Impact of Medicare Drug Price Negotiation on Cardiovascular Disease Product Development and Patient Access

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Executive Summary

Across the product development lifecycle, pharmaceutical manufacturers must prioritize products and indications for investment. Significant policy changes, such as those introduced by the Inflation Reduction Act (IRA), are likely to impact key elements of manufacturer and investor strategies and shape product development plans. Specifically, the IRA's Medicare drug price negotiation provision subjects selected products to a maximum fair price (MFP) after a certain number of years on the market; this policy may shift incentives for manufacturers pursuing new indications of approved drugs.

In August 2023, the Centers for Medicare & Medicaid Services (CMS) announced the list of 10 drugs selected for Medicare negotiations beginning in 2026—the first year of the IRA program. Five of the 10 selected drugs treat cardiovascular disease (CVD), likely because CVD affects a large proportion of Medicare beneficiaries. In 2019, almost half of American adults had been diagnosed with a CVD condition, and more than 8 million Medicare beneficiaries were taking one of the five CVD drugs selected for negotiation in 2026.

Despite CVD's high prevalence in the United States (US), new drug development has diminished for CVD relative to other therapeutic areas during recent years. The need to continue to encourage innovation and improve outcomes for patients creates an environment in which the development of cardiovascular treatments may be particularly affected by the IRA.

To assess the potential implications of Medicare negotiation on the CVD landscape, the Partnership to Advance Cardiovascular Health commissioned Avalere to analyze the unique dynamics facing CVD drug development and how IRA incentives may affect the timing of core development decisions and timelines. Specifically, Avalere reviewed published literature and Phase III clinical trial data to assess the resource requirements for CVD drug development, including statistics on late-stage CVD clinical trial success rates, trial duration, patient enrollment, and study populations.

The findings from this review inform how Medicare negotiation timelines may affect decisions by manufacturers of CVD drugs regarding new indications. To that end, Avalere mapped the development timeline for two FDA approved products that will be subject to MFP in 2026, each with multiple CVD indications, to the Medicare negotiation timeline to understand emerging product lifecycle pressures.

Select Findings

The study revealed that CVD trials involve distinct challenges, including the following, compared to trials on other chronic conditions analyzed:

- Larger study enrollment: Phase III CVD trials averaged 67% greater enrollment than respiratory disease trials and 107% greater enrollment than metabolic disease trials.

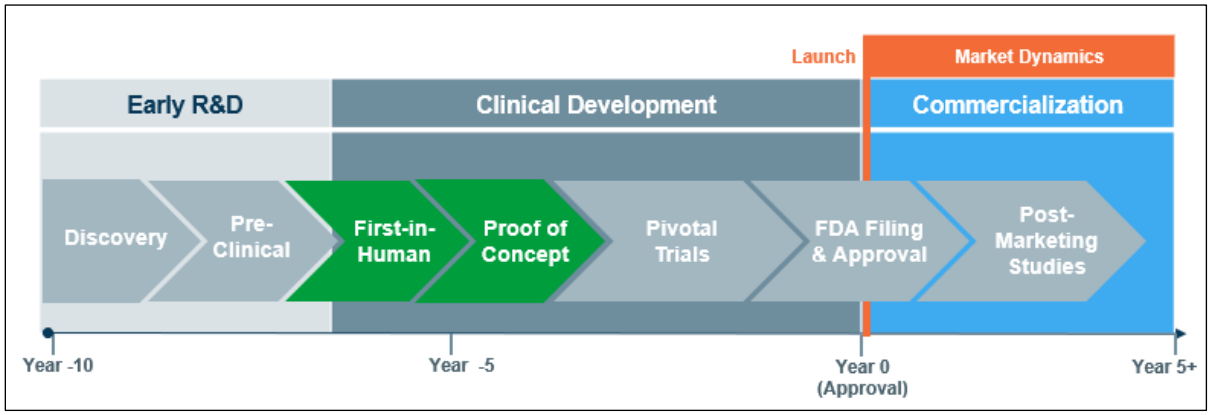
- Longer clinical trials: Phase III CVD trials took between 28%-32% longer to complete than metabolic and respiratory disease trials.
- More trial sites: The average number of sites per trial was more than 40% greater for Phase III CVD trials than it was for respiratory or metabolic disease trials.
- Lower success rates: The likelihood of success from Phase I trial to FDA approval was 150% greater for respiratory disease and 300% greater for metabolic disease compared to CVD. CVD trials had the second-lowest likelihood of success among the conditions analyzed.

