U.S. Department of Health and Human Services
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High-expenditure Medicare drugs often qualified for Orphan Drug Act incentives designed to encourage the development of treatments for rare diseases

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Report in Brief

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Why OIG Did This Review

The Orphan Drug Act (ODA) provides financial incentives to encourage the development of drugs for rare diseases or conditions for which treatments might not be developed otherwise.

When the Food and Drug Administration (FDA) grants a drug an orphan designation, the drug sponsor (typically a manufacturer) is generally eligible for **certain financial incentives:**

If a drug is **granted orphan designation**, the manufacturer may qualify for:

- A **tax credit** equaling 25 percent of qualifying clinical trial costs
- An **exemption from marketing application fees**, currently valued at nearly $3 million

If a drug is **approved for marketing** of an orphan indication, the manufacturer may qualify for:

- 7 years of **market exclusivity** for the approved orphan indication within the designated disease or condition

Manufacturers may obtain multiple designations and orphan indication approvals (e.g., if a drug is used to treat different rare diseases or multiple indications under the same designation) for the same drug. By doing so, **manufacturers are generally eligible for ODA financial benefits for each different orphan indication for the same drug**, and 7 years of market exclusivity for each approved orphan indication.

Note: A manufacturer that is granted an orphan designation for a drug is generally eligible for the financial incentives; however, each incentive has its own criteria and the incentives apply narrowly to the drug's use in the designated rare disease or condition.

In addition to the direct incentives specified in the ODA, an orphan designation excludes a manufacturer from requirements to sell its drug at a discounted price to some types of entities (i.e., certain providers eligible for the 340B drug discount program) even if the drug is being used for a common disease or condition. For a drug to qualify for an orphan designation, and for the associated financial incentives, the manufacturer must document that the drug is intended for a rare disease or condition that affects a small U.S. patient population (less than 200,000 persons), or that there is no reasonable expectation to recover costs associated with developing the drug.

What OIG Found

OIG examined a nonrepresentative, purposive sample of 40 high-expenditure Medicare drugs, and determined the following:

- A majority of the highest-expenditure drugs in Medicare—some of the best-selling drugs in the world—have been granted at least one orphan designation, qualifying their manufacturers for ODA financial incentives.
- Some orphan drugs in our review have generated significant Medicare expenditures and billions of dollars in annual revenue while treating only rare diseases or conditions, a result of (1) their considerably higher prices and (2) being FDA-approved to treat multiple orphan indications, thereby increasing sales.
- Orphan drugs are not limited to the treatment of rare diseases or conditions. Although the vast majority of orphan drugs treat only rare diseases or conditions, many of the high-expenditure orphan drugs included in our review were originally approved—and are still primarily used—to treat relatively common conditions.
- Orphan drug exclusion from the 340B Drug Pricing Program may provide significant financial incentives for manufacturers to seek orphan designation for drugs approved to treat common diseases or conditions.

Why This Matters

The ODA, enacted by Congress in 1983, provides financial incentives to encourage the development of drugs to treat, diagnose, or prevent rare diseases or conditions for which treatments might not be developed otherwise. As a result, manufacturers have received approval for hundreds of orphan drugs that provide a benefit to previously overlooked populations. However, research has raised concerns that the ODA may also result in some manufacturers increasing their profits by setting high prices for drugs that generate billions of dollars in revenue despite treating small populations or by repurposing high-revenue mass-market drugs to acquire certain ODA incentives.

When it was originally enacted in 1983, the ODA required manufacturers to show the "nonprofitability" of a drug for a rare disease or condition when seeking an orphan designation. However, a year later, Congress revised the ODA's language such that a manufacturer was no longer required to provide evidence that a drug would not generate a profit as long as the affected population fell below 200,000 persons. In doing so, Congress anticipated that Government and industry would monitor the profitability of orphan drugs and inform Congress if the population threshold "becomes a problem."

On one hand, the examples highlighted in our findings may illustrate the ODA functioning as intended. By encouraging manufacturers to study whether existing drugs could also be used to treat rare diseases or conditions, the financial incentives offered under the ODA subsidize manufacturers' investment costs for numerous orphan indications. From another perspective, however, our findings raise questions for further consideration, including the following:

- How do the trends and patterns observed in this purposive sample of 40 high-expenditure Medicare drugs align with the overall goals of the ODA?
- Are current eligibility requirements and incentives the most effective way to ensure the continued development of affordable drugs to treat patients suffering from rare diseases and conditions?
- How has the increasing number of drugs granted orphan designations in recent years affected other Federal programs outside of FDA (for example, Medicare or the 340B Drug Pricing Program)?

This report provides an independent analysis on a specific subset of orphan drugs—those with the highest Medicare expenditures—and serves to both inform ongoing discussions and support congressional and decisionmakers' efforts to improve the Orphan Drug Designation Program. OIG encourages the policymaking, oversight, and research communities to seek answers to the additional questions raised by our findings. In debating any potential changes, it will be vital to ensure that the program continues to successfully encourage the development of drugs to treat rare diseases and conditions while taking into consideration questions surrounding affordability, profitability, and the meaning of rare use.

How the Agency Responded

In its comments to the draft report, FDA expressed concern with the narrow scope of OIG's report, stating that the high-expenditure drugs included in our sample are not representative of the spectrum of orphan-designated drugs and subsequently noting that OIG does not speak to the role that orphan-drug designation plays in drug pricing, or if it plays one at all.

OIG notes that our current work's focus on high-expenditure Medicare drugs and the resulting limitations of our sample are discussed throughout the report. Further, OIG agrees that this study is not focused on drug pricing; rather our findings offer insights related to a particular subset of blockbuster drugs, providing descriptive context about their orphan status, associated Medicare expenditures, and the revenue that manufacturers are able to generate. We believe this approach is generally responsive to Congressional interests in providing appropriate oversight of ODA and will help to support any efforts to ensure that the Orphan Drug Designation Program is best able to meet its vital goals.

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GLOSSARY

For the purposes of this report:

Term	Definition
Orphan designation	The Orphan Drug Act provides for granting special status to a drug or biological product (drug) to treat a rare disease or condition upon request of a sponsor (i.e., manufacturer). This status is referred to as orphan designation (or sometimes "orphan status"). When the Food and Drug Administration (FDA) grants a drug an orphan designation, the manufacturer is generally eligible to earn certain financial incentives.
Orphan drug	A drug that has been granted at least one orphan designation. This includes drugs that have been granted an orphan designation but may not currently have marketing approval for any orphan indications (i.e., the drug's only FDA-approvals apply to nonorphan indications).
Marketing approval	FDA grants marketing approval for a drug once the agency finds there is substantial evidence of safety and effectiveness for the intended population. Marketing approval of a drug is specific to an indication (i.e., the use of that drug for treating a particular disease or condition).
Orphan indication	An FDA-approved indication to treat an orphan-designated rare disease or condition.
Nonorphan indication	An FDA-approved indication to treat a common disease or condition (i.e., the disease or condition does not meet the ODA criteria to be considered rare).

BACKGROUND

Objectives

1. To determine how many high-expenditure Medicare drugs in 2018 have been granted orphan designations and received approval for orphan indications from the Food and Drug Administration (FDA).
2. To determine the extent to which high-expenditure Medicare orphan drugs were used for their orphan indications compared to any nonorphan indications in Medicare in 2018.

Over 7,000 rare diseases affect more than 30 million Americans.[1] The Orphan Drug Act (ODA), enacted in 1983, provides financial incentives to encourage the development of drugs to treat, diagnose, or prevent (hereinafter, treat) rare diseases or conditions.[2] FDA has granted orphan designations to almost 4,200 drugs as of February 1, 2021. Following designation, manufacturers generally qualify for statutory incentives, such as tax incentives and an exemption of application fees, to support development related to the orphan designation.[a] In total, 615 of these orphan drugs ultimately received FDA approval to treat 938 orphan indications. Sixty percent of these approvals have occurred in the past decade, with more than a quarter of the total approved in the last 3 years alone. FDA approval generally qualifies the drug for the additional benefit of 7 years of market exclusivity for the orphan indication.[b]

The ODA has resulted in manufacturers developing orphan drugs that have provided a benefit to previously overlooked populations, including new drugs offering breakthrough therapies and existing drugs providing medical benefits for new populations. However, research has shown that some manufacturers increase profits for their orphan drugs by setting high prices and subsequently seeking approval for multiple orphan indications or by repurposing high-revenue mass-market drugs to acquire certain ODA incentives.[3, 4, 5] Researchers' critiques of the ODA raise questions concerning potential unintended effects on manufacturers' behaviors and whether a realignment of eligibility requirements and incentives, at least in certain instances, may be warranted. OIG's analysis aims to provide stakeholders with relevant information on a specific subset of high-expenditure drugs that have qualified for ODA incentives.

[a] The ODA provides for granting special status to a drug or biological product (drug) to treat a rare disease or condition upon request of a sponsor (e.g., manufacturer). This status is referred to as orphan designation (or sometimes "orphan status"). Drugs that have been granted at least one orphan designation are hereinafter referred to as orphan drugs—regardless of whether such drug ever receives approval for the orphan indication.

[b] See Exhibit 2 on page 5 for a more detailed explanation.

