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Conducting Drug Affordability Reviews

Considerations for State Prescription Drug Affordability Boards (PDABs)

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Executive Summary

In response to the impact of rising medication costs on patients and insurers in the public and private sectors, several states have recently established **Prescription Drug Affordability Boards (PDABs)** tasked with assessing the affordability of specific prescription drugs. As part of these drug reviews, Boards must consider many factors that influence access to a drug, its affordability, and its value.

To fulfill their statutory missions, PDABs must perform comprehensive drug reviews, subject to statutory requirements and resource limitations. To support state PDABs, this white paper outlines key considerations for the affordability review process, including:

- **Defining Affordability.** There are many ways to assess a drug's affordability. We recommend considering three different perspectives: 1) the drug's cost relative to therapeutic alternatives; 2) the drug's out-of-pocket costs to patients and the impact of these costs on access; and 3) the drug's budgetary impact on the state's public and private payers.
- **Drug Evidence.** Drugs selected for affordability review often have several clinical indications across a range of patient populations. A thorough understanding of the regulatory processes through which these drugs obtain FDA approval and the body of evidence supporting approval and appropriate use (e.g., via medical professional guidelines) is a valuable starting point for PDABs to ensure fair and accurate review.
- **Drug Price and Spending.** Central to understanding a drug's affordability is understanding its state-specific costs and use. The plethora of stakeholders in the prescription drug supply chain means there are a variety of cost metrics PDABs may consider, in addition to the rebates and discounts that impact the drug purchase price set by manufacturers.
- **Therapeutic Alternatives.** PDABs may be tasked with assessing a drug's affordability relative to its therapeutic alternatives. Defining what constitutes a therapeutic alternative for this assessment requires Boards to draw on careful clinical judgment and decide how to draw the boundaries of a similar treatment for each drug's indications.

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- **Comparative Effectiveness.** In assessing a selected drug relative to its alternatives, PDABs must review literature that compares these treatments' safety and effectiveness for each indication. Such comparisons can provide important insight into a drug's clinical value. However, these reviews require technical expertise and must account for missing data and other limitations.
- **Economic Evaluation.** Understanding a selected drug's value relative to its costs and its impact on state budgets can involve analyses that unify many criteria central to PDABs' functions. Ensuring adequate review of cost-effectiveness and budget impact literature for a selected drug is critical, and PDABs can rely on such reports from independent outside organizations when they exist. PDABs should also ensure any statutory limitations are followed for such review (e.g., prohibitions on using QALY-based analyses).
- **Patient Costs and Access.** While consumers ultimately bear a drug's costs through taxes and insurance premiums, patient out-of-pocket costs pose the most immediate and obvious burden. Understanding how insurers cover a drug, the costs for patients who take the drug, and the tools patients can use to afford expensive medications are vital considerations for PDABs when assessing a drug's affordability.
- **Market Dynamics.** Prescription drugs prices are highly influenced by the market forces driving manufacturer behavior. PDABs should evaluate how manufacturers leverage a drug's patent protection and regulatory exclusivities to maintain market share and the downstream impact of such protections on patient access and costs. Similarly, recognizing the potential of market competition to reduce drug costs is essential for PDAB review.

Though not necessarily inclusive of all crucial elements that may influence a drug's affordability, these factors are an essential starting point for an effective PDAB review. A holistic, thorough analysis that considers the realities of conducting such a review and provides ample opportunity for stakeholder engagement can help ensure that PDABs can be a meaningful contributor to prescription drug affordability in their states.

Background

As of September 2023, seven states have enacted Prescription Drug Affordability Boards (PDABs) to address high prescription drug costs that can limit patient access to important medications and place burdens on institutional and personal budgets. The **affordability or cost review process** is central to these Boards' function. Upon selecting an eligible drug for review, PDABs must then determine whether the drug poses an affordability challenge to state stakeholders, including consumers.

There are many considerations when deciding whether drugs are affordable or unaffordable. Most PDAB statutes list factors that must be considered when conducting these affordability or cost reviews, including the drug's price, safety and effectiveness, accessibility, and development cost.¹

This White Paper outlines the factors PDABs may consider in conducting affordability reviews, highlighting foundational information and key challenges states may face in their assessment. We focus on elements included in existing state PDAB statutes as of September 2023. The purpose of this White Paper is to help states develop a process for conducting each part of their review. Each PDAB will, within its statutory authority and Board priorities, need to determine how these different components are combined and balanced.

Defining Affordability

There are many different factors to consider when assessing a drug's affordability. As a result, we recommend that Boards consider affordability from several perspectives:

- 1. Cost Relative to Therapeutic Alternatives.** Drugs priced higher than comparable therapeutic alternatives and disproportional to their added benefit can pose important affordability challenges. Not only does this mean that patients and payers are overpaying for the drug, but that payers and pharmacy benefit managers (PBMs) may impose access restrictions on the drug to steer patients toward lower-cost treatments. Better aligning a drug's price with therapeutic alternatives can improve patient access to the full range of therapeutic options and save money for patients and the health care system.
- 2. Out-of-Pocket Costs to Patients.** High out-of-pocket costs burden patients who need prescription drugs and pose an access barrier; these costs are associated with lower adherence and more patients abandoning their prescriptions at the pharmacy.^{2,3} The size of out-of-pocket costs depends on a combination of the drug's price and formulary decisions made by health insurers and PBMs. In addition, manufacturers and patient advocacy groups sometimes offer patient assistance that offsets out-of-pocket costs. Understanding the interplay of these costs and the potential impact on patient affordability and access is crucial to PDAB work.
- 3. Budget Impact.** Even if a drug is effective, Boards should consider how too high a price will affect total patient and insurer spending. If spending is high on one drug, public and private payers may be unable to afford the drug's cost without cuts to other benefits or services; this

¹ Bendicksen L, Rome BN, Avorn J, Kesselheim AS. Pursuing Value-Based Prices for Drugs: A Comprehensive Comparison of State Prescription Drug-Pricing Boards. *The Milbank Quarterly*. 2021;99(4):1162-1197. doi:[10.1111/1468-0009.12533](https://doi.org/10.1111/1468-0009.12533)

² Rome BN, Gagne JJ, Avorn J, Kesselheim AS. Non-warfarin oral anticoagulant copayments and adherence in atrial fibrillation: A population-based cohort study. *American Heart Journal*. 2021;233:109-121. doi:[10.1016/j.ahj.2020.12.010](https://doi.org/10.1016/j.ahj.2020.12.010)

³ Dusetzina SB, Huskamp HA, Rothman RL, et al. Many Medicare Beneficiaries Do Not Fill High-Price Specialty Drug Prescriptions. *Health Affairs*. 2022;41(4):487-496. doi:[10.1377/hlthaff.2021.01742](https://doi.org/10.1377/hlthaff.2021.01742)

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could adversely impact the entire health care system. Understanding such short-term budget impacts is important.

