An Assessment of Regulatory Interpretation of Qualifying Single-Source Drugs in Medicare Negotiation

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Executive Summary

The drug development process is complex and involves continued learning about a product's safety and efficacy in potential new patient populations. Based on continued learnings about a product after original approval, manufacturers may seek to invest in new uses and treatment areas. Manufacturers and other stakeholders consider evolving market dynamics, including those brought about by major policy changes such as the Inflation Reduction Act (IRA)'s Medicare Drug Price Negotiation Program, as they weigh the benefits and risks associated with investments for a given product.

The IRA directs the Centers for Medicare & Medicaid Services (CMS) to select certain qualifying single-source drugs with the highest Medicare expenditures for negotiation and establish maximum fair prices (MFPs) for these products. The IRA sets broad parameters for the selection of drugs for negotiation, but delegates to CMS decisions about specific methodology and program implementation. In June 2023 guidance on the implementation of the Medicare Drug Price Negotiation Program for the 2026 plan year, CMS adopted a broad interpretation of the definition of a "qualifying single-source drug." Specifically, to identify qualifying single-source drugs and rank them for negotiation selection, CMS is aggregating expenditures from all forms and strengths of approved drugs with the same active moiety/ingredient, including across different New Drug Applications (NDAs) or Biologics License Applications (BLAs). This aggregation will impact products with additional approvals for new uses that are pursued after the original NDA or BLA approval. Because development of new uses for a product involves additional clinical trials and resource investments, this aggregation may shift manufacturer strategies for product development.

Avalere was commissioned by Novo Nordisk to examine the potential implications of CMS's interpretation of a "qualifying single-source drug" under the Medicare Drug Price Negotiation Program. Because eligibility for negotiation is based on the initial product approval date, CMS's interpretation to aggregate products by active moiety/ingredient (including across different NDAs or BLAs) will affect which drugs are eligible for selection and when they may be subject to an MFP. This paper features case studies of real products that illustrate how post-approval research of existing products to new patient populations and treatment areas can occur under new licenses, often several years after a product's original approval. If the IRA had been in effect for the entire lifecycle of these case study products, the aggregation of multiple license approvals may have influenced manufacturer investment decisions for post-approval research, potentially impacting various patient populations' access to the new product uses that were subsequently approved.

Introduction

The drug development lifecycle is often a lengthy and iterative process. Based on technological advancements, initial testing, and an accumulation of evidence on specific benefits of a product, manufacturers may seek to gain marketing approval from the Food and Drug Administration (FDA) for initial indications. Following approval, more evidence can be uncovered on new uses, disease areas, and subpopulations for the product. As this new evidence emerges, either from post-marketing studies requested by the FDA or other studies independently designed by the manufacturer, companies may opt to expand upon currently approved indications based on evolving patient needs. Research into new uses for a product requires additional clinical studies to support product efficacy regarding the new or expanded treatment or use. Although both initial approval and post-approval studies require time and resource investments, post-approval research into new uses of existing drugs can accelerate the FDA review process and allow manufacturers to bring new treatment options to patients more quickly than they could develop a new molecular entity.

Clinical and safety considerations such as disease state and patient characteristics (e.g., adult vs. pediatric populations) can dictate the initial target populations for a product. As part of a product's initial approval, the FDA may require post-marketing studies that explore product effectiveness in additional populations. Through these required post-marketing studies and other real-world evidence, manufacturers may continue to learn about a product's safety and efficacy in different populations following initial approval.

When assessing significant investment decisions, manufacturers and other stakeholders consider changes to the market environment. The IRA's Medicare Drug Price Negotiation Program will shift manufacturer development strategies and investment decisions by selecting drugs for negotiation and setting MFPs. CMS's regulatory interpretation to aggregate drugs by active moiety/ingredient may further impact manufacturers' evaluation of post-approval investment for new product uses due to the shortened timeline for a product to be on the market before the potential application of an MFP.