The resource requirements for CVD trials will likely present unique considerations for CVD drug manufacturers' development strategies in the future. The high prevalence of cardiovascular conditions in the US suggests that most CVD drugs on the market will be at a high risk for IRA negotiations. Moreover, most CVD drugs are small molecules, which, according to IRA statute, renders them eligible for negotiation 4 years earlier in their post-approval lifecycle than biologics. IRA negotiations will also be applicable at the drug level, across indications and formulations, which may force manufacturers to make difficult decisions on post-marketing research to achieve secondary indications for drugs, potentially affecting what types of products will be available to patients.

Background

The development and regulatory process for drug approval is lengthy and complex. Pharmaceutical manufacturers pursue development of a product during the proof-of-concept phase, years before seeking US Food and Drug Administration (FDA) approval (Figure 1). FDA mandates manufacturers to collect post-marketing evidence following approval, leading to ongoing learnings about product safety and effectiveness. As such, manufacturers make strategic decisions about whether to pursue indication expansion, which requires revisiting conduct of clinical trials and submission to FDA. This sequential learning process provides an opportunity for manufacturers to uncover use cases in new patient populations, leading to additional product indications and expanded patient benefits.

Figure 1. Example Product Development Timeline



Although key steps of the drug development process remain constant, considerations associated with these steps vary depending on the therapeutic area and potential opportunity for return on investment (ROI) for the asset. Changes in the health policy landscape that shift dynamics in key payer markets can impact the timing or sequence of when product development decisions need to be made by manufacturers, both for lead indication approvals and for label expansion decisions. Policy changes may also alter the market outcomes of those development decisions.

The IRA is a landmark policy change that will shift the healthcare landscape. One provision of the IRA is the Medicare Drug Price Negotiation Program, through which CMS will select a specific number of drugs with the highest Medicare spending each year and negotiate with the manufacturers of those products to set an MFP. To be eligible for selection for the negotiation list, a product must have been approved for at least 7 years for small molecule drugs and at least 11 years for biologics and must have no generic or biosimilar competition during that period on market. After considering various factors, such as research and development (R&D) costs, clinical evidence and treatment alternatives, CMS will set an MFP for each selected drug. The number of drugs selected for negotiation will increase each year, ultimately reaching 20 new drugs per year beginning in 2029. The 100 Medicare Part B and D drugs deemed likely to be selected for government negotiation from 2026-2031 will represent almost half of total 2020 Part B and D drug spending.[1]

CMS revealed the initial list of 10 drugs selected for negotiation on August 29, 2023.[2] The list is based on total Medicare spending for products that are not for rare diseases and lack generic or biosimilar competition. Therefore, the therapeutic areas represented are generally chronic diseases with high prevalence among American seniors. Five of the 10 drugs selected for the first negotiation year were products with at least one CVD indication, likely because CVD affects a large proportion of Medicare beneficiaries. In 2019, nearly half of American adults had a CVD condition, and more than 8 million Medicare beneficiaries were taking one of the five CVD drugs selected for negotiation.[3,4]

To examine the impact of IRA drug price negotiations on CVD drugs, Avalere analyzed current product development trends and unique dynamics affecting development of CVD drugs in the context of the IRA negotiation process. Specifically, Avalere reviewed published literature and Phase III clinical trial data to assess the resource requirements of CVD drug development, including statistics on late-stage CVD clinical trial success rates, trial duration, patient enrollment, and study populations. The development timeline for two case study products was then mapped to the Medicare negotiation timeline.