In some cases, drugs could be seen as affordable through one of these lenses but unaffordable through another. For example, highly effective drugs like the novel hepatitis C virus (HCV) direct-acting antivirals first approved in 2013 were deemed cost-effective even at high prices. Still, the enormous budget impact and lack of immediate clinical implications on chronic HCV infection led many payers to restrict access to these treatments and prioritize patients with the most complicated disease.⁴ As a result, we recommend the Boards holistically consider all of these aspects when assessing a drug's affordability.

The purpose of an affordability review should be to collect relevant evidence that informs affordability through these varying perspectives. The next sections of this White Paper will discuss these data elements in detail.

Drug Evidence

Once a drug is selected for affordability review, understanding the fundamental aspects of the drug's evidentiary basis and regulatory development serves as a useful starting point for analysis.

Regulatory Pathways

All drugs approved by the FDA are regulated as **small molecule products** or **biologics**; the latter are more complex products often derived from living material, including monoclonal antibodies, cell therapies, and gene therapies.⁵ The FDA regulates small molecules under a **New Drug Application (NDA)** pathway, while biologics are regulated via a parallel process known as the **Biologic License Application (BLA)**.⁶

Understanding whether a drug is a small molecule or biologic is important. Before any follow-on products can enter the market, new drugs are granted a period of monopoly protection due to patents and other statutory exclusivities. For small molecule drugs, the total exclusivity period is typically 12-17 years; for biologics, it can be over 20 years.⁷ After this period of exclusivity ends, small-molecule drugs face competition from **generics**. Since the Hatch-Waxman Act of 1984, generic manufacturers can enter the market using an **Abbreviated New Drug Application (ANDA)** process that requires them to test the product's bioequivalence to the original drug. Follow-on biologics, called **biosimilars**, also have an abbreviated pathway created under the Biologics Price Competition and Innovation Act (BPCIA) of 2009 (their regulatory filing occurs via an **Abbreviated Biologic License Application**). However, this process still requires biosimilar manufacturers to compare the safety and effectiveness to that of the originator biologic in head-to-head clinical trials. Generics deemed therapeutically equivalent by the FDA can be automatically substituted for the brand-name drug (and each other) by pharmacists; biosimilars require additional testing to be deemed interchangeable by the FDA, and many states have restrictions on whether pharmacists can automatically substitute biosimilars for the original biologic.⁸

⁴ Najafzadeh M, Andersson K, Shrank WH, et al. Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus. *Ann Intern Med*. 2015;162(6):407-419. doi:[10.7326/M14-1152](https://doi.org/10.7326/M14-1152)

⁵ FDA. Biological Product Definitions. <https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf>

⁶ FDA. Drugs@FDA - Approved Drugs. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>

⁷ Rome BN, Lee CC, Kesselheim AS. Market Exclusivity Length for Drugs with New Generic or Biosimilar Competition, 2012–2018. *Clinical Pharmacology & Therapeutics*. 2021;109(2):367-371. doi:[10.1002/cpt.1983](https://doi.org/10.1002/cpt.1983)

⁸ Sacks CA, Van De Wiele VL, Fulchino LA, Patel L, Kesselheim AS, Sarpatwari A. Assessment of Variation in State Regulation of Generic Drug and Interchangeable Biologic Substitutions. *JAMA Intern Med*. 2021;181(1):16. doi:[10.1001/jamainternmed.2020.3588](https://doi.org/10.1001/jamainternmed.2020.3588)

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Brand-name and biologic drug manufacturers can also sell versions of their drugs without a brand name on the label, using the same NDA or BLA as the brand-name drug. These are known as **authorized generics** or **unbranded biologics**.

The **NDA, ANDA, or BLA number** assigned to a drug as it moves through the approval process is attached to the product throughout its life cycle, making it an important identifier for PDABs. These approval applications can also be amended via supplements as changes are made to an approved drug's composition, labeling, or use.

Before a drug comes to market, it is assigned a **National Drug Code (NDC)**. The NDC identifies the drug's labeler (usually the manufacturer, unless the drug is repackaged), product name, and package size.⁹ Because most drugs have many dosage forms and strengths, this typically translates into many different NDCs. States are encouraged to use NDCs because they are the uniform drug identifier used by pharmacies and insurance companies. However, the NDC is typically too granular, so it is in PDABs' best interest to aggregate these codes when conducting an affordability review. Such aggregation is sometimes conducted by data providers.

The FDA has several **expedited programs** for manufacturers to advance the approval timeline. These programs include **priority review, accelerated approval, breakthrough therapy, and fast track** designations. These pathways, designed to speed the development of clinically important drugs, have been used increasingly over the past several decades such that now the majority of new drugs qualify for one or more of these pathways.^{10,11} Thus, qualifying for one of these alone does not necessarily signify an important new drug.

Of these pathways, only **accelerated approval** changes the basic FDA approval standard, requiring only that a drug affects intermediate (surrogate) measures, such as a laboratory test or imaging study, deemed reasonably likely to predict a drug's eventual benefit to patients (e.g., length of life or improved quality of life).¹² Drugs granted accelerated approval must complete confirmatory trials and can then be converted to traditional approval, though compliance with such expectations has been found to often be delayed or incomplete.^{13,14} As such, PDABs should closely examine the body of evidence supporting selected drugs that may have proceeded through the FDA accelerated approval pathway.

Indications and Uses

FDA approval of a drug or biologic is based on a determination of its safety and effectiveness for a specific clinical use or **indication**. These indications are included on the product's labeling and are the uses for which the FDA has determined the drug's safety and efficacy meet regulatory requirements.¹⁵ The breadth of a given indication can vary, encompassing an entire disease or condition or focusing on a particular sub-population (e.g., patients who have failed two or more existing therapies).

⁹ FDA. National Drug Code Directory. <https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm>

¹⁰ Kesselheim AS, Wang B, Franklin JM, Darrow JJ. Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ*. Published online September 23, 2015:h4633. doi:10.1136/bmj.h4633

¹¹ FDA. NDA and BLA Approvals. <https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/nda-and-bla-approvals>

¹² FDA. Accelerated Approval Program. <https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program>

¹³ Moneer O, Brown BL, Avorn J, et al. New Drug Postmarketing Requirements and Commitments in the US: A Systematic Review of the Evidence. *Drug Saf*. 2022;45(4):305-318. doi:10.1007/s40264-022-01152-9

¹⁴ Gyawali B, Hey SP, Kesselheim AS. Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs. *EClinicalMedicine*. 2020;21:100332. doi:10.1016/j.eclinm.2020.100332

¹⁵ FDA. Online Label Repository. <https://labels.fda.gov/>

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Over its lifespan, a drug can accumulate multiple indications. After the FDA first approves a drug, additional indications are often added through supplements to an original NDA or BLA, with the manufacturer required to submit supporting data to justify each new or modified indication.