Avenues to Pursue Expanded Use of Approved Medicines

When evidence demonstrates potential to expand an approved product for new uses or patient populations, manufacturers can pursue a separate NDA or BLA or an efficacy supplement to the existing NDA or BLA (referred to as an sNDA or sBLA). Each pathway has different considerations for the level of resources required and implications for the product's label (Table 1).

Table 1. Comparison of Resource and Evidence Requirements and Label Considerations for Expansions via a Separate NDA/BLA vs. a sNDA/sBLA

	Expansion via Separate NDA/BLA	Efficacy Supplement (sNDA/sBLA)
Studies/ Evidence Burden	• Generally requires at least two placebo-controlled studies • Pediatric and post-marketing studies may be required	• Generally requires one placebo-controlled study
Timing	• May take three to six years to complete trials and receive regulatory review for separate NDAs/BLAs (after original approval), depending on the number of additional clinical studies conducted • More likely to require facility inspection, particularly if approval includes manufacturing or formulation changes	• Likely to take less than four years for clinical trial data to be collected and for the supplemental application to be reviewed by the FDA • May require facility inspection, but inspection may be completed as part of a separate supplemental application
Label Language	• Opportunities for unique label and different product branding	• Updates the existing product's label and new use falls under the same brand name

Both pathways involve additional clinical studies with similar evidence requirements and associated costs. Average costs for one Phase III placebo-controlled study are approximately $138 million, although costs vary significantly depending on the patient populations studied.[1] The number of studies required for a new NDA or BLA is likely to be higher than for a supplemental application, which could increase the time and resources associated with getting the product approved for a new condition or therapeutic area. Ultimately, manufacturer decisions to pursue a separate versus a supplemental application may be driven by factors such as variability in patient populations being treated and differences in prescriber specialization, as well as to provide clarity to stakeholders on a product's use for different patient populations.

The FDA published guidance in 2004 to inform manufacturer decisions for filing an sNDA/sBLA versus a separate NDA or BLA for a new use. However, this guidance has not been updated since its initial release. Although the FDA's guidance recommends that sponsors file a separate application if there are changes to the product's route of administration or dosage forms, both pathways have been used in various instances by manufacturers.

[1] Estimates derived from: PhRMA. "Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies." Available here, and FDA. "The Drug Development Process, Step 3: Clinical Research." Available here.

Interaction of the Medicare Drug Price Negotiation Program with Manufacturer Decisions on Post-Approval Research for New Uses

The IRA's Drug Price Negotiation Program establishes MFPs beginning in 2026 and introduces new considerations for manufacturers regarding product development strategies, particularly as they relate to new treatments and uses. Under Medicare negotiation, CMS will set MFPs for certain qualifying single-source drugs with the highest Medicare spending. Drugs without generic or biosimilar competition qualify for selection if they have been approved for at least seven years for small molecule drugs and for at least 11 years for biologics.

In June 2023, CMS issued revised guidance to implement the Medicare Drug Price Negotiation Program for the 2026 plan year. This guidance defines qualifying single-source drugs broadly. Section 1192(d)(3)(B) of the IRA specifies that to determine whether a qualifying single-source drug satisfies the negotiation selection criteria, "the Secretary shall use data that is aggregated across dosage forms and strengths of the drug, including new formulations of the drug." CMS's June 2023 guidance interprets this passage to mean that, for purposes of selecting drugs for negotiation and setting MFPs, all dosage forms and strengths of a drug with the same active moiety/ingredient are aggregated, including products with different NDAs or BLAs. This approach treats products with the same active moiety/ingredient effectively as a single product, despite potential differences in disease areas, patient populations, and time on market following FDA approval.