CVD Drug Development and Timeline Burdens

Late-Stage Resource Requirements of CVD Drug Development

Published literature detailing CVD drug development demonstrates that CVD trials involve distinct challenges for manufacturers because of dynamics unique to the therapeutic area. Endpoints in CVD trials often assess the risk of rare, severe future events, which requires longer periods of patient observation.[5] Additionally, CVD trials for new agents require demonstration of noninferiority to proven available treatments, contributing to the need for large patient populations and resulting high mean costs for CVD Phase III studies.[6]

Although CVD drug developers have attempted to increase use of alternative endpoint strategies to save on costs and provide quicker access to therapies, these efforts have not been especially successful. Measures such as surrogate or intermediate endpoints have the potential to provide efficacy data years before the availability of validated clinical outcomes.[7] However, while trials have demonstrated positive results against some surrogate endpoints in CVD, they have not linked those results to the variability of clinical outcomes observed. Some of these trials have also overlooked comorbidities associated to treatment use.[8,9] CVD stakeholders representing patients, providers, and industry have thus resolved that CVD medicine must continue to rely on proven clinical outcomes for future drug development.[10]

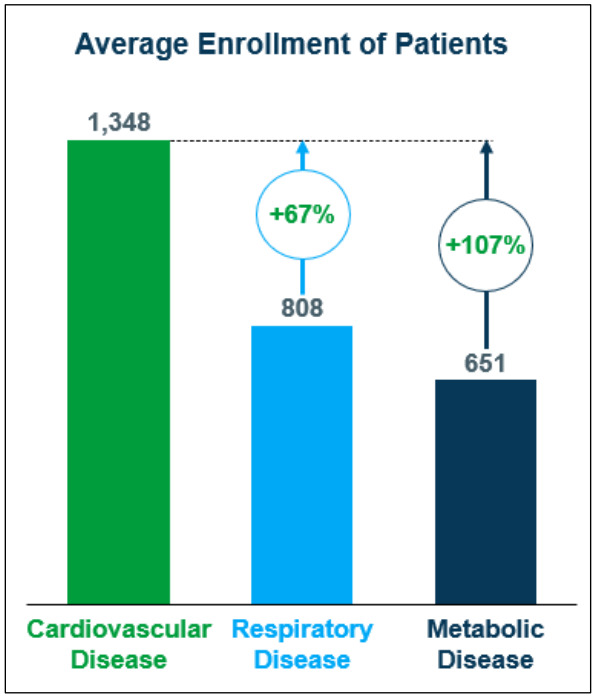
Clinical programs in CVD have been halted due to lack of commercial viability rather than lack of drug safety or effectiveness, which is another unique observation in this TA.[11] Lack of commercial viability has been attributed to expectations of increasing future development costs, decreasing revenues, and the abundance of clinical guidelines that establish a competitive standard of care.[12] Literature also indicated that the likelihood of success from Phase I studies to FDA approval was 150% greater for respiratory disease and 300% greater for metabolic disease compared to CVD. When compared to other therapeutic areas, CVD drugs had the second-lowest likelihood of successful advancement from early clinical development to FDA approval.[13,14]

ROI considerations appear to play a significant role in decisions to discontinue development. Additionally, the long timeline required to collect patient outcomes in CVD compared to other therapeutic areas has led to larger, longer, and costlier trials.[15] To assess whether recent trial data supported these previously published observations, attributes of Phase III clinical trials from 2011–2023 were quantified to observe trends in enrollment size, trial duration, number of trial sites, and total number of trials.

Trial Size

The size of clinical trials is a critical variable in measuring the burden of R&D for a drug or therapeutic area because larger clinical trials require more effort and resources to conduct. The analysis found evidence that CVD trials are larger than trials in other therapeutic areas with high disease prevalence. Specifically, CVD trials averaged 67% higher enrollment than respiratory disease trials and 107% greater enrollment than metabolic disease trials (Figure 2).

Figure 2: Average Number of Patients Enrolled in Phase III Studies in Three Therapeutic Areas, 2011–2023



Further, the maximum enrollment observed in a CVD trial (27,564 participants) was over 10,000 more patients than the highest enrollment observed in either of the other two therapeutic areas analyzed (Figure 3).