Orphan Drug Act Designation

Under the Orphan Drug Act of 1983, Congress created special incentives for drugs that treat rare conditions, subsequently defined as conditions affecting fewer than 200,000 patients in the US. When drug makers decide to study their drug for such a condition, they can apply for an **orphan drug designation**, which grants tax credits to offset clinical trial costs and additional regulatory incentives.¹⁶ Note that the FDA-labeled indications may not exactly match the definition of an orphan designation; in some cases, multiple indications all fall within the same orphan designation (e.g., first- vs. second-line use in multiple myeloma are both under the umbrella of multiple myeloma); in other cases, drugs may have an indication that is narrower or broader than the original orphan designation.

Many drugs that have one or more orphan-designated indications also have indications to treat more common conditions. For PDABs, this is an important distinction, as any policies or assessments aimed specifically at rare disease treatments must be carefully defined. For example, states may wish to stratify drugs that treat a single rare disease, drugs that treat multiple rare diseases, and drugs that treat a mix of rare and non-rare diseases by comparing the drug's labeled indications to its orphan designations.

Off-Label Use

Once drugs are approved, prescribers may use the drug for purposes beyond those approved by the FDA, known as **off-label use**. Clinicians are free to prescribe drugs off-label if they deem that the benefits outweigh the risks. Manufacturers, however, are generally prohibited from promoting off-label prescribing of their drug. In cases when off-label use of a selected drug may be widespread, PDABs may wish to consider these off-label uses alongside the FDA-labeled ones. This may be particularly true if professional guidance documents and other reputable sources support off-label use.

Drug Shortages

Many PDABs may also consider whether a selected drug is currently undergoing a shortage in the US. This can be a meaningful data point in considering current access to a selected drug. The FDA maintains a database of ongoing drug shortages.¹⁷ The source of such shortages can, however, sometimes be challenging to determine, as is the impact of such a shortage on drug access and price.

Drug Price and Spending

Understanding how much a drug costs and how much patients and payers are spending on the drug is important but challenging to measure. This is partly due to a complex pharmaceutical supply chain with multiple actors influencing price, resulting in multiple definitions of “price” for the same drug.

Stakeholders in the Pharmaceutical Supply Chain

Several key players affect the cost of a prescription drug. The **pharmaceutical manufacturer** sets the price. For **retail pharmacy drugs** (i.e., those dispensed to patients at a pharmacy), manufacturers generally sell drugs to pharmacies via **wholesalers**. Pharmacies are paid by patients and reimbursed by their health plan or **pharmacy benefit manager** (PBM) when a prescription is filled.

¹⁶ FDA. Orphan Drug Designations and Approvals. <https://www.accessdata.fda.gov/scripts/opdlisting/ood/>

¹⁷ FDA. FDA Drug Shortages. <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>

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For **clinician-administered drugs** (i.e., medications administered in a doctor’s office, hospital, or infusion center), hospitals and clinics typically purchase drugs through **group purchasing organizations** and are subsequently reimbursed by patients and insurers at negotiated rates. Because of this, the **acquisition cost** for a drug (i.e., the cost paid by pharmacies or providers to have the drug in stock) can differ from the **reimbursed cost** by patients and insurers. This is particularly true for drugs purchased by hospitals and clinics at steep discounts through the **340B Drug Pricing Program**.¹⁸

Determining Drug Cost

Because of the complexities described above, there is no single measure of a drug’s cost. Instead, PDABs should look at several different measures. Typically, costs are defined for each drug’s **National Drug Code (NDC)**.

Table 1. Overview of common cost metrics relevant for prescription drugs.

Price Type	Description	Method of Calculation	Includes Rebates & Discounts?	Derived from Actual Drug Sales?	Data Access
Wholesale Acquisition Cost (WAC) or “List Price”	Price at which a manufacturer offers a drug for sale to wholesalers or direct purchasers.	Set by manufacturers	No	No	Accessible via third-party pricing databases (e.g., First Databank, Medispan) ^{19,20}
Average Manufacturer Price (AMP)	Average price paid by a wholesaler for a drug from the manufacturer after accounting for some discounts.	Calculated using regulatory definition. ²¹	No	Yes	Proprietary; only disclosed to CMS for the Medicaid Drug Rebate Program ²²
Average Wholesale Price (AWP)	List price that sometimes serves as the basis for pharmacy purchases from wholesalers. Previously thought of as list price but now recognized to be higher than WAC (usually by about 20%).	Not statutorily defined; estimated WAC + 20%	No	No	Accessible via third-party pricing databases (e.g., First Databank, Medispan)
Average Sales Price (ASP)	For clinician-administered drugs, price at which a manufacturer sells the drug after accounting for any rebates/discounts.	Calculated using procedure set forth by CMS. ²³	Yes	Yes	Publicly reported by Medicare ²⁴
National Average Drug Acquisition Cost (NADAC)	Average price at which community retail pharmacies purchase a drug from a wholesaler.	Calculated using surveys of retail pharmacy acquisition costs ²⁵	No	Yes	Publicly reported by Medicaid, including equivalencies to other measures ^{26,27}

¹⁸ Health Resources & Services Administration (HRSA). 340B Drug Pricing Program. Updated August 2023. <https://www.hrsa.gov/opa>

¹⁹ First Databank (FDB). AnalySource Drug Pricing Software. <https://www.fdbhealth.com/solutions/analysource-drug-pricing-software>

²⁰ Wolters Kluwer. Medi-Span Prescription Drug Pricing Data. <https://www.wolterskluwer.com/en/solutions/medi-span/medi-span/drug-pricing-data>

²¹ 42 CFR 447.504

²² CMS. Medicaid Drug Rebate Program. <https://www.medicaid.gov/medicaid/prescription-drugs/medicaid-drug-rebate-program/index.html>

²³ CMS. Medicare Part B Drug Average Sales Price (ASP) User Manual. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Downloads/ASP_Data_Collection_Validation_Macro_User_Guide.pdf

²⁴ CMS. Medicare Part B Drug ASP Pricing Files. <https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/asp-pricing-files>

²⁵ CMS. Medicaid Retail Price Survey. <https://www.medicaid.gov/medicaid/prescription-drugs/retail-price-survey/index.html>

²⁶ CMS. Pharmacy Pricing. <https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html>

²⁷ Myers and Stauffer LC. NADAC Equivalency Metrics. <https://www.medicaid.gov/sites/default/files/2023-07/nadac-equiv-metrics-06222023.pdf>

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Of these measures, most PDABs use a drug's WAC in assessing whether a drug qualifies for affordability review (among other eligibility criteria). Other measures like NADAC can also be useful.

In using these metrics, it is important to note that each has limitations, including the types of drugs to which such prices apply, the entity calculating the price, and the accessibility of the price to PDABs. Average wholesale price, for example, has faced scrutiny as a means for manufacturers and wholesalers to game reimbursement by reporting artificial prices; as a result, Medicaid programs now reimburse pharmacies based on acquisition costs (e.g., NADAC) rather than the AWP. In addition, there are some discounts (e.g., volume purchase discounts) built into the system that mean actual prices paid to manufacturers (e.g., AMP) are lower than the list prices (e.g., WAC).²⁸ Considering these limitations when assessing pricing data is critical to an evidence-based affordability review.