The Orphan Drug Act

Definition of a Rare Disease or Condition. The ODA originally defined a "rare disease or condition" as "any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."[6] However, because of stakeholders' concerns that demonstrating unprofitability would be overly burdensome, Congress revisited this definition a year later.[7, 8]

Congress amended the ODA by redefining a rare disease or condition as one that (1) "affects less than 200,000 persons in the United States" or (2) one that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."[9] In other words, as long as the affected population falls below 200,000 persons, a manufacturer is not required to show that a drug would not generate a profit treating the rare disease or condition to qualify for an orphan designation. In adopting the amendment, Congress recognized the possibility that a drug granted orphan status might be commercially viable for the rare disease or condition and anticipated that Government and industry would monitor the profitability of orphan drugs and inform Congress if the population threshold "becomes a problem."[10] All but three of several thousand designations granted by FDA have qualified under the low-population criteria, meaning that their manufacturers did not have to demonstrate that their drugs would not generate profits treating the rare diseases or conditions.[11]

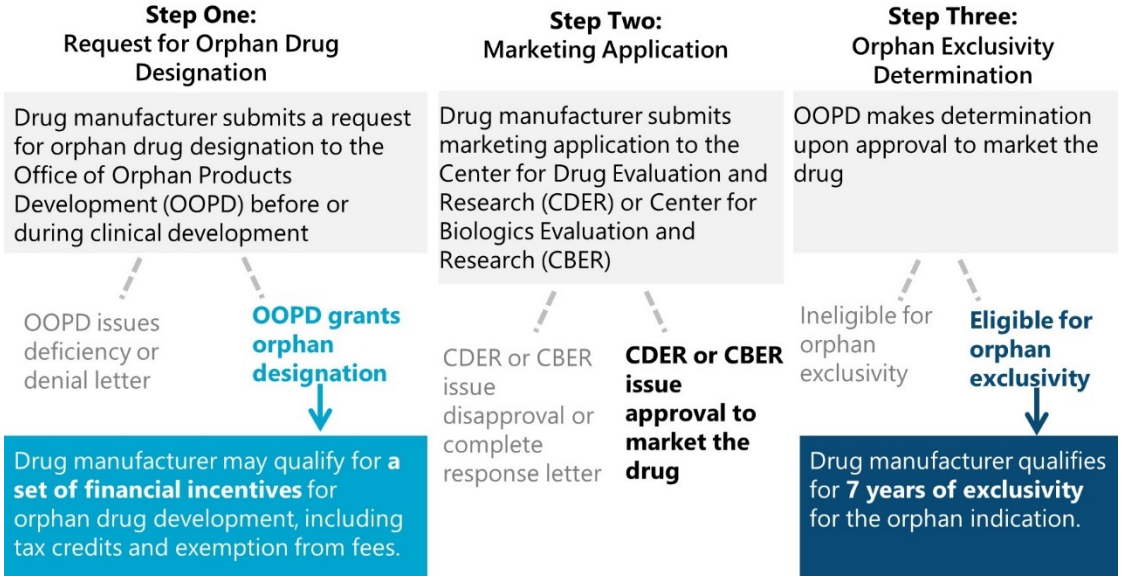
Orphan Drug Designation. As of February 1, 2021, FDA has granted nearly 5,800 orphan drug designations to more than 4,000 drugs. An orphan designation is specific to a rare disease or condition; as a result, a drug may be granted a designation for each distinct disease or condition for which it qualifies.

FDA's Office of Orphan Products Development administers the Orphan Drug Designation Program and evaluates requests for orphan designation. A drug manufacturer may submit an orphan drug designation application at any point in a drug's development process prior to submitting a marketing application for that rare disease or condition.[c, 12] The designation application must include a description of the rare disease or condition, documentation of the number of people affected by the disease or condition in the United States, and a scientific rationale explaining why the drug may effectively treat the disease or condition.[13] If the population affected by the rare disease or condition exceeds 200,000 persons within the U.S., the manufacturer must demonstrate that there is no reasonable expectation to recover the cost of developing and producing the drug from U.S. sales alone.[14]

[c] A drug manufacturer may request an orphan drug designation for a previously unapproved drug or for a new use of an already marketed drug.

Marketing Approval for an Orphan Indication. In total, 615 of the more than 4,000 drugs for which FDA has granted orphan designations have subsequently received marketing approval to treat 938 orphan indications. FDA applies the same statutory standards for safety and effectiveness (for New Drug Applications[15]) or safety, purity, and potency (for Biologics License Applications[16]) when considering marketing approval for all drugs (i.e., including orphan drugs), but the overall benefit-risk evaluation and the clinical trials may vary depending on the circumstances.[17] The Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) evaluates clinical trial data provided in a submitted and filed marketing application to determine whether the safety and efficacy of the drug (or safety, purity, and potency of the biological product) in the intended population are adequately supported by the data and whether the drug provides benefits that outweigh its known and potential risks for the intended population.[18] (See Exhibit 1.) FDA may approve the same drug for multiple orphan indications under a single designation (i.e., for the same rare disease or condition). For example, the orphan drug Velcade—designated for the treatment of mantle cell lymphoma—has been approved for two orphan indications: (1) as a first-line therapy and (2) for patients who have received at least one prior therapy.

Exhibit 1: Orphan drug designation and marketing approval application process



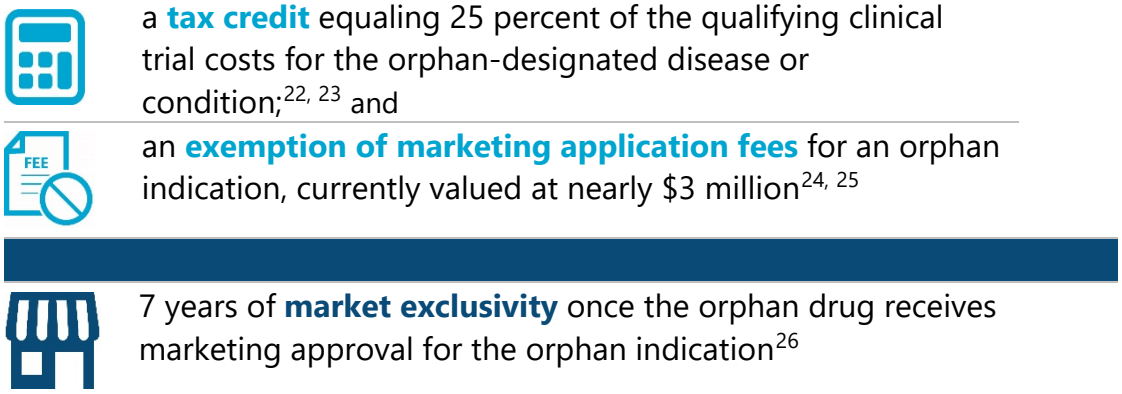
Source: OIG review of FDA orphan drug designation and marketing approval application process.

An orphan drug may receive marketing approval for a single orphan indication, multiple orphan indications, or a combination of orphan and nonorphan indications. In many cases, despite being granted an orphan designation, a drug may never receive marketing approval for any orphan indications (e.g., studies fail for the rare disease indication and the drug's only FDA approvals apply to nonorphan indications). Even without an approval, these drugs generally will maintain their orphan status indefinitely unless the designation is withdrawn by the manufacturer or revoked by FDA.

Orphan Drug Incentives

As shown in Exhibit 2, receiving an orphan designation allows a drug manufacturer to benefit from financial incentives for the development of the orphan drug (or in the case of an existing drug, to benefit from the exploration of its effectiveness in treating a rare disease or condition).[19] If an orphan drug is then approved for marketing for an orphan indication, the manufacturer may receive the added benefit of 7 years of market exclusivity for that specific orphan indication.[20, 21]

Exhibit 2: Incentives for the development of qualified orphan drugs



Source: OIG review of orphan drug benefits.
Note: Not every orphan drug will qualify for every incentive.

In addition to the direct incentives specified in the ODA, orphan drugs may also be eligible for other programs FDA administers for drugs in development. For example, OOPD administers two Orphan Products Grants programs for clinical trials and natural history studies of rare diseases.[27]

Orphan Drug Exclusion from the 340B Drug Pricing Program. Separate from the ODA, an orphan designation also excludes a manufacturer from requirements to sell its drug at a discounted price to certain providers eligible for the 340B Drug Pricing Program (hereinafter referred to as the orphan drug exclusion).[d] The 340B Drug Pricing Program enables eligible providers—generally, those that serve a disproportionate share of needy patients—to purchase drugs at statutorily discounted prices.[28] Congress intended the savings from these discounts to enable eligible providers "to stretch scarce Federal resources, thereby reaching more eligible patients and providing more comprehensive services."[29] On average, the estimated discount has ranged from 20 to 50 percent off what the providers would have otherwise paid.[30] However, because of the orphan drug exclusion a drug manufacturer is not required to sell an orphan drug to certain 340B providers at the statutory discount even if the drug is being purchased for a more common disease or condition.

[d] 42 U.S.C. § 256b(a)(4) and (e). Manufacturers are not required to provide the 340B statutory discount to four types of participating health care providers—freestanding cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals—when purchasing an orphan drug.

Medicare Prescription Drug Programs

Medicare Part B. Medicare covers a limited number of outpatient drugs under its Part B benefit.[31] Part B-covered drugs generally fall into the following three categories: drugs furnished incident to a physician's service (e.g., injectable drugs used in connection with the treatment of cancer); drugs explicitly covered by statute (e.g., some vaccines and oral anticancer drugs); and drugs used in conjunction with durable medical equipment (DME) (e.g., inhalation drugs).[32] Medicare beneficiaries can receive Part B drugs through physician offices; hospital outpatient departments; DME suppliers; and in certain specific instances, pharmacies.