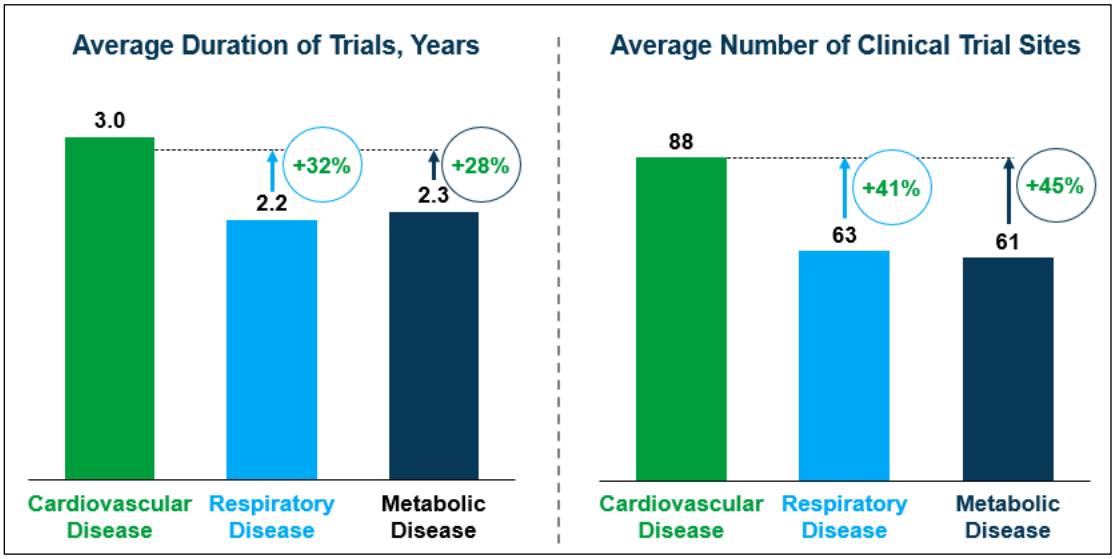
Figure 3: Highest Enrollment Tested in Phase III Studies in Three Therapeutic Areas, 2011– 2023

Phase III Trials	Cardiovascular Disease	Respiratory Disease	Metabolic Disease
Largest Enrollment	27,564	17,183	14,752

Trial Duration and Number of Trial Sites

Phase III CVD trials took between 28%-32% longer to complete than metabolic and respiratory disease trials, respectively. Additionally, the average number of trial sites was more than 40% greater for Phase III CVD trials than for respiratory or metabolic disease trials (Figure 4). This latter difference in sites may be reflective of the higher number of patients enrolled in CVD Phase III trials and may also be attributable to other geographic and epidemiological characteristics outside the scope of this analysis.

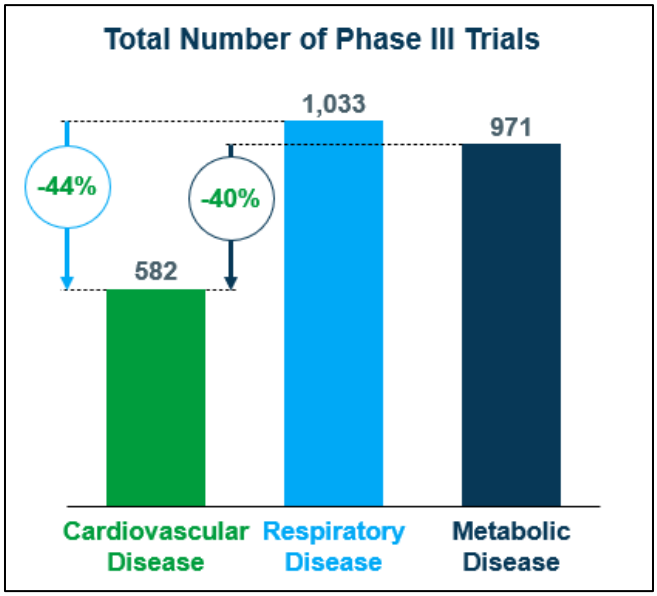
Figure 4: Average Duration (Years) and Number of Trial Sites for Phase III Studies in Three Therapeutic Areas, 2011-2023



Number of Completed Trials

The analysis found that 40%-44% fewer CVD trials were conducted compared to the number conducted in the other therapeutic areas (Figure 5). This aligns will previously published analyses on the CVD pipeline and investment as compared to other therapeutic areas.[16,17] Such a disparity may correlate to the relatively longer duration and larger size of CVD Phase III trials.