Clinician-Administered Drugs

For clinician-administered drugs, most insurers reimburse hospitals and providers based on **Healthcare Common Procedure Coding System (HCPCS) codes** for medical claims. These are colloquially called **J-codes** based on the usual prefix for prescription drug codes. These codes are assigned by the Centers for Medicare and Medicaid Services (CMS). Not all medical claims for clinician-administered drugs will include both a J-code and an NDC, although there is a public crosswalk provided by CMS.²⁹

There are a few additional considerations for the price of clinician-administered drugs. First, Medicare reimburses these drugs based on the **average sales price (ASP)**, which is reported by manufacturers and is supposed to reflect the average price of the drug to wholesalers or providers net of all discounts and rebates; these ASP-based pricing limits are public.³⁰ Private insurers typically reimburse for these drugs at rates far exceeding Medicare.³¹ Second, many hospitals and clinics can purchase drugs from manufacturers at steeply discounted rates under the **340B Drug Pricing Program**.³² The discounts for specific drugs are similar to rebates available to Medicaid, including the Best Price discount, and hospitals and clinics are frequently still reimbursed by insurers at similar rates to non-340B institutions. As a result, the 340B program represents an important revenue source for some hospitals and clinics.

Rebates and Discounts

Many confidential fees and discounts are built into the prescription drug supply chain. The most important are **manufacturer rebates** negotiated by PBMs for brand-name drugs. Manufacturers offer rebates to obtain more favorable formulary placement, potentially making their drugs more accessible and affordable to insured patients. Rebates are confidential and vary by drug class and insurer.

The rebates negotiated by the PBM are then, theoretically, shared with the health plan, and the cost savings can be used to lower premiums or improve coverage. However, **rebates are not directly shared with patients**, meaning patients who owe deductibles or coinsurance (a percent of the drug's cost) often pay those based on the drug's list price.³³

²⁸ HHS OIG. Medicaid Drug Price Comparisons: Average Manufacturer Price to Published Prices (OEI-05-05-00240). 2005. <https://oig.hhs.gov/oei/reports/oei-05-05-00240.pdf>

²⁹ CMS. ASP Pricing Files. <https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/asp-pricing-files>

³⁰ CMS. ASP Pricing Files. <https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/asp-pricing-files>

³¹ Feldman WB, Rome BN, Brown BL, et al. Payer-Specific Negotiated Prices for Prescription Drugs at Top-Performing US Hospitals. *JAMA Internal Medicine*. 2022;182(1):83-86. doi:10.1001/jamainternmed.2021.6445

³² Kishore S, Nayak RK, Kesselheim AS. 340B—Where Do We Go From Here? *JAMA*. 2023;330(7):593-594. doi:10.1001/jama.2023.11056.

³³ Rome BN, Feldman WB, Desai RJ, Kesselheim AS. Correlation Between Changes in Brand-Name Drug Prices and Patient Out-of-Pocket Costs. *JAMA Netw Open*. 2021;4(5):e218816. doi:10.1001/jamanetworkopen.2021.8816

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For some drug classes – particularly when there is competition among multiple brand-name drugs – rebates can offset half or more of the drug’s cost. As such, PDABs may find it necessary to consider rebates as part of the affordability review process for the drug of interest and its therapeutic alternatives. Actual rebate data are typically confidential and only available from health plans and PBMs. Some companies, including SSR Health, estimate rebates based on aggregated national sales data.³⁴ States should recognize that rebates can vary widely among payers, so considering average rebates does not fully capture a drug’s cost.

Understanding the cost of a drug and its therapeutic alternatives net of rebates is important for measuring affordability. However, states should consider the limitations of rebates, which do not offset patient out-of-pocket costs. Thus, drugs with substantial rebates may still be unaffordable to consumers if the high list price leads to high out-of-pocket costs.

Utilization

A drug’s **utilization** can be measured in several ways: number of prescriptions dispensed, number of units, or number of patients using the drug. For PDABs, information on drug use can usually be obtained through **pharmacy or medical claims**. Many state PDABs can access this claim information from state all-payer claims databases or via direct payer solicitation.

In many cases, there is an inverse relationship between a drug’s use and its price, with manufacturers setting higher prices for drugs used by fewer patients. This means that even drugs used by a small number of people in the state could pose affordability challenges for those individual patients and the health care system.

It is also important that PDABs consider how to report the use of drugs. This information is typically collected in claims at the NDC level, meaning that a drug’s total patient count may be disaggregated across strengths and dosage forms. Aggregating NDCs before tabulating use is important, especially because some patients may change treatment regimens (e.g., increasing or decreasing strength) within a given year and may be included in multiple NDC-level values. This means that obtaining a fully comprehensive assessment of a drug’s use across the state may be technically limited if such aggregation is not performed.

Therapeutic Alternatives

Authorizing language for many state PDABs requires these bodies to consider drugs’ cost, safety, and effectiveness relative to therapeutic alternatives. Comparisons to alternative treatments can be a valuable tool to ensure that drug prices are aligned with others that offer similar benefits. However, there is no standardized definition for what constitutes a therapeutic alternative.

Defining Therapeutic Alternatives

It is important to understand common terminology that can influence the definition of eligible therapeutic alternatives for affordability reviews:

- **Therapeutic equivalent** is a regulatory term of art. To meet the FDA’s therapeutic equivalence standards, drugs must be pharmaceutically equivalent (e.g., identical dosage, route of administration, amount of active ingredient), bioequivalent (e.g., similar bioavailability at the site

³⁴ SSR Health, LLC. <http://www.ssrhealth.com/>

of action), and have the same labeling.³⁵ When the FDA approves therapeutically equivalent generic drugs, it certifies that the product shares the same clinical effect and safety profile as the comparator drug. All states have laws permitting pharmacists to automatically substitute drugs deemed therapeutically equivalent by the FDA.

- **Therapeutic class** categorizes drug products according to similar chemical structure, mechanism of action, or therapeutic effect. There is no single definition of what constitutes a therapeutic class. FDA has put forth guidance on using established *pharmacologic classes* for labeling purposes.³⁶ This guidance recommends that pharmacologic class be scientifically valid *and* clinically meaningful as derived from three general drug attributes: mechanism of action, physiologic effect, or chemical structure.

Common nomenclature systems include the American Society of Health-System Pharmacists (ASHP) AHFS Pharmacologic-Therapeutic Classification system;³⁷ the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) system;³⁸ and the US Pharmacopeia Drug Classification System (USP DC).³⁹ Pharmacists, PBMs, insurers, and others within the supply chain use these classification systems, for example in the case of PBMs when setting formularies; however, there is variation in how each nomenclature system separates therapeutic classes. Some drugs, such as immunomodulating agents that treat various autoimmune conditions, can be particularly hard to classify within one therapeutic class.

- **Therapeutic alternatives** may include treatments analogous in therapeutic use or treatment effect. We provide additional considerations for this term below.