This aggregation of drugs by active moiety/ingredient will affect negotiation eligibility and drug selection. Based on the IRA parameters for selection and the regulatory interpretation to aggregate by active moiety/ingredient, a treatment's first approved use and any new uses and/or subsequently approved products will be eligible for negotiation based on the initial approval of the first indication (i.e., 7 years since initial NDA approval or 11 years since the initial BLA approval). Application of an MFP based on the original approval may therefore shift manufacturer cost-benefit assessments when considering research investments. Moreover, since separate NDA/BLAs with the same active moiety/ingredient are combined to rank drugs for negotiation selection, some drugs may rank higher on the list because spending is consolidated across multiple NDAs or BLAs. Conversely, some products with high spending may become ineligible for selection if a generic or biosimilar with the same active moiety/ingredient has been launched in reference to only one of the originator product NDAs or BLAs. A generic or biosimilar need not be available for all NDAs or BLAs to remove the originator product from negotiation selection.

Case Studies

Avalere evaluated the product lifecycle of real products to examine how the regulatory interpretation of a qualifying single-source drug for negotiation may have affected manufacturer decisions to invest in new uses and treatments for existing products. The six case studies highlighted below (Figures 1–6) include a range of products originally approved for chronic disease, rare disease, or cancer. Separate NDAs or BLAs were later approved for new uses, either within the same disease area or for different therapeutic areas targeting new patient populations. For example, three of the products initially approved as treatments for rare diseases expanded via new NDAs/BLAs into chronic disease areas and/or for pediatric indications (Figures 2–4).

Each new indication shown in the figures below was approved through separate NDA/BLA licenses. All case study products had at least one additional approval via a separate NDA/BLA, with four case study products having at least two additional NDA/BLA approvals (Figures 1–6). While not shown in the figures, five case study products also leveraged sNDAs/sBLAs to add additional indications to the label associated with a particular NDA/BLA.

Across all case study products, there were 15 separate NDAs/BLAs that were approved after the time of the original NDA approval(s). Seven of these separate NDAs/BLAs were approved at approximately the same time or after the product would have been eligible for negotiation selection, had the IRA's negotiation policy been in effect during the product's lifecycle.

For some products, expansions included chronic diseases with millions of addressable patients, while others were for smaller patient populations with rare or pediatric conditions that had unmet medical needs. Due to the investment and time required to pursue these new indications, the risk of negotiation may have changed manufacturer evaluations related to continued research and investments had the IRA's negotiation policy been in place during the products' lifecycles.