Figure 5: Total Number of Completed Phase III Studies in Three Therapeutic Areas, 2011-2023



Small Molecule vs. Biologic Development

Pressures from different negotiation timelines for small and large molecule drugs may inhibit development of future CVD products. Small molecule drug products are eligible for negotiation after 7 years on the market, whereas large molecule biologics are eligible after 11 years. Thus, manufacturers have 4 fewer years to recoup investment in small molecule drugs than in biologics. Only approximately 6% of Phase III CVD drug trials tested biologics (Figure 6), whereas approximately 80% tested small molecule drugs. This disparity demonstrates the importance of small molecule drugs for CVD. The IRA's differential in negotiation eligibility between biologics and small molecule drugs may steer manufacturers toward developing biologics instead of small molecule drugs—a trend that may reduce even further investment in CVD drug development.[18]

Figure 6: Percentage of Biologics Tested in Phase III Studies in Three Therapeutic Areas, 2011-2023

Phase III Trials	Cardiovascular Disease	Respiratory Disease	Metabolic Disease
% Testing Biological Interventions	6.2%	22.3%	6.8%

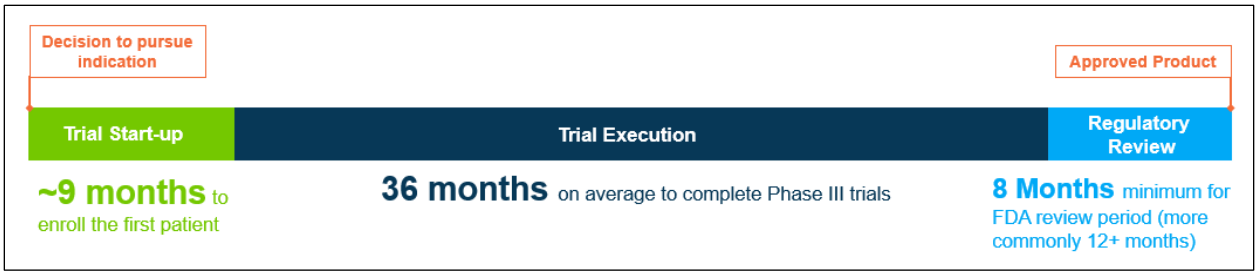
Case Studies on CVD Product Lifecycle Decisions

In addition to the broad assessment of clinical trial data, this analysis examined two specific FDA approved products with multiple CVD indications that will be subject to MFP in 2026. These case studies provide insight into the substantial time and resources required to generate evidence for new patient populations. Overlaying these case study timelines with the Medicare negotiation timeline forecasts how manufacturer decision making on product development could omit, deprioritize, or reshuffle the order of planned indications.

Follow-On Indication Timelines

In examining Phase III trials, which are most often used as pivotal trials (i.e., the reference trial for regulatory filing and product approval), the literature assessment and trial analysis estimated that it takes at least 4 years from the beginning of the Phase III trial to receipt of FDA approval. This timeline includes approximately 9 months for a study to enroll its first patient in a Phase III CVD trial after a manufacturer chooses to pursue that indication.[19] Analysis of the total CVD landscape showed that on average, Phase III trials take 3 years to complete (Figure 7).

Figure 7: Estimated Lead Time for Phase III CVD Study Execution and Addition to FDA Label



Trial and Evidence Gathering

The indications for each case study were informed by at least 12 Phase III trials conducted over more than 8 years (Figure 8). Development continued post FDA approval— this sequential label expansion is vital to delivering products to new patients.