Setting the Scope of Therapeutic Alternatives

Because there is no single definition of the term “therapeutic alternatives,” PDABs will need to make strategic decisions about which therapeutic alternatives to consider. Defining therapeutic alternatives may be based on several considerations:

- **Drugs with multiple indications.** Many drugs are used to treat multiple diseases. In these cases, therapeutic alternatives may vary among a drug’s uses. As a result, **we recommend that PDABs consider therapeutic alternatives at the indication level.** This will more accurately reflect the context of treatment considerations and costs for each clinical scenario.
- **Data sources.** There is no uniform database that lists the FDA-approved drug indicated to treat each health condition. As a result, PDABs will need to rely on various sources to identify therapeutic alternatives. One option is to start with drugs in the same therapeutic class, although drugs in the same class may have different indications, so not all within-class drugs will also be deemed therapeutic alternatives. In addition, many therapeutic alternatives will include drugs in

³⁵ FDA. Evaluation of Therapeutic Equivalence (FDA-2022-D-0528). 2022. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-therapeutic-equivalence>

³⁶ FDA. Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information (FDA-2007-D-0302). 2009. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-human-prescription-drug-and-biological-products-determining-established-pharmacologic-class>

³⁷ ASHP. AHFS Therapeutic Classification System. <https://www.ashp.org/products-and-services/database-licensing-and-integration/ahfs-therapeutic-classification>

³⁸ WHO. Anatomical Therapeutic Chemical (ATC) Classification. <https://www.who.int/tools/atc-ddd-toolkit/atc-classification>

³⁹ USP. USP Drug Classification (USP DC). <https://www.usp.org/health-quality-safety/usp-drug-classification-system>

different classes. PDABs may wish to primarily rely on guideline documents from professional organizations to identify these drugs. However, these guidelines are updated infrequently and may need to be supplemented with a targeted review of clinical sources.

- **Non-pharmaceutical alternatives.** Under the broadest possible definition, a drug’s therapeutic alternatives could extend to non-pharmaceutical alternatives, such as devices, procedures, or other health care services. Including such interventions in PDAB analysis may result in a more inclusive examination of a drug’s clinical benefits but may bring technical and resource challenges. In its final guidance for the initial prescription drug negotiation program, CMS has stated that it will only consider pharmaceutical therapeutic alternatives.⁴⁰
- **Patient- and clinician-level dynamics.** Individual patients and their physicians may face different therapeutic alternatives depending on clinical circumstances. While this is an important consideration, PDABs are encouraged to consider drugs as therapeutic alternatives if they meet the definition across a patient population rather than at the level of an individual patient.

Clarifying the Purpose of Therapeutic Alternatives

When PDABs select therapeutic alternatives, it is important to communicate that while two treatments may be alternatives, that does not mean they are the same. Some treatments may have meaningful differences in safety, efficacy, or mode of delivery (e.g., injected vs. oral). States should be cautious to ensure stakeholders understand that selecting therapeutic alternatives does not suggest that these products are interchangeable for individual patients.

Relatedly, narrowly defining therapeutic alternatives could limit Boards’ ability to fully assess a treatment’s affordability. By contrast, too broad a definition (i.e., one that attempts to categorize all possible treatment modalities as “alternatives”) could draw criticism as being insufficiently grounded in clinical practice.

To address such criticism, PDABs may emphasize that the purpose of selecting therapeutic alternatives is to establish a frame of reference for affordable prices and patient access. Currently, price differences among therapeutic alternatives may result in important access barriers if payers restrict access to more expensive options (even if they are more effective) or if high out-of-pocket costs preclude patients from choosing more expensive options. By comparing the prices of therapeutic alternatives, PDABs have an important opportunity to improve patient access by providing clinicians and patients with greater choice to select the clinically appropriate intervention without creating or exacerbating financial burdens.

Comparative Effectiveness

The clinical comparison of these treatment options is integral to assessing a drug’s affordability relative to its therapeutic alternative. Such information can serve as an important benchmark of a drug’s value upon which PDABs can ground a robust review. In most cases, new drugs are tested in clinical trials, often against a placebo control, which provides important information about the drug’s absolute safety and efficacy. However, it is perhaps more important to consider a drug’s **comparative effectiveness**

⁴⁰ CMS. Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026. 2023. <https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf>

relative to its therapeutic alternatives. Assessment of comparative effectiveness can examine several factors:

- **Clinical effectiveness:** the drug’s performance across key clinical outcomes, such as life extension, reduced disease symptoms, or improved condition management. An example of clinical effectiveness includes a meaningful improvement in quality of life (e.g., improved mobility, reduced pain).

However, in some cases, a drug’s efficacy may only be assessed using surrogate measures at the time it is approved by the FDA. These endpoints should ideally be correlated with clinical outcomes such as reduced symptoms or improved longevity; examples of surrogate measures include laboratory values (e.g., lipid levels, hemoglobin A1c) or tumor size reduction. In the case of accelerated approval drugs, such clinical validation, by definition, does not exist, and many surrogate measures used to support marketing of non-accelerated approval drugs are also not fully validated.

- **Side effects and interactions:** how the drug compares in its side effects (e.g., toxicity), interactions with other drugs, and contraindications (i.e., conditions under which the drug should not be prescribed). These factors can have important implications for patients’ well-being, which must be weighed against the effectiveness of the drug.
- **Ease of use:** how the drug’s route of administration affects dosing frequency or care setting. For example, a drug that can be administered via self-injection at home may provide a greater ease of use than an infusion that requires regular visits to a doctor’s office or hospital. The duration of therapy (e.g., 4-week treatment vs. 8-week treatment) would also factor into this element.

Sources of Comparative Effectiveness Analyses

The evidence generated for the various elements of comparative effectiveness can be derived from a variety of sources, including:

- **Pre- and post-marketing clinical trials.** The key trials supporting a drug’s approval are often the largest and highest quality trials that support a drug’s FDA-approved indication, but they may compare the drug to a placebo control rather than an active comparator (i.e., a therapeutic alternative).
- **Comparative effectiveness trials or meta-analyses.** In some cases, industry- or government-sponsored trials will directly compare multiple treatment options, which can provide the highest-quality comparative effectiveness data. Network meta-analyses that use multiple placebo-controlled trials to infer differences in safety and effectiveness among different treatments are a valuable alternative when direct comparative effectiveness data are unavailable.
- **Observational studies (e.g., “real-world evidence”).** High-quality observational studies can augment clinical trials or identify a drug’s effectiveness in populations for which trials are unavailable.⁴¹

⁴¹ Wang SV, Schneeweiss S, RCT-DUPLICATE Initiative, et al. Emulation of Randomized Clinical Trials with Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA*. 2023;329(16):1376. doi:[10.1001/jama.2023.4221](https://doi.org/10.1001/jama.2023.4221)

- **Health technology assessments (HTA).** Many countries, including France, the UK, Canada, and Germany, have independent HTA organizations that conduct comparative assessments of new drugs relative to existing therapies.⁴² While there is no formal HTA organization in the US, the Institute for Clinical and Economic Review (ICER) has emerged as one of the most active small non-profit groups in the US organized for a similar purpose.⁴³ These assessments may even be conducted independent of cost (with cost data considered later). They can provide important information for states about a treatment’s added clinical benefit. However, HTA assessments may, in some cases, have been performed soon after a drug was first approved and may not reflect clinical evidence accumulated after a drug has been on the market for many years.
- **Clinician and patient consultation.** Boards can solicit information about the drug from clinicians and patients. While valuable, such information must be cautiously interpreted to avoid drawing conclusions based on individual anecdotal experiences.