Medicare Part D. Medicare Part D, also known as the Medicare Prescription Drug Benefit, is an optional prescription drug benefit available to Medicare beneficiaries to supplement their Medicare benefits. Individuals enrolled in Part D can choose to receive benefits through stand-alone prescription drug plans or through Medicare Advantage prescription drug plans that provide integrated medical coverage, including drugs. Part D typically covers a broad range of outpatient drugs, including cardiovascular drugs, insulin, antibacterial drugs, and some vaccines. The Centers for Medicare & Medicaid Services (CMS) contracts with private companies, known as plan sponsors, that offer Part D prescription drug plans with varying drug coverage and cost-sharing requirements.

Methodology

Scope

This review is national in scope. It focuses on the orphan status of 40 high-expenditure drugs—the 20 drugs with the highest Medicare expenditures in Part B and the 20 drugs with the highest Medicare expenditures in Part D. This review is not designed to (1) provide insight into the full array of economic forces involved in drug manufacturer decisions to seek orphan status or establish drug prices; (2) evaluate the value of the ODA incentives; or (3) review whether the public health goals of the ODA are being met.

We determined how many of these high-expenditure drugs were orphan drugs (i.e., had at least one orphan designation) as of March 2020; reviewed the rare diseases or conditions for which the orphan drugs had been granted orphan designations and the approved indications within those diseases; and determined the extent to which these orphan drugs were utilized for their approved orphan indications.

Sample. We developed our list of top Medicare drugs using 2018 data on Medicare drug expenditures from CMS's Medicare Part B Drug Spending Dashboard and Medicare Part D Drug Spending Dashboard (2018 was the most recent year for which complete data was available at the time of our analysis). We then selected a nonrepresentative, purposive sample of 40 drugs—20 with the highest expenditures in Part B and 20 with the highest expenditures in Part D.

Data Analysis

Determining how many high-expenditure Medicare drugs have orphan designations and approvals. We used FDA's Orphan Drug Product Designation Database to determine which drugs in our sample had been granted an orphan designation. Because a drug may have multiple orphan designations, we counted the number of orphan designations each drug has received. We also determined how many, if any, orphan indications had been approved for marketing. We reviewed each drug's orphan designation(s) to identify the rare disease or condition and patient populations associated with each designation and orphan indication. Lastly, using the Drugs@FDA Database, we determined whether the orphan drugs had also received marketing approval for any nonorphan indications.

Determining total expenditures and sales for high-expenditure Medicare orphan drugs. To determine how much Medicare spent on the orphan drugs in our sample, we calculated the expenditures for each orphan drug using Part B and Part D claims data from 2018. We also compiled each orphan drug's total sales revenue in the U.S. and globally in 2018 from manufacturers' publicly available annual financial reports.

Determining the extent to which high-expenditure Medicare orphan drugs are utilized for their approved orphan indications in Medicare. Using the ICD-10-CM code set, we matched the FDA-approved orphan indications to any associated diagnosis codes for each of the orphan drugs in our sample. In Medicare Part B, the ICD-10 code(s) related to a patient's diagnosis are included on the drug claim. However, in Medicare Part D, drug claims do not list diagnosis codes. Therefore, for Part D claims listing an orphan drug in our sample, we examined a beneficiary's associated claims in Part B or Part C encounter data to determine the diagnosis code(s) associated with the drug.

See the Detailed Methodology section for more information.

Limitations

We selected a nonrepresentative, purposive sample of 40 high-expenditure Medicare drugs; therefore, our findings are limited to the orphan drugs in our sample and not generalizable to all orphan drugs. Because we did not conduct a medical record review, this analysis relied on the accuracy of Part B claims, Part C encounter data, and Part D prescription drug event (PDE) records for drug utilization and diagnosis information.

Standards

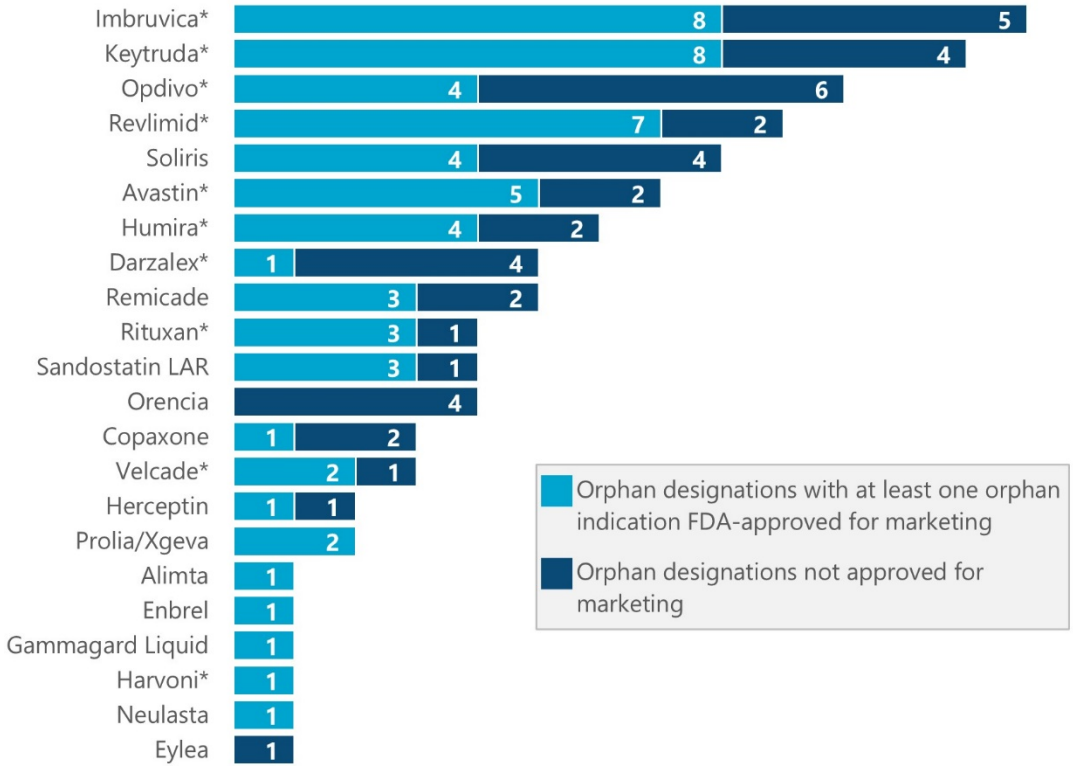
We conducted this study in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

More than half of the high-expenditure Medicare drugs in our review, which generate billions of dollars in annual sales, are eligible for orphan drug incentives for treating rare diseases

Twenty-two of the 40 high-expenditure Medicare Part B and Part D drugs included in our review have been granted at least one orphan designation as of March 2020. All but 6 of the 22 received multiple designations—each for a different rare disease or condition—and thus were generally eligible for one or more statutory incentives for each orphan designation (see Exhibit 3 and Appendix A). Furthermore, 20 of these 22 orphan drugs have received FDA approval for marketing of at least 1 orphan indication, with 12 approved to treat multiple rare diseases or conditions. For example, the orphan drug Imbruvica has been granted 13 orphan designations, of which 8 have at least one FDA-approved orphan indication. Eylea and Orencia, on the other hand, have both been granted at least one orphan designation but had not received FDA approval to market any orphan indications in the U.S. at the time of our review.

Exhibit 3: Nearly three-quarters of the orphan drugs in our review have been granted multiple orphan designations.



Source: OIG analysis of FDA's Orphan Drug Product Designation database, as of March 30, 2020.
*Note: These orphan drugs have been approved to treat multiple orphan indications under a single designation for at least one of their orphan designations. The manufacturers of these drugs may have received incentives for each approved indication under a designation.

Orphan drugs accounted for billions of dollars in Medicare drug spending, with high-cost physician administered drugs more likely to have orphan status than drugs dispensed through pharmacies

The Part B drugs in our review are much more likely to have orphan status. Specifically, 16 of the 20 highest-expenditure Medicare Part B drugs—generally drugs that are injected or infused in physicians' offices or outpatient settings—have been granted at least one orphan designation.[33] Conversely, only 6 of the top 20 Part D drugs—drugs that are primarily dispensed by pharmacies—are orphan drugs (see Appendix B for the orphan status of each drug in our review).

In 2018, Medicare and its beneficiaries spent over $17 billion on the 16 Part B orphan drugs in our review, representing 52 percent of all Part B drug expenditures that year.[34] On average, Medicare paid between $2,600 and $341,000 per patient for each of the orphan drugs in 2018, with 7 of the 16 having annual per-beneficiary costs exceeding $25,000.[e, 35] Medicare beneficiaries were responsible for 20 percent of these annual drug costs through coinsurance.[f] See Appendix D for further details.

Medicare Part D spent $14 billion on the 6 Part D orphan drugs in our review, representing 8 percent of all Part D drug spending in 2018. On average, Medicare Part D paid between $38,000 and $103,000 per beneficiary for each of the orphan drugs, with 4 of the 6 orphan drugs having annual per-beneficiary costs exceeding $50,000. Medicare Part D and its beneficiaries are directly affected by high drug prices, with total out-of-pocket costs for these orphan drugs potentially totaling thousands of dollars per year including deductibles, copayments (fixed payment amounts), and coinsurance (payments based on a percentage of the drug's cost).[g]

The orphan drugs in our review included some of the best-selling drugs in the world

According to manufacturer reports, U.S. sales alone—across all orphan and nonorphan indications—exceeded $1 billion per drug in 2018 for 19 of the 22 orphan drugs in our review.[h] As shown in Exhibit 4, global sales for these orphan drugs reached close to $20 billion for a single drug.