Figure 8: Product Lifecycle Statistics for Two Case Study Products

Case Study	Product 1	Product 2
Total Number of Approved Indications at Time of Analysis	8	5
Duration of Approval Lifecycle	10.4+ years	8.8+ years
Number of Phase III Studies on FDA Label	12	12

Additionally, although manufacturers frequently include multiple clinical trials in their FDA submission for a product's lead indication, subsequent indications often require similar or even larger clinical trial enrollment and associated resources. For both case study products, total Phase III enrollment averages for follow-on indications were greater than the total enrolled for the initial approval (Figure 9). This observation on follow-on indication trial sizes is compounded when looking at the number of patients enrolled in studies that support CVD follow-on indications as opposed to non-CVD indications. Enrollment statistics for Product 2 trials showed a more than a 500% increase in enrollment for studies testing CVD patient populations in follow-on indications as opposed to non-CVD populations (Figure 9).

Figure 9: Phase III Enrollment Statistics for Two Case Study Products

Case Study	Product 1	Product 2
Total Phase III Enrollment for Initial Approval (Number of Phase III studies)	~9,500 pts (3)	~3,000 pts (4)
Average Phase III Study Enrollment for a Follow-on Indication	~9,700 pts	~4,200 pts
Total Phase III Enrollment for Non-CVD Indications	*N/A*	~3,000 pts
Average Number of Trial Sites for Non-CVD Indications	*N/A*	~100
Total Phase III Enrollment for CVD Indications	~75,000 pts	~16,800 pts
Average Number of Trial Sites for CVD Indications	~400	~450

For both these products, the difference in trial site numbers was substantial, with 400% as many sites for CVD-indication trials compared to non-CVD-indication trials for Product 2 (Figure 9). Because of these differences in trial design and size, per-patient cost reports estimated that CVD indication studies cost at least 500% the cost of studies of the same molecular entity for a non-CVD indication.[20]

Although these findings focus only on Phase III trials, clinical trials conducted before pivotal studies—such as Phase I and Phase II trials—only add to the development timeline associated with marketing a product for a new CVD indication. Time and resource requirements to pursue a new indication are therefore likely to remain a major driver of manufacturer decision making. IRA policy changes will exacerbate strains on CVD R&D by shifting the timeframe that manufacturers have to recover their investments after FDA approval.

Potential Impact of the IRA on CVD Product Development Strategies

Negotiation Factors That May Shift Development Approaches

Medicare negotiation dynamics under the IRA may impact manufacturer development incentives and strategies across therapeutic areas. As previously noted, application of an MFP for selected drugs will impose new pricing constraints that manufacturers will need to consider when pursuing label indications. In some instances, an MFP may limit the time available to recoup investments, creating pressure on label indications pursued later in the product's lifecycle.

More broadly, Medicare negotiation may change manufacturer decisions regarding the types of products or indications to pursue. Because drugs with the highest Medicare spending will be selected for negotiation, products for the treatment of indications with higher Medicare exposure

(i.e., those that treat primarily Medicare patient populations) are at higher risk for early selection for negotiation. This dynamic may create incentives for manufacturers to focus development on different types of products or indications (e.g., products that treat a larger share of younger patients with commercial insurance as opposed to Medicare). Such changes could influence the number or types of products developed against CVD, given that Medicare beneficiaries constitute a large portion of the CVD population.[21]

Other parameters of the IRA negotiation policy, such as the different eligibility timelines for small vs. large molecule drugs, as well as the exemption of drugs for only one but not multiple orphan indications, are also expected to influence manufacturer choices regarding the types of products developed and indications pursued. For example, the longer timeframe from product approval to negotiation eligibility for biologics compared to small molecule drugs, may cause manufacturers to shift development focus away from small molecule drugs.