Typically, the longer a drug has been on the market, the greater body of comparative effectiveness evidence exists.

Assessing Comparative Effectiveness

In assessing the body of comparative effectiveness data that may exist for a given drug, PDABs may create a structured set of criteria by which to judge such information relative to therapeutic alternatives. Such an approach must consider both the size of a drug’s added benefit and the quality of evidence. Many HTA organizations, such as ICER, use rating systems that group drugs into different categories depending on how much added benefit they confer (e.g., major, moderate, or minor added benefit) and the quality of the evidence.⁴⁴ Doing so would allow the Board to consider the totality of evidence.

Importantly, comparative effectiveness assessments **must be performed separately for each indication.** For example, a drug might offer substantial added benefit for one condition but be no better than therapeutic alternatives for another. Boards may wish to summarize indication-specific assessments into an overall assessment based on the scope of each indication.

Economic Evaluation

As part of the affordability review, PDABs must also assess the drug’s cost relative to therapeutic alternatives. Under the simplest assumptions, this could be done by comparing the prices of various treatment choices. However, such an approach could miss important details about a drug’s economic impact. For example, if a drug is more effective at reducing hospitalizations than its alternatives, the cost savings from fewer hospitalizations could offset its higher cost. In some cases, PDABs are explicitly required to consider a drug’s relative financial effects on health, medical, or social services costs.

There are many standardized methods to perform economic analyses. Such economic evaluation can take several forms, with each approach differing in evaluating clinical outcomes. This White Paper will

⁴² Beletsi A, Koutrafouris V, Karampli E, Pavi E. Comparing Use of Health Technology Assessment in Pharmaceutical Policy among Earlier and More Recent Adopters in the European Union. *Value in Health Regional Issues*. 2018;16:81-91. doi:[10.1016/j.vhri.2018.08.002](https://doi.org/10.1016/j.vhri.2018.08.002)

⁴³ Institute for Clinical and Economic Review (ICER). 2023 <https://icer.org/>

⁴⁴ Ollendorf DA, Pearson SD. ICER Evidence Rating Matrix: A User’s Guide. 2017. <https://icer.org/wp-content/uploads/2020/10/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf>

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primarily focus on cost-effectiveness analysis (CEA), as this is the economic analysis PDABs are most likely to encounter.

Cost-Effectiveness Analysis (CEA)

CEA generally compares the cost and clinical outcomes for two treatments, such as a drug versus its therapeutic alternative. Performing a formal CEA is a laborious process requiring many data inputs and modeling assumptions. Because of resource limitations, PDABs may not be able to conduct their own CEAs but can still incorporate findings from other independent organizations that perform CEA, including academics and HTA agencies. Independence of the organization being relied upon is crucial because the outcome of a CEA is highly dependent on the methodological approach which can be subject to even subconscious bias on the part of those conducting the analysis.

Though the methodology of specific CEAs may vary, there are three general characteristics of these analyses to consider:

- **Analytical perspective.** This indicates the viewpoint from which the CEA is conducted. Many analyses are conducted from the perspective of a health care system, concentrating only on the direct health care costs from a given treatment incurred by the government or third-party payer. Some CEAs take a broader approach, using a societal perspective that might factor in costs associated with lost wages, decreases in productivity, caregiver costs, and other elements.
- **Discount rate.** This value captures the impact of time on costs and benefits. Generally, costs or benefits incurred or gained in the future will be valued less than those incurred or gained in the present. HTA bodies that conduct CEA generally use a discount rate between 1.5-5% in assessing benefits and 3-5% for costs.⁴⁵
- **Time horizon.** Also key to CEA is the window of time during which the analysis examines costs and benefits. In some cases, CEA studies model costs and outcomes over a patient's lifetime. However, this requires extrapolating long-term outcomes and costs based on short-term data, which can reduce the predictive value of the exercise. The horizon can also be shorter (e.g., 5 or 10 years), though doing so may not fully capture the selected therapy's clinical or economic effects over time.

For each of these characteristics, HTA agencies generally set a **reference case** that enables the comparison of different CEAs.

The final output of a CEA is a drug's **incremental cost-effectiveness ratio**. This value is determined by calculating the difference between a new drug's costs and that of the current standard of care. A similar process is done for the drug's clinical benefits. The drug's incremental costs are then divided by its incremental benefits to determine the incremental cost-effectiveness ratio or its cost per unit of benefit gained.

$$\text{Incremental Cost-Effectiveness Ratio} = \frac{(\text{Costs}_{\text{new}} - \text{Costs}_{\text{standard of care}})}{(\text{Benefits}_{\text{new}} - \text{Benefits}_{\text{standard of care}})}$$

⁴⁵ Mathes T, Jacobs E, Morfeld JC, Pieper D. Methods of international health technology assessment agencies for economic evaluations- a comparative analysis. *BMC Health Serv Res.* 2013;13(1):1-10. doi:[10.1186/1472-6963-13-371](https://doi.org/10.1186/1472-6963-13-371)

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If a drug leads to improved outcomes and lower costs than the alternative, it is cost-saving. If it leads to worse outcomes and higher costs, it is “dominated” by the alternative and rejected. However, more commonly, a drug offers greater benefits at a higher cost. In these cases, the incremental cost-effectiveness ratio can be used to understand whether the price established by a drug’s manufacturer is commensurate with the amount of benefit the drug provides relative to its alternatives. An expensive drug that provides little clinical benefit (costs >> benefits) is likely to have a larger, less favorable incremental cost-effectiveness ratio than a cheaper alternative with greater improvements to quality of life or life extension (costs << benefits).

Willingness to Pay Thresholds

In some cases, policymakers compare a drug’s incremental cost-effectiveness ratio to a **willingness-to-pay threshold**, an agreed-upon threshold that a treatment is cost-effective. There are generally agreed-upon thresholds if the outcomes are measured in terms of quality-adjusted life years (QALYs) gained, but these thresholds may not be applicable if a different clinical outcome is used. This approach is used by the UK’s National Institute for Health and Care Excellence (NICE), but due to the politicization of the use of QALYs in the US, it is not clear that such an approach would be feasible for states.⁴⁶

Incorporating cost-effectiveness literature in PDAB decision-making does not commit a Board to setting specific thresholds above which a drug is not cost-effective. Rather, Boards may wish to consider cost-effectiveness alongside other criteria as part of a holistic assessment of a drug’s affordability.

