivity — five from NCE, and an additional seven from ODE.

In Figure 5, we show the total years of NCE and ODE — i.e., exclusivity — for Type 1 drugs that received at least one orphan drug approval. Each dot represents one or more Type 1 drugs that also received orphan drug approval, and they are plotted based on the drug's initial marketing approval year — see the horizontal axis.

The blue box shows the initial five years of NCE from the drug's initial approval as a Type 1 drug, and the blue bars show the seven years of ODE from the drug's approval for an orphan designation.

For example, in 1999, one or more drugs received initial marketing approval and initial orphan drug approval in the same year. The 1999 bar extends only two years beyond the blue box, showing a total of seven years of exclusivity for that year's orphan drugs.

Figure 5. Years of NCE and ODE by year of initial marketing approval for Type 1 drugs



Notes: [1] Excludes 3 drugs with initial FDA marketing approval before 1995. [2] Blue box represents initial 5 years of NCE after initial marketing approval for Type 1 drugs. Blue bars represent 7 years of ODE after initial orphan drug approval. [3] Based on year of initial marketing approval. [4] Some drugs may obtain additional orphan drug approvals which would increase the time with ODE. [5] Limited to Type 1 drugs.

This chart highlights the potential for extended exclusivity for drugs whose initial orphan drug approval occurs after initial marketing approval. For example, Figure 5 shows that one or more Type 1 drugs that received initial marketing approval in 1996 had NCE until 2001.

However, at least one drug received initial orphan drug approval in 2001, granting ODE until 2008. For Type 1 drugs with an initial orphan drug approval just shy of completing the NCE, the total length of exclusivity comes quite close to the maximum 12 consecutive years.

In our analysis, five distinct Type 1 drugs received initial orphan drug approval between three and five years after initial marketing approval.

If pharmaceutical companies were both intent and successful in leveraging ODE to prolong exclusivity, we might expect to see high numbers of initial orphan drug approvals on or around the time that NCE ends for Type 1 drugs, but the five examples mentioned above are the only cases between 1995 and 2021 where this occurs.

For the vast majority of Type 1 drugs in this time — 190 of 216 — initial orphan drug approval coincides with the drug's initial marketing approval, giving the drug only two additional years of orphan exclusivity relative to NCE.

Conclusions

Overall, recent trends suggest that more and more pharmaceutical companies are pursuing marketing approvals for orphan drug designations. We found that initial orphan drug approvals are not systematically leveraged to extend drugs' exclusivity — on the contrary, the vast majority of initial orphan drug approvals are granted on the same day as a drug's initial marketing approval.

This early start to orphan drug approval means that the ODE is likely to overlap with other forms of exclusivity.

We examined the specific case of Type 1 drugs and did not find evidence that pharmaceutical companies were both intent and successful in leveraging ODE to prolong exclusivity. For the vast majority of Type 1 drugs that we examined — 190 of 216 — initial orphan drug approval coincides with the drug's initial marketing approval, giving the drug only two additional years of orphan exclusivity relative to NCE, just one type of exclusivity available to new drugs.

We also recognize that some drugs pursue multiple orphan designations, which could potentially prevent generic entry longer than our analysis would suggest. While we hope to explore that inquiry with further research, these findings are encouraging in that they suggest initial orphan drug approvals are often granted at the time of initial marketing approval, if not commonly soon after, and are not pursued later solely to deter generic entry as some may allege.

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[1] Ian Swanson, "House Passes Drug Bill That Stalled over Jan. 6 Tensions," Text, TheHill, May 19, 2021, https://thehill.com/homenews/house/554398-house-passes-drug-bill-that-stalled-over-jan-6-tensions.

[2] "Pallone and Eshoo on House Passage of the Fairness in Orphan Drug Exclusivity Act," Democrats, Energy and Commerce Committee, May 19, 2021, https://energycommerce.house.gov/newsroom/press-releases/pallone-and-eshoo-on-house-passage-of-the-fairness-in-orphan-drug.

[3] "Rep. Dean Reintroduces Fairness in Orphan Drug Exclusivity Act," Congresswoman Madeleine Dean, March 9, 2021, https://dean.house.gov/2021/3/rep-dean-reintroduces-fairness-orphan-drug-exclusivity-act.

[4] "Pallone and Eshoo on House Passage of the Fairness in Orphan Drug Exclusivity Act."

[5] Mathew T Thomas, "The Orphan Drug Act and the Development of Products for Rare Diseases," US Food and Drug Administration, https://rarediseases.info.nih.gov/files/fda%20orphan%20drugs.pdf.

[6] Dana P. Goldman et al., "The Benefits From Giving Makers Of Conventional 'Small Molecule' Drugs Longer Exclusivity Over Clinical Trial Data," Health Affairs 30, no. 1 (January 2011): 84–90, https://doi.org/10.1377/hlthaff.2009.1056; "The Orphan Drug Act and the Development of Products for Rare Diseases;" Office of the Commissioner, "The Story Behind the Orphan Drug Act," FDA, February 9, 2019, https://www.fda.gov/industry/orphan-products-development-events/story-behind-orphan-drug-act.

[7] "The Orphan Drug Act and the Development of Products for Rare Diseases"; "The Orphan Drug Act: Implementation and Impact," Department of Health and Human Services, May 2001, https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf.

[8] New drugs refer to drugs receiving marketing approval through the new drug application (NDA) process.

[9] The patents referred to in the above sentence are those listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" which is aptly known as the "Orange Book."

[10] "Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Guidance for Industry," n.d., 2–3.

[11] "Search Orphan Drug Designations and Approvals," accessed November 9, 2021, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

[12] The "Orange Book" is officially titled the "Approved Drug Products with Therapeutic Equivalence Evaluations." Although it was first published before the passage of the Hatch-Waxman Act in 1984, the scope of the publication was expanded by its passage. A pdf version of the Orange Book is available at https://www.fda.gov/media/71474/download. The "Purple Book" contains a list of FDA-licensed biological products. A searchable database of the Purple Book is available

at https://purplebooksearch.fda.gov/.

[13] We classified orphan drugs listed in the Orange Book as small-molecule drugs and all other orphan drugs were classified as large-molecule drugs. In a small number of cases, we assigned matches when immaterial differences existed between trade names but other drug information matched.

[14] As an additional measure, we compared our deduction of molecule size to a dataset containing information on molecule size that was used by researchers in the following publication: Miller, K.L., Lanthier, M. "Investigating the landscape of US orphan product approvals," Orphanet J Rare Dis 13, 183 (2018).

[15] "Patents and Exclusivity," FDA/CDER SBIA Chronicles, 2, https://www.fda.gov/media/92548/download.