Changing incentives for development toward biologics instead of small molecule drugs may impact CVD pipeline products in particular. Historically, most product innovations that have redefined standards of care in CVD have come from small molecule drugs.[22] In the analysis of Phase III CVD trials, greater than 80% of the trials analyzed involved small molecule drugs. Although biologics remain in development for CVD, fundamental mechanisms of action that have established effectiveness in CVD management, such as clotting factor inhibition, are currently best addressed using small molecule products.[23]

The IRA may affect manufacturers' product modality strategies and timelines for making these strategic development decisions. Therefore, development decisions, particularly those related to indication expansion, may transition from a sequential process to a more concurrent approach, as concurrent development decisions may be necessary to maximize time available on the market and to recoup investments for all indications before MFP implementation. Although MFP is not applicable until 2 years after a drug is selected for negotiation, manufacturers will need to consider the evidence necessary to support negotiations with CMS years before implementation of a product's MFP. This dynamic may increase resource burden on manufacturers, which may in turn affect their R&D priorities and decisions.

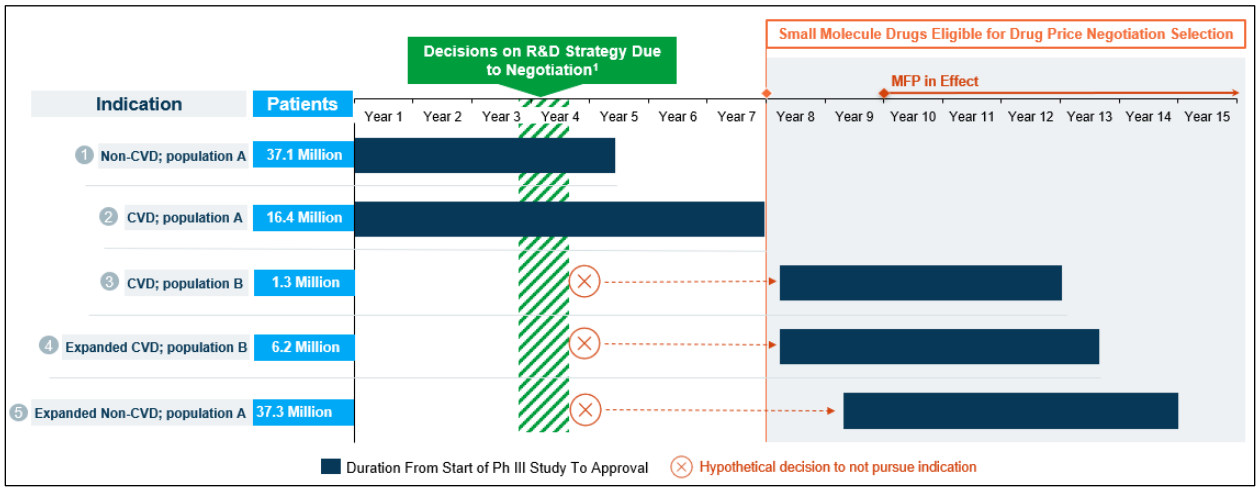
Case Study: Effects of Medicare Negotiation on Follow-on Indication Development

To demonstrate how Medicare negotiation dynamics could impact a manufacturer's approach to product development, this case study features a highly utilized CVD product originally indicated for both a CVD and a non-CVD indication. The manufacturer then pursued two additional CVD indications, each for a relatively smaller patient population. Nine years after the initial product approval, the manufacturer sought an expanded label indication for a non-CVD indication. The product was selected for negotiation in 2023 and will be subject to MFP in 2026.

If this product had been developed in a post-IRA environment, indication selection may have occurred differently. Considering the possibility of the product being selected for negotiation in year 7—especially given the sizable patient populations for the first two indications and likely

high Medicare spending—the manufacturer may have opted not to pursue the last three indications. That decision may have resulted from downward pricing pressure of the MFP, which could erode the commercial potential for follow-on indications (Figure 10).

Figure 10: Illustrative Impact of Medicare Negotiation on Case Study Product Development Timeline



1. Placement was informed by an assessment of average time associated for the case study to move from conducting a Phase III study to the date of FDA approval for that new indication

Alternatively, the manufacturer could have chosen to focus on developing indications three and four as the product's first indications. These indications treat smaller patient populations and could minimize the potential risk of selection for negotiation. However, if the manufacturer had only chosen to develop indications three and four, more than 50 million people for whom the drug is currently indicated would not have access to the treatment.