Efficiency Frontiers

Rather than using willingness-to-pay thresholds, another way to analyze cost-effectiveness data is via **efficiency frontiers**. This approach works particularly well when there are multiple different treatment options. This method involves plotting drugs’ costs and drawing a frontier to connect those treatments for which no other option is more effective and less costly. Drugs not included in the frontier are not cost-effective because other treatments are less costly and offer similar or better therapeutic benefit.

One of the benefits of an efficiency frontier approach is that it can easily accommodate any outcome. This works well for health conditions for which a single outcome measure captures most or all safety and efficacy differences between treatments. For example, differences in efficacy among biologic drugs to treat plaque psoriasis can be captured using the Psoriasis Area and Severity Index (PASI) scale, while the drugs do not vary significantly in safety.^{47,48} However, many drugs vary across several distinct outcomes that must either be assessed separately or combined in a composite measure such as the QALY.

The efficiency frontier approach is one way to ensure that a drug’s price is aligned with the prices of therapeutic alternatives, accounting for differences in the safety and efficacy of these alternatives. One downside of the efficiency frontier approach is that it is highly sensitive to the prices of therapeutic alternatives. Germany’s Institute for Quality and Efficiency in Health Care uses an efficiency frontier approach to compare prices of drugs.⁴⁹

⁴⁶ McCabe C, Claxton K, Culyer AJ. The NICE Cost-Effectiveness Threshold. *Pharmacoeconomics*. 2008;26(9):733-744. doi:[10.2165/00019053-200826090-00004](https://doi.org/10.2165/00019053-200826090-00004)

⁴⁷ Armstrong AW, Puig L, Joshi A, et al. Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A Meta-analysis. *JAMA Dermatol*. 2020;156(3):258–269. doi:[10.1001/jamadermatol.2019.4029](https://doi.org/10.1001/jamadermatol.2019.4029)

⁴⁸ Shear NH, Betts KA, Soliman AM, et al. Comparative safety and benefit-risk profile of biologics and oral treatment for moderate-to-severe plaque psoriasis: A network meta-analysis of clinical trial data. *J Am Acad Dermatol*. 2021;85(3):572-581. doi:[10.1016/j.jaad.2021.02.057](https://doi.org/10.1016/j.jaad.2021.02.057)

⁴⁹ Institute for Quality and Efficiency in Health Care (IQWiG). General Methods. 2022. <https://www.iqwig.de/en/about-us/methods/methods-paper/>

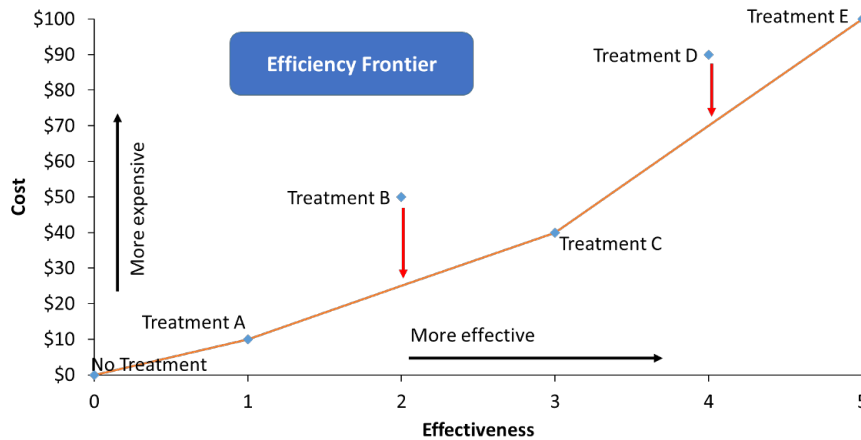


Figure 1. A sample efficiency frontier. In this example, treatments B and D would not be considered cost-effective.

The Quality-Adjusted Life Year (QALY)

Perhaps the most common benefit measure for CEA is the QALY, which assesses the length of time a person spends in a specific health state, weighted by a health-related quality of life score ranging from 0 (death) to 1 (full health).⁵⁰ This metric was designed specifically for health care system cost-effectiveness evaluations and remains the most common method health economists use to measure the value of a drug.

The QALY combines two measures, quality and quantity of life, into a standardized unit. It enables comparison of a drug’s net benefit across different health impacts, including a drug’s influence on life extension, improved symptom management, reduced pain, and others. QALYs are also condition-agnostic, enabling the direct comparison of many different types of treatment across conditions.⁵¹

QALYs have faced substantial political scrutiny in the US.⁵² One main criticism is that QALYs discriminate against vulnerable populations, including individuals with disabilities, the terminally ill, and older adults. Critics also suggest that such measures unfairly set a price on human life. This explains why some state PDABs are restricted from considering QALY-based cost-effectiveness data. Though the QALY, like all analytical methods, has its limitations, in general, such criticisms misconstrue the true use of the QALY in cost-effectiveness research. **QALYs do not measure individuals’ value or worth; they measure a treatment’s impact on health.**

In fact, the absolute health-related quality of life values associated with a given health state provide little information without a comparator group. In some cases, a low quality of life utility can even indicate a greater potential treatment gain. Furthermore, understanding a drug’s clinical benefit relative to its cost can enable greater care for vulnerable populations by concentrating scarce health care resources on treatments shown to have true clinical value.

⁵⁰ Wouters OJ, Naci H, Samani NJ. QALYs in cost-effectiveness analysis: an overview for cardiologists. *Heart*. 2015;101(23):1868-1873. doi:[10.1136/heartjnl-2015-308255](https://doi.org/10.1136/heartjnl-2015-308255)

⁵¹ Garrison LP, Neumann PJ, Willke RJ, et al. A Health Economics Approach to US Value Assessment Frameworks—Summary and Recommendations of the ISPOR Special Task Force Report [7]. *Value in Health*. 2018;21(2):161-165. doi:[10.1016/j.jval.2017.12.009](https://doi.org/10.1016/j.jval.2017.12.009)

⁵² Rand LZ, Kesselheim AS. Controversy Over Using Quality-Adjusted Life-Years in Cost-Effectiveness Analyses: A Systematic Literature Review. *Health Affairs*. 2021;40(9):1402-1410. doi:[10.1377/hlthaff.2021.00343](https://doi.org/10.1377/hlthaff.2021.00343)

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Example: A patient population with a disabling health condition is found to have a health-related quality of life weighted 0.2. Drug A improves their condition to 0.7, adding 0.5 QALYs per life year. This indicates a greater clinical benefit for Drug A among this population than if the same treatment were assessed in a healthy population (e.g., with a health-related quality of life weighted 0.9), as the maximum additional QALYs to be gained is only 0.1.

In assessing QALY-based CEAs, PDABs should nonetheless be attentive to such criticism and evaluate whether critics raise specific concerns about a review's methods. Using QALY-based assessments in combination with other evidence sources can provide a meaningful way to overcome these obstacles.

In the last few years, several alternative health outcome measurements have also been proposed to address the criticisms of the QALYs, such as the **equal value of life years gained** or **health years in total**. Equal value of life years gained ensures that time in life extension is valued the same regardless of disability status, while still capturing the improvements in quality of life offered by new treatments.⁵³ Health years in total aims to separate a therapy's life extension impact from quality-of-life factors using an additive scale.⁵⁴ Although these measurements are newer than QALYs, they may be useful alternatives for PDABs seeking to include cost-effectiveness analyses as part of their affordability reviews.