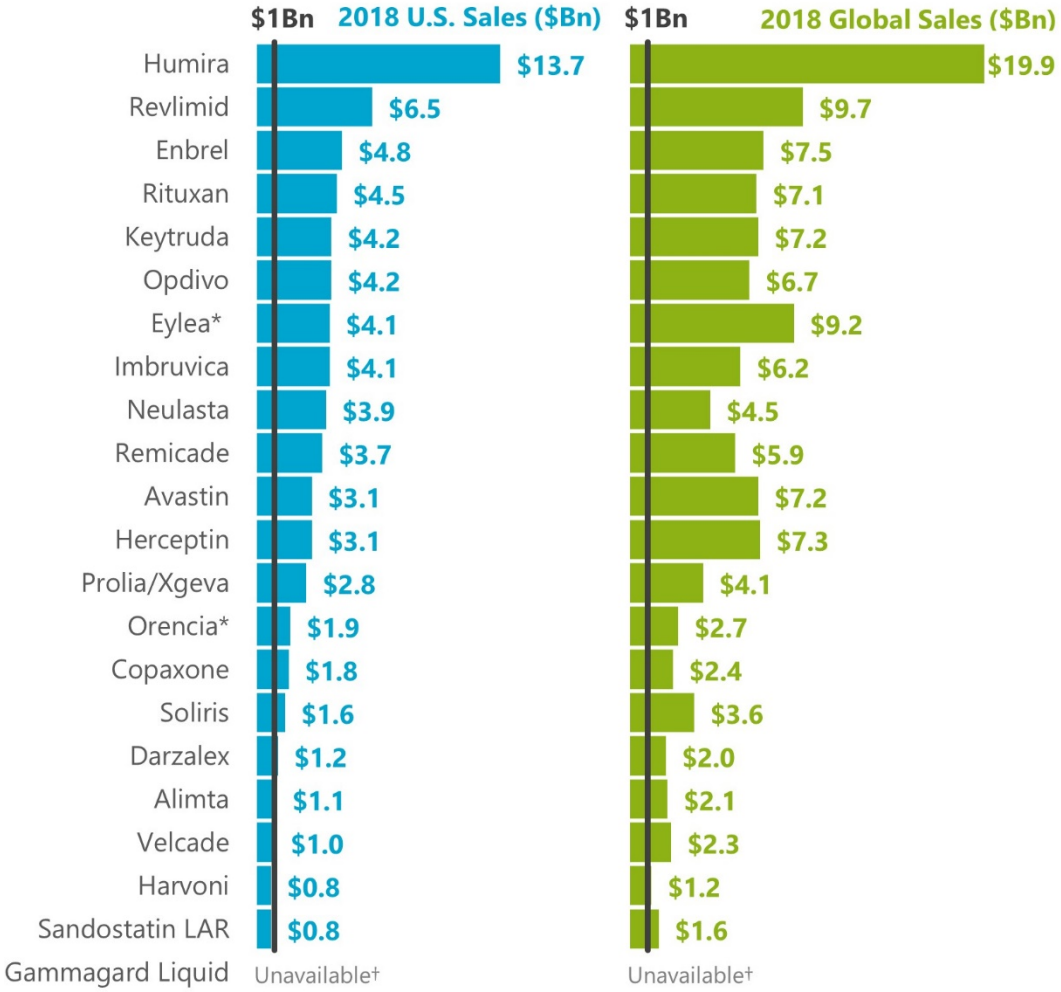
[e] Part B spending and annual per-beneficiary costs are based on all utilization for the drug (i.e., utilization for both orphan and nonorphan indications).

[f] In 2016, 8 in 10 beneficiaries in traditional Medicare (81%) had some type of supplemental insurance to cover some or all of Medicare Part B cost-sharing requirements. Supplemental insurance helps protect beneficiaries from incurring high medical expenses; however, high-cost Part B drugs may still financially affect individual patients through higher premiums as insurers redistribute costs across beneficiaries.

[g] When a drug is covered under Part D, beneficiaries could end up owing thousands of dollars out of pocket because supplemental insurance would not apply.

[h] Annual 2018 U.S. sales and global sales data were not available for Gammagard Liquid.

Exhibit 4: Nearly all of Medicare's high-expenditure orphan drugs reported total U.S. sales of over $1 billion in 2018.



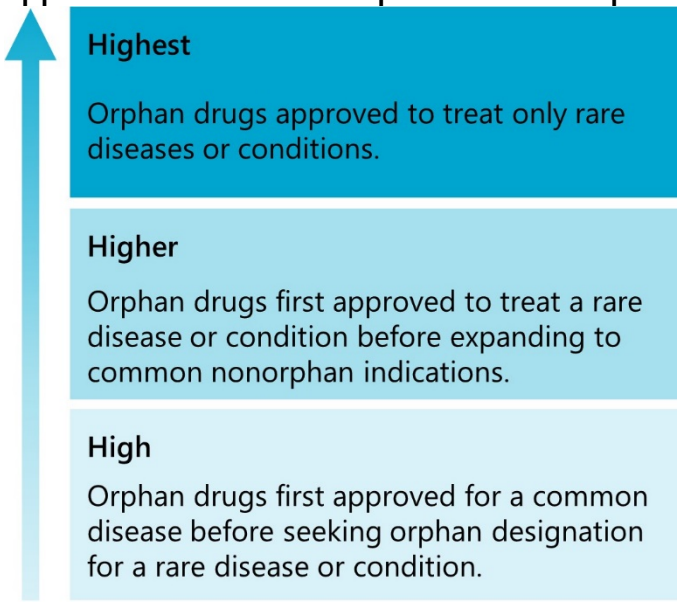
Source: OIG analysis of manufacturers' 2018 annual financial reports.
Note: The reported sales in this exhibit are for total annual sales in 2018 for each drug, and therefore do not distinguish whether the drug was sold to be used for an orphan indication or a nonorphan indication.
* Note: Eylea and Orencia did not have any approved orphan indications in 2018, meaning that all reported sales for these drugs were for use in more common diseases.
† Note: Annual 2018 U.S. sales and global sales data were not available for Gammagard Liquid.

Seven orphan drugs in our review that were approved for only rare diseases or conditions generated significant Medicare expenditures and billions of dollars in sales

While some orphan drugs—such as Humira and Eylea—first reached blockbuster status treating nonorphan indications, 7 of the 22 orphan drugs in our review have not received FDA approval for any nonorphan indications. Yet despite primarily treating rare diseases or conditions, the drugs generate significant Medicare expenditures and billions of dollars in annual revenue. This revenue is generally a result of the orphan drugs receiving approval to treat multiple rare diseases or conditions (i.e., a larger combined population) and their considerably higher costs (see Exhibit 5).[36] For example, Revlimid—a drug with no nonorphan approvals—has

achieved $6.5 billion in 2018 U.S. drug sales for the treatment of rare diseases with 9 orphan indications. Three of these indications are distinct patient populations within the same rare disease—multiple myeloma. In 2018, multiple myeloma accounted for over 90 percent of Revlimid's total orphan use, with Medicare spending $3.7 billion on the drug to treat slightly more than 35,000 beneficiaries with the disease (an average of $106,000 per patient).[37] Under Medicare Part D, beneficiaries potentially had to pay thousands of dollars in out-of-pocket costs to cover the high cost of the drug.[38]

Exhibit 5: In general, orphan drugs approved to treat only rare diseases or conditions had the highest annual per-beneficiary costs compared to drugs approved to treat both orphan and nonorphan indications.



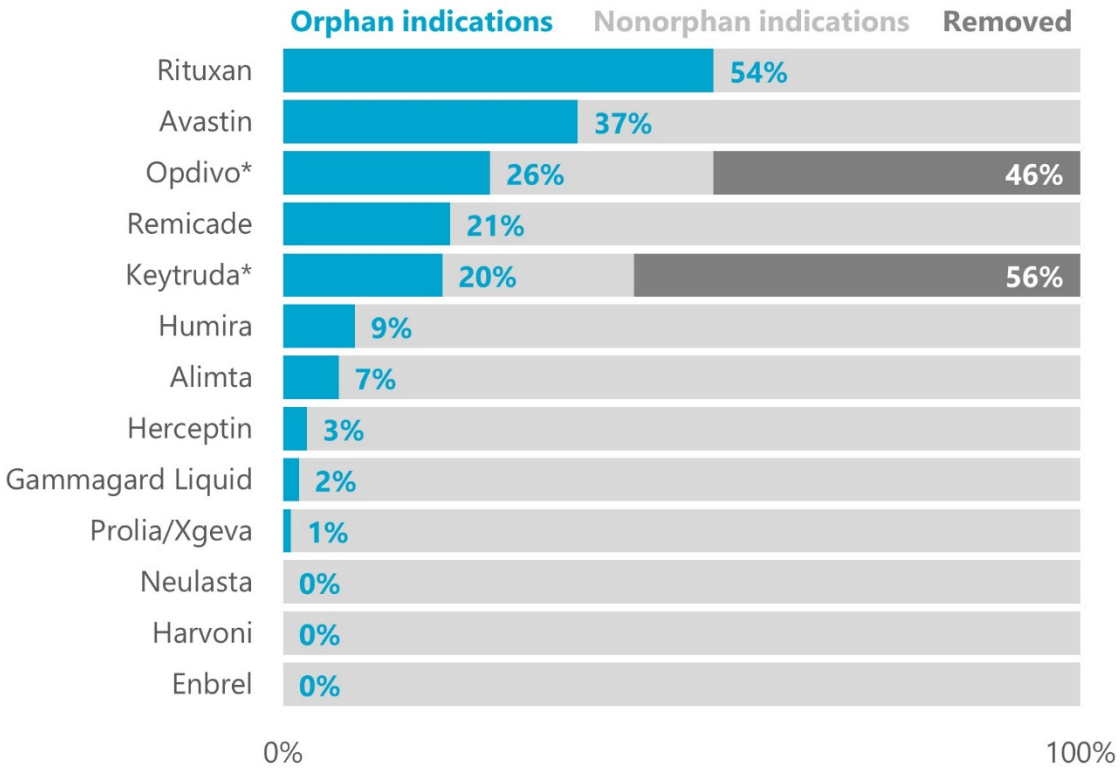
Source: OIG analysis of Medicare Part B and Part D 2018 drug spending data.