Conclusion

Medicare negotiation and other IRA policies will introduce new market dynamics for many healthcare stakeholders. For manufacturers, these changes can create new incentives that may alter the types and timing of decisions made during the early stages of product development. Avalere's analysis emphasizes how the impact of the IRA on manufacturers' development strategies may vary by therapeutic area. For CVD, factors related to the resource requirements of clinical trials are likely to present unique considerations for the types of indications pursued and the timing of decisions related to follow-on indications.

As manufacturer development strategies change in response to the IRA, this dynamic will likely affect the range of products available on the market and the patient populations they treat. Manufacturers will also need to account for the impacts of other IRA policy changes, such as Part D benefit redesign and inflation rebates, on their pipeline development strategies and on patient access to treatments.

Methodology

Targeted Literature Review

Avalere performed secondary research in July 2023 using publicly available data to uncover sources that assess clinical development considerations for CVD, respiratory disease, and/or metabolic disease. Sources that were prioritized for review were published on or after March 2015, with a focus on academic reviews and meta-analyses. In certain cases, government reports and industry-funded position papers were referenced for cross-validation. In total, 12 sources were included in the landscape assessment.

While publication occurred within the last 8.5 years, product data reviewed in meta-analyses (particularly for those focused on CVD) were older, with some studies including data originally collected in the 1990s. The dearth of recent CVD product data is a limitation of the targeted literature assessment.

Independent Clinical Trials Assessment

Avalere exported clinical trial information in July 2023 and independently analyzed trial features to uncover trends in clinical development that are representative of the three therapeutic areas in question. Clinical trial information was collected from the National Library of Medicine's Clinicaltrials.gov website. The criteria for trial selection for the analysis included Phase III trials completed in or after 2011 that were funded by industry (manufacturers), rather than the federal government or third parties. Three keyword searches in Clinicaltrials.gov were "Cardiovascular Disease," "Respiratory Disease," and "Metabolic Disease." Data sets were exported separately for each therapeutic area product bucket. Trials with missing information on enrollment numbers or study completion dates were excluded from the assessment.

In the exported CVD trial dataset, certain indications were excluded from the analysis to ensure that outputs were representative of only CVD indications These included clincialtrials.gov results on type 2 diabetes mellitus, diabetic complications, hematological malignancies, and ophthalmic conditions. In the respiratory disease trial dataset, all studies related to SarS-CoV2 infection or COVID-19 were excluded from the analysis. In the metabolic disease trial dataset, all studies related to CVD, heart failure, or hypertension were excluded from the analysis.

CVD Drug Case study Assessment

Avalere identified a series of products for consideration in the case study assessment, based on known features of the product lifecycle that could elucidate details on the clinical development resource requirements associated with getting the product approved. Two products were selected for analysis. Two products contained a variable number of indications, some for large patient populations, some for rare diseases, and some for non-CVD indications.

To uncover details surrounding each case study's evidence package, Avalere reviewed label history provided on the Drugs@FDA database. Supplemental approvals associated to the "Efficacy- new indication" supplement category were assessed for details surrounding the

clinical study(ies) submitted as part of that application. FDA label sections 2 (Indications & Usage), 8 (Warnings and Precautions) and 14 (Clinical Studies) were assessed at each label update timepoint for information on evolving indication language and clinical studies supporting the labeling change. Data in the assessment were current as of July 2023. This information was logged in MS Excel to form timelines associated with the label expansion of each case study product.

To estimate clinical development resource requirements associated with each specific case study product, Avalere performed a search on the National Library of Medicine's clinicaltrials.gov database for all completed trials in Phase-III that had were funded by the commercializing sponsor (manufacturer marketing the drug). Each Phase III study associated with the label was extracted from this data set for a supplemental analysis on the late-stage development that the manufacturer underwent to obtain the current label. In certain cases where the study identifier on the FDA label differed from the national clinical trials # on clinicaltrials.gov, information on intention to treat enrollment numbers, study start or completion dates, or the "other study names" category on clinicaltrials.gov were manually referenced to determine the appropriate clinical trial for the supplementary analysis.

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