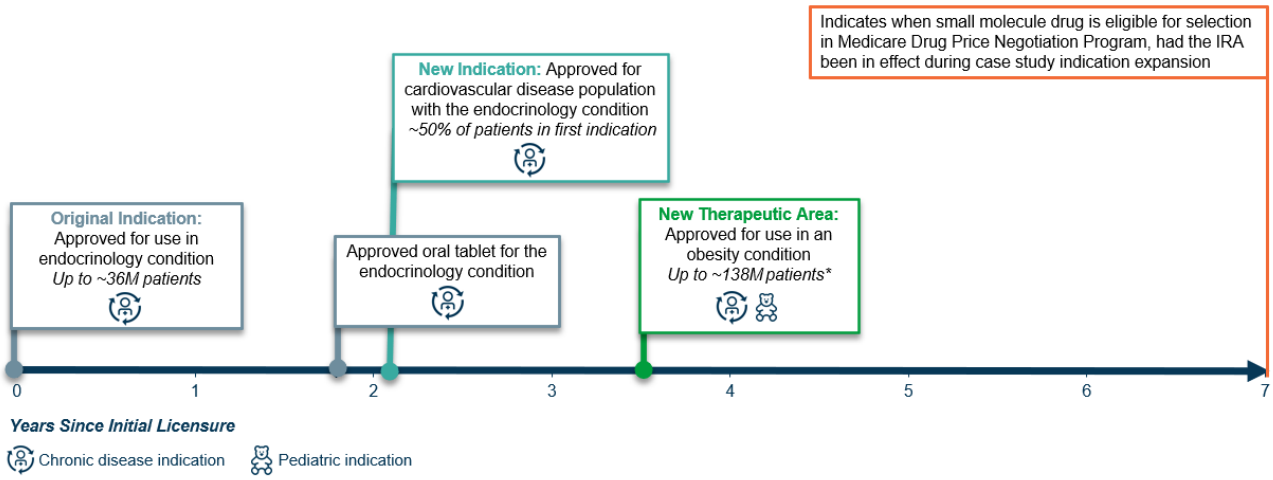
Products Treating Chronic Diseases

Case studies 1 and 2 (Figures 1 and 2) represent products developed for multiple uses addressing large patient populations with chronic disease. Treatments tailored to larger patient populations can increase a product's utilization and balance the required investments for research and development. However, under Medicare negotiation, higher utilization by large patient populations is likely to increase Medicare spending associated with a product (defined based on active moiety/ingredient), potentially resulting in the product being selected earlier for negotiation. Given the level of investment needed to conduct research into treatments for larger patient populations, the risk of negotiation selection may have shifted manufacturers' strategies for investing in new uses pursued either before or after the product would have been eligible for negotiation.

Case study product 1 (Figure 1) was originally approved for a chronic condition with approximately 36 million addressable patients. The product expanded via three separate NDAs,

with the third NDA indicated for a chronic and pediatric patient population of more than 130 million potential patients. These expansions occurred over a shorter time period and prior to when the drug would be eligible for negotiation selection. However, had Medicare negotiation been in effect, increased utilization due to each new use would have elevated the product on the negotiation list.

Figure 1. Timeline of New Uses Approved Using Separate Licenses, Case Study 1



*Patient estimates are illustrative, derived by extrapolating most recent incidence and death rates to the 2021 US census estimate for the population (331,445,000 people)

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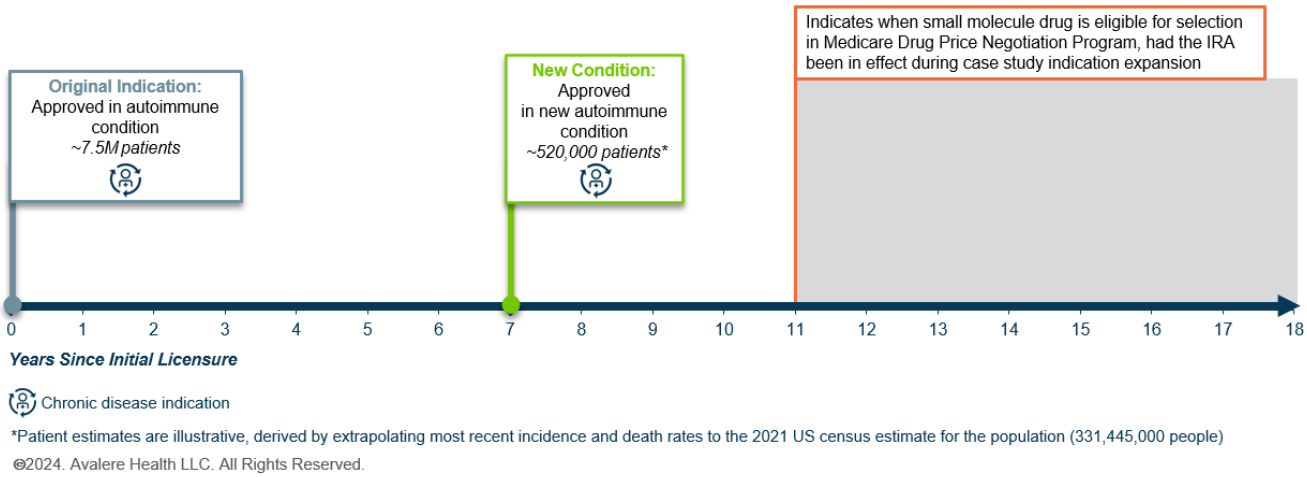
Case study product 2 (Figure 2) is a biologic first approved for a chronic, autoimmune condition with approximately 7.5 million addressable patients. Seven years after initial approval, the product expanded via a new BLA to another chronic autoimmune condition treating approximately half a million patients. Although biologics—compared to small molecule drugs—are subject to a longer timeframe before negotiation eligibility, the approval for the new condition would have begun a four-year countdown before the product would have been eligible for negotiation selection. This reduced timeframe and the potential increased spending associated with additional utilization for the new use may have shifted the manufacturer's risk-benefit assessment of the additional investment that was required for approval.