Many orphan drugs in our review were also approved—and primarily used—for more common indications

Less than 20 percent of all orphan drugs are approved to treat a common diseases or conditions in addition to their orphan-designated rare diseases or conditions. However, 68 percent (15 of the 22) of orphan drugs in our sample have approvals for common diseases or conditions (see Appendix C for details). This includes 10 drugs that were originally approved for one or more common nonorphan diseases or conditions before being FDA-approved for a rare disease (see Appendix A for details).[39] For example, Avastin—one of the best-selling drugs in the world—was originally approved by FDA in 2004 for a nonorphan common disease indication (i.e., metastatic colorectal cancer). Since then, Avastin has been approved to treat five rare diseases as well.

Of the 15 orphan drugs in our review that were also approved for a nonorphan indication, only 1 (Rituxan) was used more often to treat a rare disease or condition (see Appendix E for details).[i] For 10 of the drugs, less than a quarter of their utilization was for an orphan-approved indication (see Exhibit 6)—a proportion not completely unexpected given the small populations affected by the associated diseases.[j] For example, approximately 5,000 Medicare beneficiaries received Prolia/Xgeva to treat hypercalcemia of malignancy or to treat giant cell tumors of the bone, its two approved orphan indications.[40] In contrast, more than 532,000 beneficiaries received the drug for more common indications, such as osteoporosis.

Exhibit 6: Drugs with both orphan and nonorphan approvals were much less likely to be used for their orphan indications.



Source: OIG analysis of 2018 Medicare Part B claims and Part D PDE records.

*Note: Opdivo and Keytruda both have FDA approval for orphan indications to treat small cell lung cancer (SCLC,) as well as nonorphan indications to treat non-small cell lung cancers (NSCLC). Because ICD-10 diagnosis codes do not distinguish between SCLC and NSCLC, we removed units related to any form of lung cancer from our analysis.

[i] We did not calculate orphan utilization for two drugs—Eylea and Orencia. Although both drugs have at least one orphan designation, they do not have FDA-approval for any orphan indications.

[j] Some of the drugs in our review, such as Enbrel and Harvoni, have only been granted orphan designations for pediatric populations. Therefore, utilization for their approved orphan indications is low in Medicare because Medicare beneficiaries are primarily at least 65 years old.

Orphan drug exclusion from the 340B Drug Pricing Program may provide significant financial incentives for manufacturers to seek orphan designation for drugs approved to treat common diseases or conditions

Orphan drug exclusion from the 340B Drug Pricing Program may provide an additional financial incentive for manufacturers to seek an orphan designation for their drugs that is separate from the incentives outlined in the ODA. The 340B program enables eligible health care providers—generally, those that serve a disproportionate share of needy patients—to purchase prescription drugs at statutorily discounted prices, which have been estimated to range between 20 to 50 percent off what the provider would have otherwise paid.[41, 42] However, a manufacturer is not required to sell an orphan drug at the statutory discount to certain types of health care providers participating in the 340B Drug Pricing Program even if the drug is being purchased for a more common disease or condition.[k] For example, fewer than 1 out of 10 Medicare beneficiaries who were prescribed Humira (the best-selling drug in the world) in 2018 received it for an approved orphan indication (i.e., hidradenitis suppurativa or uveitis).[l] However, because of Humira's orphan status, the manufacturer would not be required to sell the drug (which costs up to $38,000 per year)[43] to certain covered entities under the 340B Drug Pricing Program at a significant statutory discount—even when it's being used for common nonorphan indications such as arthritis, psoriasis, or Crohn's disease.[44]

Even further, a drug needs only to be granted an orphan designation to be excluded from the 340B program (i.e., the drug does not need FDA market approval for an orphan indication). For example, two of the orphan drugs in our review—Eylea and Orencia—have both been granted at least one orphan designation but had not received FDA marketing approval for any orphan indications in the U.S. at the time of our review. The manufacturers of both drugs are not required to sell their drugs at the 340B discount price to certain covered entities because the drugs have been granted an orphan designation.

[k] 42 U.S.C. § 256b(a)(4) and (e). Manufacturers are not required to provide the 340B statutory discount to four types of participating health care providers—freestanding cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals—when purchasing an orphan drug.

[l] Humira also has two FDA-approved orphan indications for pediatric conditions including juvenile idiopathic arthritis and pediatric Crohn's disease.

CONCLUSION

The ODA provides financial incentives to encourage the development of drugs for rare diseases or conditions for which treatments might not be developed otherwise. As a result, manufacturers have received approval for hundreds of treatments for diseases or conditions affecting small, previously overlooked populations—treatments that likely would have never been developed without the incentives offered under the ODA. However, as the Orphan Drug Designation Program continues to grow— with more than a quarter of orphan indication approvals occurring in the last 3 years alone—it is important that stakeholders have relevant information on the orphan drugs that have qualified for ODA incentives to inform ongoing discussions and support congressional and decisionmakers' efforts.

Although this report does not represent a comprehensive view of all orphan drugs, it provides several insights on a subset of blockbuster drugs that have benefited from ODA incentives:

- A majority of the highest-expenditure drugs in Medicare—some of the best-selling drugs in the world—have been granted at least one orphan designation, qualifying their manufacturers for ODA financial incentives.
- Some orphan drugs in our review have managed to generate significant Medicare expenditures and billions of dollars in annual revenue while treating only rare conditions.
- Although the vast majority of orphan drugs treat only rare diseases or conditions, many of the high-expenditure orphan drugs included in our review were originally approved—and are still primarily used—to treat relatively common conditions.
- Orphan drug exclusion from the 340B Drug Pricing Program may provide significant financial incentives for manufacturers to seek orphan designation for drugs approved to treat common diseases or conditions.

On one hand, these findings may illustrate the ODA functioning as intended. For example, by encouraging manufacturers to study whether existing drugs could also be used to treat rare diseases (i.e., drug repurposing), the financial incentives offered under the ODA subsidize manufacturers' investment costs for numerous orphan indications. From another perspective, however, these insights raise important questions for further consideration:

- How do the trends and patterns observed in this purposive sample of 40 high-expenditure Medicare drugs align with the overall goals of the ODA?

- Are current eligibility requirements and incentives the most effective way to ensure the continued development of affordable drugs to treat patients suffering from rare diseases and conditions?
- How has the increasing number of drugs granted orphan designations in recent years affected other Federal programs outside of FDA (for example, Medicare or the 340B Drug Pricing Program)?

OIG encourages the policymaking, oversight, and research communities to seek answers to these compelling questions. In debating any potential changes to the Orphan Drug Designation Program, it will be vital to ensure that the program continues to successfully encourage the development of drugs to treat rare diseases or conditions while taking into consideration questions surrounding affordability, profitability, and the meaning of rare use.

AGENCY COMMENTS AND OIG RESPONSE

In its comments to the draft report, FDA highlighted the success of ODA incentives in advancing Congress's goal of ensuring available drugs for rare diseases while emphasizing that ODA remains vital today given that many rare diseases still lack FDA-approved treatment. To that end, FDA expressed concern with the narrow scope of OIG's report, noting that the high-expenditure drugs included in our sample are not representative of the spectrum of orphan-designated drugs that the ODA helped bring to market. FDA then goes into greater detail about the steps sponsors who seek orphan status for a drug must take to receive the various incentives, and that without such incentives, sponsors may decide not to undertake the significant investment necessary to study the safety and effectiveness of the drug for a rare disease use.

FDA also acknowledged the need to examine drug development incentives to ensure that they remain tailored to achieving their purpose. However, the agency notes that there are many factors that drive Medicare drug expenditures, and that the OIG report does not speak to the role that orphan-drug designation plays in drug pricing, or if it plays one at all.

OIG notes that our current work's focus on high-expenditure Medicare drugs and the resulting limitations of our sample are discussed throughout the report. Further, OIG agrees that this study is not focused on drug pricing; rather our findings offer insights related to a particular subset of blockbuster drugs, providing descriptive context about their orphan status, associated Medicare expenditures, and the revenue that manufacturers are able to generate. We believe this approach is generally responsive to Congressional interests in providing appropriate oversight of ODA and will help to support any efforts to ensure that the Orphan Drug Designation Program is best able to meet its vital goals.