Figure 2. Timeline of New Uses Approved Using Separate Licenses, Case Study 2



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Products Originally Approved for Rare Diseases

The IRA also changes manufacturer incentives to develop products for rare diseases. Although products indicated for only one rare disease are exempt from negotiation, products that treat more than one rare disease or condition are eligible for selection. This potential for selection may change manufacturer evaluations for balancing investments in research and development for new uses, particularly for additional approvals of a rare disease product that occur after the drug would be eligible for negotiation. Due to the small target patient populations and resources needed to invest in treatments for rare and orphan diseases, an MFP could complicate the typical research and development approaches taken by manufacturers.

Case study products 3 and 4 (Figures 3 and 4) represent products that were originally approved for rare diseases with fewer than 20,000 addressable patients but later expanded via additional NDA approvals to chronic dermatology conditions with addressable populations of nearly 25 million patients. More than 20 years after the original NDA approval, the product in case study 3 also expanded to a novel dosage form for the dermatology condition.

These expansions to large patient populations may balance the required investments for research and development particularly for products initially indicated to treat rare diseases; however, expansion beyond the initial rare disease would also have made the product eligible for negotiation. Increased utilization by these large patient populations may have increased the product's likelihood of being selected for negotiation and changed manufacturer's investment strategies for either the large chronic disease indications or the initial rare disease indications.

Figure 3. Timeline of New Uses Approved Using Separate Licenses, Case Study 3

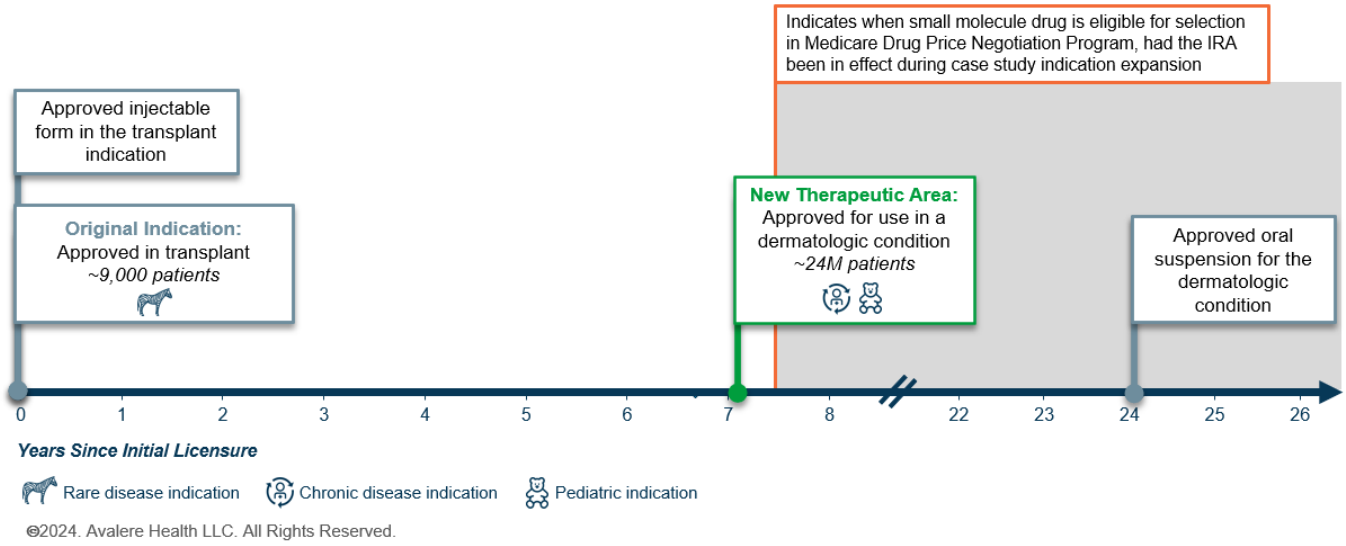

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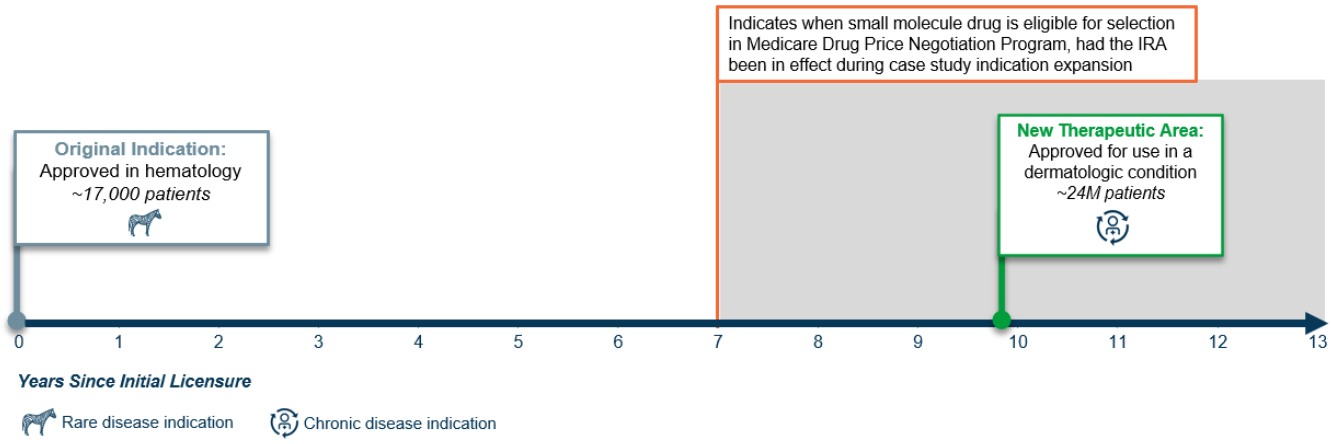
Figure 4. Timeline of New Uses Approved Using Separate Licenses, Case Study 4



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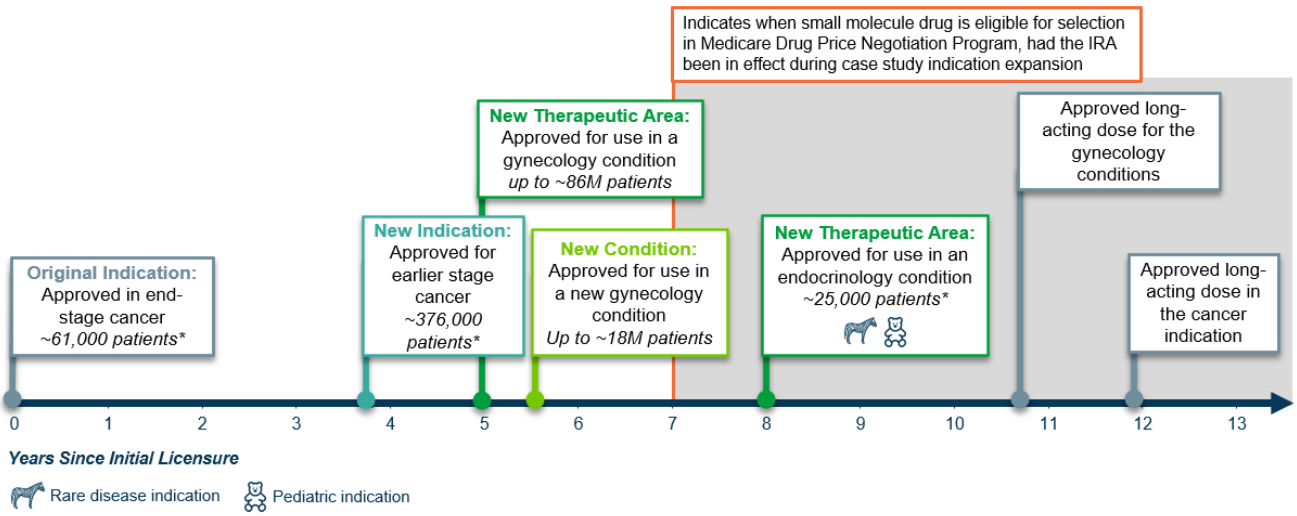
Products Originally Approved for Cancer