DETAILED METHODOLOGY

Data Sources

Medicare Part B Drug Spending Dashboard. We obtained 2018 Part B drug spending data from CMS's Medicare Part B Drug Spending Dashboard (2018 is the most recent year for which complete data was available at the time of our analysis). This dashboard is an interactive, web-based tool that presents Medicare spending and utilization information for Part B drugs at the Healthcare Common Procedure Coding System (HCPCS) code level.[45]

Medicare Part D Drug Spending Dashboard. We obtained 2018 Part D drug spending data from CMS's Medicare Part D Drug Spending Dashboard (2018 is the most recent year for which complete data was available at the time of our analysis). This dashboard is an interactive, web-based tool that presents Medicare spending and utilization information for Medicare Part D drugs at the drug brand name and generic name level.[46]

Orphan Drug Product Designation Database. We obtained data on orphan drug designations and approvals for drugs included in our review from FDA's Orphan Drug Product Designation Database on March 30, 2020. These data contain information on the drug's generic and trade name, the orphan designation (i.e, the disease or condition the drug is intended to treat), and the orphan designation status. The database also lists whether the drug received FDA approval for marketing, the approved label indication, and the market exclusivity end date.[47]

Drugs@FDA Database. We obtained all marketing approval data for orphan drugs in our review, including approvals for nonorphan indications. These data contain patient information, labels, approval letters, and reviews for drug products. CDER imports this information daily from FDA's Document Archiving, Reporting, and Regulatory Tracking System.[48]

Paid Medicare Part B Claims. We obtained all 2018 Part B-paid claims (i.e., claims from the hospital outpatient and physician-office settings) for HCPCS codes associated with the orphan drugs in our sample (i.e., the 20 highest-expenditure drugs in Part B) from CMS's National Claims History File. Each record contains information about the drug received, diagnosis, and beneficiary as well as the identification numbers for the provider who billed Medicare.

Prescription Drug Event (PDE) Data. We obtained all 2018 Part D-paid claims for the orphan drugs in our sample (i.e., the 20 highest-expenditure drugs in Part D) from CMS's PDE File. Part D sponsors submit a PDE record to CMS each time a drug is dispensed to a beneficiary enrolled in its plans. Each record contains information about the drug and beneficiary, as well as the identification numbers for the

pharmacy and the prescriber. PDE claims do not include diagnosis information on the claim.

Part B Medical Claims and Part C Encounter Data. We obtained 2017-2018 Part B medical claims and Part C encounter data claims from CMS's Integrated Data Repository (IDR) for beneficiaries who had a PDE for an orphan drug in our sample. Part B medical claims (for beneficiaries with a standalone Part D plan) and Part C encounter data (for beneficiaries with a Medicare Advantage plan) contain diagnosis codes for a beneficiary's corresponding PDEs because the PDE record itself does not contain diagnosis codes.

International Classification of Diseases Code Set. We obtained the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD 10 CM) code set from CMS. This code set contains the diagnosis codes that providers report on certain Medicare claims. Providers select codes on the basis of documentation in the patient's medical record.

Drug Manufacturers' 2018 Financial Reports. We obtained drug manufacturers' publicly available 2018 annual financial reports for the orphan drugs in our sample. These reports contain information on U.S. and global drug sales.

Sample

We obtained 2018 data on Medicare drug expenditures from CMS's Medicare Part B Drug Spending Dashboard and Medicare Part D Drug Spending Dashboard. We then selected a purposive sample of 40 drugs—20 with the highest expenditures in Part B and 20 with the highest expenditures in Part D.

Data Analysis

Determining how many high-expenditure Medicare drugs have orphan designations and approvals. We used FDA's Orphan Drug Product Designation Database to determine which drugs in our sample had been granted an orphan designation. Because a drug may have multiple orphan designations, we counted the number of orphan designations each drug has received. We also determined how many, if any, of those orphan designations had been approved for marketing. We reviewed each drug's orphan designation(s) to identify the patient populations indicated for each designation. Lastly, using the Drugs@FDA Database, we determined whether the orphan drugs had also received marketing approval for any nonorphan indications and counted the total number of approvals.

Determining total expenditures and sales for high-expenditure Medicare orphan drugs. To determine how much Medicare spent on the orphan drugs in our sample in 2018, we calculated the expenditures for each orphan drug using Part B and Part D claims data. We also compiled each orphan drug's total sales revenue in the U.S. and globally in 2018 from manufacturers' publicly available annual financial reports.

Determining the extent to which high-expenditure Medicare orphan drugs are utilized for their approved orphan indications in Medicare. Using the ICD-10-CM code set, we matched the FDA-approved orphan indications to any associated diagnosis codes for each of the orphan drugs in our sample. For each Part B orphan drug, we calculated the number of beneficiaries and the total units associated with its approved orphan indication(s) as well as nonorphan utilization.[49] In Medicare Part B, ICD-10(s) related to a beneficiary's diagnosis are included on the drug claim. Therefore, we determined whether a beneficiary was using the drug for an orphan indication on the basis of whether the claim contained an orphan-indication diagnosis. Beneficiaries may have multiple claims for an orphan drug in 2018. To be conservative in our estimates of orphan utilization, if an orphan indication's diagnosis code was present on any of a beneficiary's claims, we categorized each of that beneficiary's claims as being utilized for that orphan indication.

For each Part D orphan drug, we calculated the number of beneficiaries and the total units associated with its approved orphan indication(s). However, in Medicare Part D, drug claims do not list diagnosis codes. Therefore, for Part D claims listing an orphan drug in our sample, we examined a beneficiary's associated claims in Part B or Part C encounter data to determine the diagnosis code(s) associated with the drug. Because a Part D drug can be refilled, the office visit with the prescriber may have been several months before the drug was dispensed. Thus, we examined Part B claims and Part C encounter data with dates of service from January 1, 2017 to December 31, 2018. If an orphan indication's diagnosis code was present on any of a beneficiary's claims in 2017 or 2018, we categorized each of that beneficiary's PDEs as being utilized for that orphan indication. See Appendix C for 2018 Medicare orphan utilization for each orphan drug in our review.

APPENDIX A

Total orphan designations with and without an FDA-approved orphan indication

Orphan Drug	Orphan Designations with at Least One FDA-Approved Orphan Indication	Orphan Designations Without an FDA-Approved Orphan Indication	Total Orphan Designations Granted	First FDA-Approved Indication
Alimta	1	0	1	Orphan
Avastin	5	2	7	Nonorphan
Copaxone	1	2	3	Orphan
Darzalex	1	4	5	Orphan
Enbrel	1	0	1	Nonorphan
Eylea	0	1	1	Nonorphan
Gammagard Liquid	1	0	1	Nonorphan
Harvoni	1	0	1	Nonorphan
Herceptin	1	1	2	Nonorphan
Humira	4	2	6	Nonorphan
Imbruvica	8	5	13	Orphan
Keytruda	8	4	12	Orphan
Neulasta	1	0	1	Nonorphan
Opdivo	4	6	10	Orphan
Orencia	0	4	4	Nonorphan
Prolia/Xgeva	2	0	2	Nonorphan
Remicade	3	2	5	Orphan
Revlimid	7	2	9	Orphan
Rituxan	3	1	4	Orphan
Sandostatin LAR	3	1	4	Orphan
Soliris	4	4	8	Orphan
Velcade	2	1	3	Orphan

Source: OIG analysis of FDA's Orphan Drug Product Designation Database and Drugs@FDA Database, as of March 30, 2020.

APPENDIX B

The orphan status of each high-expenditure Medicare drug in our review

High-expenditure Part B drugs are much more likely to have orphan status than are high-expenditure Part D drugs.

20 Highest-Expenditure Part B Drugs			
Alimta	Herceptin	Prolia/Xgeva	Velcade
Avastin	Keytruda	Remicade	Gammaked
Darzalex	Neulasta	Rituxan	Lucentis
Eylea	Opdivo	Sandostatin LAR	Ocrevus
Gammagard Liquid	Orencia	Soliris	Xolair
20 Highest-Expenditure Part D Drugs			
Copaxone	Revlimid	Eliquis	Novolog
Enbrel	Abiratone Acetate	Invega Sustenna	Spiriva
Harvoni	Admelog	Januvia	Symbicort
Humira	Advair Diskus	Levemir	Tresiba Flextouch
Imbruvica	Basaglar Kwikpen	Lyrica	Victoza

Source: OIG analysis of FDA's Orphan Drug Product Designation Database, as of March 30, 2020.

APPENDIX C

FDA approvals for orphan and nonorphan indications for each orphan drug in our review

Medicare's high-expenditure orphan drugs were typically approved for nonorphan indications as well.

Orphan Drugs with FDA-Approved Orphan and Nonorphan Indications			
Alimta	Harvoni	Neulasta	Rituxan
Avastin	Herceptin	Opdivo	
Enbrel	Humira	Prolia/Xgeva	
Gammagard Liquid	Keytruda	Remicade	
Orphan Drugs with FDA-Approved Nonorphan Indications Only (Designation Only)			
Eylea	Orencia		
Orphan Drugs with FDA-Approved Orphan Indications Only			
Copaxone	Imbruvica	Sandostatin LAR	Velcade
Darzalex	Revlimid	Soliris	

Source: OIG analysis of FDA's Orphan Drug Product Designation and Drugs@FDA Databases, as of March 30, 2020.