Manufacturers have also developed certain cancer products for different forms of cancer or entirely different therapeutic areas. Case studies 5 and 6 (Figures 5 and 6) demonstrate how negotiation could introduce new considerations for manufacturers related to post-approval investment into new uses.

Case study product 5 (Figure 5) had the most additional NDA approvals among the products analyzed. Although the product was initially approved for cancers with relatively small addressable patient populations (fewer than 500,000 total patients for the first two indications), licenses three and four expanded the product to treat conditions with more than 100 million potential patients a few years before the product would have been eligible for negotiation. As with case studies 1–4, these expansions would increase the product's utilization and risk for earlier selection for negotiation.

After the product would have been eligible for negotiation selection, it received three new NDAs, including one (license 5) addressing a rare, pediatric patient population (Figure 5). Due to the investments needed for additional research into treatments for rare and orphan diseases, an MFP could have shifted the manufacturer's evaluations related to this rare condition and/or for the conditions with larger treatment populations that were approved before eligibility for selection.

Figure 5. Timeline of New Uses Approved Using Separate Licenses, Case Study 5



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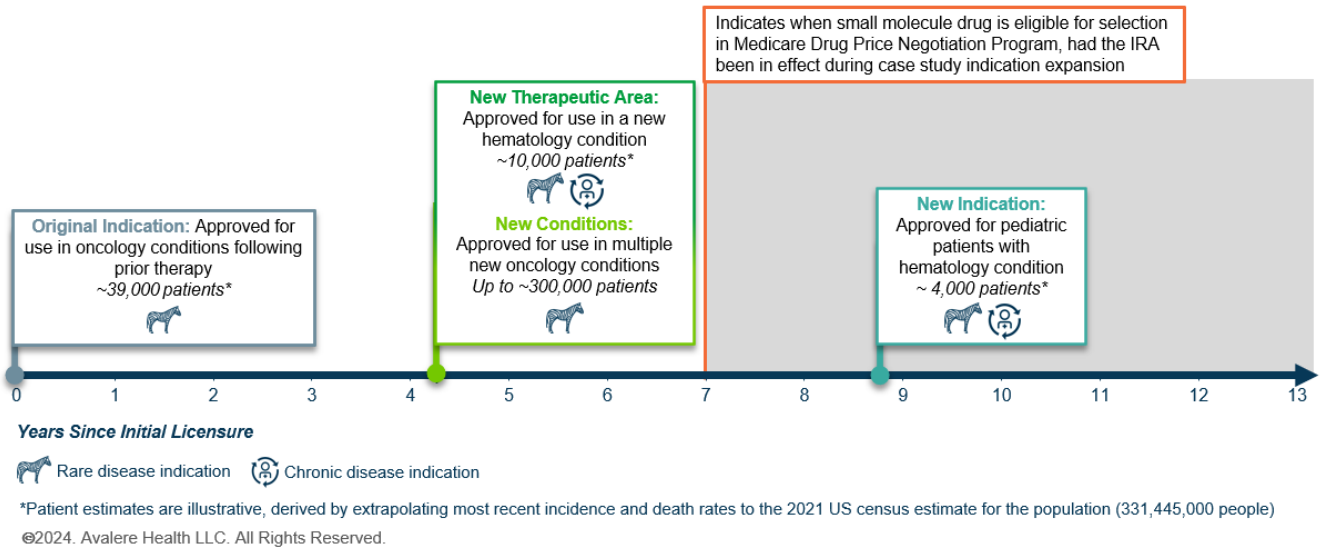
Case study product 6 (Figure 6) was originally approved for a rare cancer and expanded to additional oncology and hematology conditions. These additional approvals would have made the product eligible for negotiation selection. Given the small patient populations for the additional product approvals and level of investment needed for research into rare and orphan diseases, an MFP could complicate the typical approach for research investments used by rare disease manufacturers.

Figure 6. Timeline of New Uses Approved Using Separate Licenses, Case Study 6



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Conclusion

These six case studies explore how CMS's aggregation of drugs by active moiety/ingredient, including across multiple NDAs or BLAs, aligns with real-world drug development scenarios to consider the potential impact of CMS's policy interpretation on manufacturer decisions to conduct additional research into new uses of drugs that have already received an initial FDA approval. Combining spending across all approvals is likely to increase a product's utilization and its overall Medicare spending, as shown in the case studies by the potential addressable patients for each expanded NDA. Higher utilization and Medicare spending moves products higher on CMS's list for negotiation selection. Additionally, because the eligibility timeframe for negotiation selection is tied to the original product approval, manufacturers may reassess investments later in a product's lifecycle (i.e., after the product would be eligible for selection) compared to the pre-IRA policy landscape.

When conducting post-approval research into new uses and treatment areas, whether through a separate NDA/BLA or supplemental application, manufacturers must weigh the risks associated with resource investments against the potential benefits of gaining approval to treat new patient populations. Medicare negotiation introduces new factors that manufacturers will need to incorporate into their cost-benefit analyses when making investment decisions. These new factors may cause manufacturers to adjust their approaches to the types of conditions and/or disease areas invested in. Shifts in investment strategies could have future implications for patient access to new treatment options, potentially affecting large numbers of patients as well as those with rare, serious conditions and/or unmet need.

Methodology

Case study products were identified using the FDA's drugs@FDA public repository of license and label information. Products were selected as case studies if they had multiple licenses approved for the same active moiety/ingredient. To derive the timeline of indication expansion, each associated NDA was examined for approval dates and indication(s) for which that approval was granted. Then, as subsequent licenses were examined, the reason for a subsequent approval was noted to determine the type of indication expansion that occurred due to the new license (e.g., expanded indication, new condition, or new therapeutic area). To assess whether labels were separated or merged, the most recent label for each license was compared to labels from all other licenses to determine whether information was consistent or divergent. To determine whether the new license approval corresponded to a rare disease indication, the FDA's orphan drug database was searched for that brand name to determine what indications were designated and approved. Chronic disease indications were assessed based solely on drug label dosing information. Diseases that require consistent administration over a patient's lifetime were considered chronic disease indications, while recurring diseases were not necessarily considered chronic disease indications, unless the product dosing corresponded to lifetime use. Pediatric indications were assessed based on the indications and usages section of the corresponding label.

The addressable patient populations for each indication or therapeutic area expansion in the case studies were determined through secondary research on disease prevalence in publicly available academic research or data sets (e.g., white papers, US Centers for Disease Control and Prevention and Surveillance, Epidemiology and End Results data) or by extrapolating most recent incidence and death rates from publicly available sources to the 2021 US census estimate for the population (i.e., 331,445,000 people).

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