APPENDIX D

2018 Medicare expenditures for the orphan drugs in our review

Orphan Drugs	2018 Medicare Expenditures	Average Spending Per Beneficiary 2018
Revlimid	$4,065,312,202	$103,028
Humira	$3,169,970,208	$38,649
Eylea	$2,630,237,218	$10,684
Enbrel	$1,905,134,334	$39,324
Imbruvica	$1,867,219,911	$85,128
Keytruda	$1,833,481,477	$51,104
Opdivo	$1,742,149,938	$52,241
Rituxan	$1,735,522,535	$23,986
Harvoni	$1,725,031,870	$78,257
Prolia/Xgeva	$1,442,335,118	$2,657
Neulasta	$1,392,385,512	$15,449
Copaxone	$1,378,539,482	$55,527
Remicade	$1,181,714,327	$22,073
Avastin	$1,030,280,650	$4,517
Herceptin	$835,765,289	$39,919
Orencia	$819,142,115	$29,907
Darzalex	$655,526,968	$69,328
Alimta	$477,289,506	$24,416
Velcade	$450,993,873	$21,882
Sandostatin LAR	$421,420,868	$41,627
Soliris	$404,038,556	$340,910
Gammagard Liquid	$341,643,109	$21,488
TOTAL	**$31,505,135,066**	**N/A**

Source: OIG analysis of Medicare Part B data and Medicare Part D data, 2018.

APPENDIX E

2018 Medicare orphan utilization for each orphan drug in our review

Orphan Drug	Units Utilized for Orphan Indications	Percentage of Units Utilized for Orphan Indications	Units Utilized for Nonorphan Indications	Percentage of Units Utilized for Nonorphan Indications	Units Removed from Analysis	Percentage of Units Removed from Analysis
Alimta	546,760	7%	7,318,020	93%		
Avastin	5,405,712	37%	9,093,651	63%		
Copaxone*	3,790,835	99%	28,754	1%		
Darzalex*	12,853,462	98%	203,370	2%		
Enbrel	0	0%	1,576,376	100%		
Eylea†						
Gammagard Liquid	177,862	2%	8,804,902	98%		
Harvoni	0	0%	1,524,726	100%		
Herceptin	288,565	3%	8,689,045	97%		
Humira	112,148	9%	1,176,256	91%		
Imbruvica*	7,607,342	96%	301,338	4%		
Keytruda‡	8,339,647	20%	9,986,106	24%	23,687,792	56%
Neulasta	18	0%	333,994	100%		
Opdivo‡	18,357,094	26%	19,858,126	28%	32,236,528	46%
Orencia†						
Prolia/Xgeva	1,268,440	1%	83,449,538	99%		
Remicade	3,201,742	21%	12,052,002	79%		
Revlimid*	5,746,547	99%	83,112	1%		
Rituxan	1,144,585	54%	973,497	46%		
Sandostatin LAR*	1,889,982	78%	521,963	22%		
Soliris*	1,920,541	96%	89,885	4%		
Velcade*	9,950,411	94%	608,128	6%		

Source: OIG analysis of 2018 Medicare Part B claims and Part D PDE records.

*Note: These are orphan drugs with FDA-approval for orphan indications only. Any nonorphan utilization for these drugs may be attributable to off-label uses for the drug or to limitations of the diagnosis codes listed on the claims.

†Note: We did not calculate orphan utilization for two drugs—Eylea and Orencia. While both drugs have at least one orphan designation, they do not have FDA-approval for any orphan indications.

‡Note: Opdivo and Keytruda both have FDA-approval for orphan indications to treat small cell lung cancer (SCLC), as well as nonorphan indications to treat other non-small cell lung cancers. However, ICD 10 diagnosis codes for SCLC are not distinguishable from other non-small cell lung cancers. Therefore, we removed units utilized for lung cancer from our analysis.

DATE: Sept. 24, 2021

TO: Deputy Inspector General Suzanne Murrin

FROM: Director, Public Health Strategy and Analysis Staff

SUBJECT: FDA's Comments to OIG Draft Report:

FDA is providing the attached general and technical comments to the OIG Draft Report, High-expenditure Medicare drugs often received Orphan Drug Act incentives designed to encourage the development of treatments for rare diseases, OEI-BL-20-00080.

We appreciate the opportunity to review and comment on this draft report before it is published.

Lisa B. Rovin -S
Digitally signed by Lisa B. Rovin -S
Date: 2021.09.24 16:27:16 -04'00'

Lisa Rovin
Director, Public Health Strategy and Analysis Staff

Attachment

FDA's General Comments to OIG Draft Report, High-Expenditure Medicare Drugs often Received Orphan Drug Act Incentives Designed to Encourage the Development of Treatments for Rare Diseases, OEI-BL-20-00080

The Agency appreciates the opportunity to review and comment on this draft report.

Persons suffering from rare diseases often have no treatments. Because their populations are so small, they cannot depend on the usual market forces (e.g., supply and demand) to address their unmet needs. Recognizing this, in 1983 Congress enacted the Orphan Drug Act (ODA), to provide incentives for developing drugs needed by patients with rare diseases. In the decade prior to enactment of the ODA, very few drugs for rare diseases had been developed and approved. However, since the ODA was enacted, FDA has approved over 500 unique drugs for the treatment, diagnosis, or prevention of rare diseases. The incentives created by the ODA have helped advance Congress's goal of ensuring patients with rare diseases have the diagnostics and therapies they need. However, despite significant advances in recent years, most rare diseases continue to lack an FDA approved treatment. The ODA remains vital to driving interest in the development of products for rare diseases.

FDA appreciates OIG's look at Medicare expenditures on certain drugs that have orphan-drug designation. However, FDA is concerned that—because the objective of the report is narrow in scope—the majority of orphan drugs are not adequately assessed or represented in OIG's findings. The 20 drugs approved for rare disease indications[1] discussed in OIG's report represent approximately **only 4%** of all orphan-designated drugs with FDA approval for rare disease indications. In significant ways, these drugs are not representative of the spectrum of orphan-designated drugs that the ODA has helped bring to market for rare disease indications. For example, most of the orphan-designated drugs discussed in the report are approved for both rare disease indications and common (i.e., non-rare) disease indications. Although OIG chose to refer to these as "orphan drugs," these drugs are primarily used for their common disease indications, and according to OIG's analysis, most of the Medicare expenditure noted in the report was for the drugs' common disease indications. This is not representative of orphan drugs generally, because most drugs with orphan-drug designation that are FDA-approved are approved only for use in rare diseases. FDA believes it important to highlight these limitations so that the report's conclusions can be viewed with appropriate perspective.

The ODA provides important incentives for drug sponsors to study the safety and effectiveness of existing drugs approved for common diseases that may also show promise in treating a rare disease. Such "re-purposing" is both resource-intensive for sponsors and valuable to patients. Re-purposing may require significant investment from the drug developer and usually requires new clinical studies to assess safety and efficacy, including proper dosage for patients with the rare disease. Incentivizing this investment can allow companies to move a rare disease development program forward. Without ODA incentives, the sponsor of a drug approved for a common disease may decide not to undertake the significant investment necessary to study the safety and effectiveness of the drug in a promising rare disease use.

Where a sponsor is developing a drug for both a common disease and a rare disease, it is important to note that the orphan drug incentives associated with the ODA apply narrowly to

[1] The OIG report discusses two other drugs that have orphan-drug designation that are FDA-approved for common (i.e., non-rare) disease indications, but those two drugs are not FDA-approved for rare disease indications.

spur development of the drug for the rare disease and do not apply when the same drug is developed for a common disease.[2] Further, the sponsor is not eligible for incentives simply upon designation of its drug as an orphan drug, but the sponsor must meet additional criteria to benefit from each incentive. For example, a sponsor is only eligible for the orphan drug tax credit for certain, qualified studies in the rare disease; a sponsor is only eligible for the exemption from the marketing application fee if it submits an original application for a use in the designated rare disease and the application does not include an indication for a common disease; and orphan-drug exclusivity only applies to the drug for the approved use or indication in the rare disease and does not block approval of the same drug for a common disease use. Therefore, when the report notes that a drug has orphan-drug designation, that does not signify that the sponsor has received any incentives. To the extent that the sponsor did receive incentives, those incentives would have been tied to the development of the drug in the rare disease only.

FDA understands that drug pricing—particularly in instances in which sponsors seek and receive exclusivity incentives—is an important issue, and that decisions about drug pricing have wide-ranging effects on public health. The Agency also acknowledges the need to examine drug development incentives, to ensure that they remain tailored to achieving their purpose. However, as noted above, the OIG report only touches on a small piece of this complex public health issue. There are many factors that drive Medicare drug expenditures, and these apply whether or not a specific drug has orphan-drug designation. Ultimately, the report does not speak to the role that orphan-drug designation plays in drug pricing, or if it plays one at all.

FDA is committed to facilitating the development of treatments for patients with rare diseases. The ODA is an important tool in achieving this goal. The enactment of the ODA in 1983 was a seminal legislative event—part of a decades long Congressional effort to ensure that everyone in this country with an illness has access to safe and effective medicines—and rare disease drug development has greatly accelerated since its enactment. Core to the ODA is the concept of equity: whether the disease is common or rare, everyone deserves treatment. Today, many countries have embraced this concept and enacted laws to encourage the development of orphan drugs. The ODA is one of the brightest lights that shine on efforts to improve public health, aspiring to ensure that all patients with rare diseases will one day have the diagnostics and therapies they need.

[2] As discussed in the report, the 340B program is not part of the ODA and is not implemented by FDA, and the orphan drug exclusion applies differently than other orphan drug related incentives.

ACKNOWLEDGMENTS AND CONTACT

Acknowledgments

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This report was prepared under the direction of Dave Tawes, Regional Inspector General for Evaluation and Inspections in the Baltimore regional office, and Heather Barton, Deputy Regional Inspector General and Louise Schoggen, Assistant Regional Inspector General.

Contact

To obtain additional information concerning this report, contact the Office of Public Affairs at Public.Affairs@oig.hhs.gov. OIG reports and other information can be found on the OIG website at oig.hhs.gov.

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ABOUT THE OFFICE OF INSPECTOR GENERAL

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ENDNOTES

[1] FDA, *Rare Diseases at FDA*, February 20, 2020. Accessed at https://www.fda.gov/patients/rare-diseases-fda on January 26, 2021.

[2] Orphan Drug Act of 1983, P.L. No. 97–414 (enacted Jan. 4, 1983). Adding Subchapter B—Drugs for Rare Diseases or Conditions to Chapter V of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[3] Meekings, Kiran N., Cory S.M. Williams, and John E. Arrowsmith. "Orphan drug development: an economically viable strategy for biopharma R&D." *Drug discovery today* 17.13-14 (2012): 660-664.

[4] Chua, Kao-Ping, Lauren E. Kimmel, and Rena M. Conti. "Spending For Orphan Indications Among Top-Selling Orphan Drugs Approved To Treat Common Diseases." *Health Affairs* 40.3 (2021): 453-460.

[5] Michael G. Daniel, et al., "The Orphan Drug Act: Restoring the Mission to Rare Diseases," *American journal of clinical oncology*, April 2016, 39.2: 210-213.

[6] Orphan Drug Act of 1983, PL. No. 97–414 (enacted Jan. 4, 1983).

[7] Senator Hatch (UT). "Health Promotion and Disease Prevention Amendments." *Congressional Record* 130: 25 (October 11, 1984) p. 31839. Available from: LexisNexis Congressional; accessed 10/20/20.

[8] Senator Kassebaum (KS). "Health Promotion and Disease Prevention Amendments." *Congressional Record* 130: 25 (October 11, 1984) p. 31840. Available from: LexisNexis Congressional; accessed 10/20/20.

[9] Health Promotion and Disease Prevention Amendments of 1984, Pub. L. 98–551, 98 Stat 2815 (1984), §§ 4 and 526 of the FD&C Act.

[10] Senator Hatch (UT). "Health Promotion and Disease Prevention Amendments." *Congressional Record* 130: 25 (October 11, 1984) p. 31839. Available from: LexisNexis Congressional; accessed 10/20/20.

[11] One of the three orphan designations granted by FDA was subsequently revoked by the agency.

[12] 21 CFR § 316.23.

[13] 21 CFR § 316.20-316.21.

[14] To do this, the manufacturer must submit a cost recovery analysis that demonstrates the costs associated with developing the drug and an estimate of the expected revenues generated during its first 7 years of marketing.

[15] The New Drug Application is the vehicle through which drug sponsors (e.g., manufacturers) formally propose that FDA approve a new pharmaceutical for sale and marketing in the U.S.

[16] The Biologics License Application is a request for permission to introduce, or deliver for introduction, a biologic product for sale and marketing in the U.S.

[17] FDA, *Delivering Promising New Medicines Without Sacrificing Safety and Efficacy*, August 2019. Accessed at https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/delivering-promising-new-medicines-without-sacrificing-safety-and-efficacy on February 10, 2020.

[18] FDA, *Development and Approval Process*, October 28, 2019. Accessed at https://www.fda.gov/drugs/development-approval-process-drugs on January 22, 2020.

[19] FDA, *Rare Diseases at FDA*, February 20, 2020. Accessed at https://www.fda.gov/patients/rare-diseases-fda on January 26, 2021.

[20] Orphan drug exclusivity (ODE) applies to that particular drug product (i.e., drug ingredient) and that specifically approved orphan indication. ODE prevents FDA from approving another manufacturer's marketing application for the same product to treat the same orphan indication that is currently protected by ODE. ODE does not prevent FDA from approving another manufacturer's application for the same product if the drug is intended to be used for another indication that is not specifically protected by ODE.

[21] 21 CFR §316.34. FDA will send the manufacturer timely written notice recognizing orphan drug exclusivity (ODE) once a marketing application for a designated orphan indication has been approved. In certain cases, an orphan drug may not be eligible for ODE if the same drug product (i.e., drug ingredient) has been previously approved for the same use or indication, unless the manufacturer can demonstrate clinical superiority over the previously approved orphan drug. For the definition of "clinically superior," see 21 CFR §316.3(b)(3).

[22] 26 U.S.C. § 45C. The Tax Cuts and Jobs Act of 2017 (Pub.L. No. 115–97) reduced the tax credit from 50 to 25 percent.

[23] The Internal Revenue Service implements this incentive. Drug sponsors (e.g., manufacturers) can only claim the tax credit for costs for clinical trials that are studying the drug in the designated rare disease or condition.

[24] 84 FR 37882 (Aug. 2, 2019).

[25] A supplement is an application to allow a company to make changes in a product that already has an approved new drug application. Applicants may submit new supplemental drug applications under Prescription Drug User Fee Act VI, and these will not incur fees regardless of orphan status. According to FDA, many approvals of orphan indications are done through supplements, and thus not subject to a fee.

[26] Section 527 of the FD&C Act.

[27] FDA, *About Orphan Product Grants*, December 11, 2020. Accessed at https://www.fda.gov/industry/about-orphan-products-grants#history on May 20, 2021.

[28] Veterans Health Care Act of 1992, Pub L. No. 102-585, § 602, 106 Stat. 4943, 4967–71.

[29] H.R. Rep. No. 102-384(II), at 12 (1992) (Conf. Rep.).

[30] GAO. *Medicare Part B Drugs: Action Needed to Reduce Financial Incentives to Prescribe 340B Drugs at Participating Hospitals*. GAO-15-442. (2015).

[31] To obtain payment for covered drugs, providers submit claims to Medicare using Healthcare Common Procedure Coding System (HCPCS) codes. In the case of prescription drugs, each HCPCS code defines the drug's name and the amount of drug represented by one unit of the HCPCS code but does not specify manufacturer or package size information. Claims also contain diagnosis codes based on documentation in the patient's medical record.

[32] 42 CFR § 414.900(b) and Medicare Benefit Policy Manual, ch. 15 § 50.

[33] Some of the orphan drugs in our sample include biological products, which are some of the most expensive drug treatments available. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

[34] One drug in our sample—Eylea—was not granted orphan status until July 2019. However, given that Eylea was the highest expenditure Medicare drug in both 2018 and 2019, including the drug in this part of the analysis is appropriate to show the large presence of orphan drugs in Part B. In 2019, expenditures for these 16 drugs continued to account for half of all Part B drug spending.

[35] For Parts B and D, average spending per beneficiary for each drug is based on total spending in 2018 divided by the total number of beneficiaries who received the drug. Because a beneficiary may have received a drug for only part of the year (e.g., he or she began treatment in November), the numbers presented here likely underestimate the actual annual cost for many patients.

[36] The orphan drugs in our review may also have active patent protections which prevent generic competition. The lack of generic competition may be a factor contributing to higher drug prices. In general, the term of a new patent is 20 years from the date on which the application for the patent was filed.

[37] This includes 1,829 beneficiaries who were treated for multiple myeloma as well as at least 1 of 4 other rare diseases Revlimid is approved to treat.

[38] Out-of-pocket costs vary depending on specific prescription drug plan designs, the drug being purchased, and which phase of Part D coverage the beneficiary is in. Beneficiaries may also receive assistance from other payors such as the low-income subsidy, State Pharmaceutical Assistance Plans, group health plans, or governmental programs that reduce their out-of-pocket costs.

[39] Seven of the 22 drugs in our sample were originally approved for a common nonorphan disease or condition before being granted an orphan designation.

[40] Specifically, Prolia/Xgeva has FDA-approval to market for two orphan indications: (1) treatment of hypercalcemia in malignancy refractory to bisphosphonate therapy and (2) treatment of patients with giant cell tumor of bone.

[41] 42 U.S.C. § 256b(a)(1).

[42] GAO. *Medicare Part B Drugs: Action Needed to Reduce Financial Incentives to Prescribe 340B Drugs at Participating Hospitals*. GAO-15-442 (2015).

[43] CMS, *Medicare Part D Drug Spending Dashboard & Data*. Accessed at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD on January 22, 2020.

[44] Although manufacturers are not required to provide the statutory discount on orphan drugs to these covered entities, manufacturers may do so at their discretion.

[45] CMS, *Medicare Part B Drug Spending Dashboard*. Accessed at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartB on January 22, 2020.

[46] CMS, *Medicare Part D Drug Spending Dashboard & Data*. Accessed at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD on January 22, 2020.

[47] FDA, *Search Orphan Drug Designations and Approvals*. Accessed at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/ on January 22, 2020.

[48] FDA, *Drugs@FDA: FDA-Approved Drugs*. Accessed at https://www.accessdata.fda.gov/scripts/cder/daf/ on January 22, 2020.

[49] Several drugs in our review received approval for new orphan indications during 2018 and 2019. Because ICD-10 codes do not always provide the granularity for subpopulations or other specific characteristics of a disease, we did not remove any utilization related to these later approvals from our analysis. As a result, any off-label use for these "future" orphan indications at any point in 2018 was considered to be orphan utilization.