Relative Financial Effects on Health, Medical, or Social Services Costs

When conducting CEA or other economic analyses, it is important to consider costs more broadly than just the price of a drug. For example, if a drug improves a patient's health and leads to fewer hospitalizations or emergency room visits, these savings could offset the cost of the drug.

CEA studies often analyze costs from the health care system's perspective, meaning that the costs of interest are all direct health care costs incurred by patients or their insurers. Doing so includes the cost of drugs, outpatient, and inpatient health care services and would capture any offset costs.

Budget Impact Analysis

Even if a treatment is deemed cost-effective based on a standardized CEA, it may lead to substantial budget impact that could strain the health care system, particularly if the drug is costly and used by a large patient population. This can lead to fewer resources for other health care and non-health care services. As a result, cost-effectiveness analyses should be accompanied by a **budget impact analysis**.

A budget impact analysis estimates how much a treatment changes the health care costs for an entire population rather than assessing a treatment's cost-effectiveness at an individual patient level. As such, it incorporates the prevalence of the condition and the number of patients who will need treatment. Like CEA, budget impact analysis incorporates both the cost of a drug and potential offset costs if the drug reduces the need for other health care use (e.g., fewer hospitalizations or emergency room visits).⁵⁵ Budget impact analyses are typically conducted on a shorter time horizon than CEA studies (e.g., five years). In addition, the perspective of a budget impact analysis is usually that of a government or private payer.

⁵³ ICER. 2020-2023 Value Assessment Framework. 2022. https://icer.org/wp-content/uploads/2020/11/ICER_2020_2023_VAF_02032022.pdf

⁵⁴ Basu A, Carlson J, Veenstra D. Health Years in Total: A New Health Objective Function for Cost-Effectiveness Analysis. *Value in Health*. 2020;23(1):96-103. doi:[10.1016/j.jval.2019.10.014](https://doi.org/10.1016/j.jval.2019.10.014)

⁵⁵ Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value in Health*. 2014;17(1):5-14. doi:[10.1016/j.jval.2013.08.2291](https://doi.org/10.1016/j.jval.2013.08.2291)

An illustrative example is the budget impact of novel hepatitis C antivirals, as discussed above. Because these treatments are curative and prevented future liver disease and hepatic failures that could occur sometimes decades after a patient first acquired HCV, they were deemed cost-effective even at the nearly \$100,000 launch price for a course of treatment.⁵⁶ However, because of the high prevalence of HCV in the US, if everyone with HCV received the drug all at once, health insurers would not have been able to accommodate the increased expenses. As a result, public and private health insurers restricted access to these treatments to the patients at most immediate risk of liver complications, which limited these drugs' public health impact.⁵⁷

Patient Costs and Access

Because PDABs are tasked with assessing affordability to consumers, the out-of-pocket costs paid by patients who use drugs will be of particular interest. Ultimately, patients and consumers bear the entire cost of prescription drugs through insurance premiums, taxes, and out-of-pocket costs. However, out-of-pocket costs are far more conspicuous to patients and serve as a major barrier to access.

Higher out-of-pocket costs are associated with abandoned medication prescriptions and worse patient adherence for various chronic conditions.^{58,59,60} Currently, 3 in 10 patients struggle to afford their prescription drugs, leading to rationing by cutting pills, skipping pills, or substituting with over-the-counter medicines.⁶¹

As part of the affordability review, it will be important for PDABs to understand the complex factors that determine a drug's accessibility to the patients who need it, particularly in terms of insurance coverage and cost. This will include understanding how access and affordability vary for different patient populations, including those with different insurance types and the uninsured.

Health Equity and Disparities

It is well-documented that racial, ethnic, and socioeconomic inequities exist in how patients can access their prescription drugs. Studies among patients with diabetes show that Asian, Black, and Hispanic patients, and those who are lower-income, struggle to afford their medications at the pharmacy more than others.^{62,63} Many PDABs are required to consider health equity in assessing the affordability of a selected drug, meaning that care should be taken to evaluate whether historically disadvantaged

⁵⁶ Najafzadeh M, Andersson K, Shrank WH, et al. Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus. *Ann Intern Med*. 2015;162(6):407-419. doi:[10.7326/M14-1152](https://doi.org/10.7326/M14-1152)

⁵⁷ Gowda C, Lott S, Grigorian M, et al. Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C: A National Specialty Pharmacy Cohort Study. *Open Forum Infectious Diseases*. 2018;5(6):ofy076. doi:[10.1093/ofid/ofy076](https://doi.org/10.1093/ofid/ofy076)

⁵⁸ Dusetzina SB, Huskamp HA, Rothman RL, et al. Many Medicare Beneficiaries Do Not Fill High-Price Specialty Drug Prescriptions. *Health Affairs*. 2022;41(4):487-496. doi:[10.1377/hlthaff.2021.01742](https://doi.org/10.1377/hlthaff.2021.01742)

⁵⁹ Rome BN, Gagne JJ, Avorn J, Kesselheim AS. Non-warfarin oral anticoagulant copayments and adherence in atrial fibrillation: A population-based cohort study. *American Heart Journal*. 2021;233:109-121. doi:[10.1016/j.ahj.2020.12.010](https://doi.org/10.1016/j.ahj.2020.12.010)

⁶⁰ Essien UR, Singh B, Swabe G, et al. Association of Prescription Co-payment With Adherence to Glucagon-Like Peptide-1 Receptor Agonist and Sodium-Glucose Cotransporter-2 Inhibitor Therapies in Patients With Heart Failure and Diabetes. *JAMA Network Open*. 2023;6(6):e2316290. doi:[10.1001/jamanetworkopen.2023.16290](https://doi.org/10.1001/jamanetworkopen.2023.16290)

⁶¹ Kirzinger A, Montero A, Sparks G, Valdes I, and Hamel L. Public Opinion on Prescription Drugs and Their Prices. KFF. Published August 4, 2023. <https://www.kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices/>

⁶² Eberly LA, Yang L, Essien UR, et al. Racial, Ethnic, and Socioeconomic Inequities in Glucagon-Like Peptide-1 Receptor Agonist Use Among Patients With Diabetes in the US. *JAMA Health Forum*. 2021;2(12):e214182. doi:[10.1001/jamahealthforum.2021.4182](https://doi.org/10.1001/jamahealthforum.2021.4182)

⁶³ Eberly LA, Yang L, Eneanya ND, et al. Association of Race/Ethnicity, Gender, and Socioeconomic Status With Sodium-Glucose Cotransporter 2 Inhibitor Use Among Patients With Diabetes in the US. *JAMA Network Open*. 2021;4(4):e216139. doi:[10.1001/jamanetworkopen.2021.6139](https://doi.org/10.1001/jamanetworkopen.2021.6139)

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populations may be facing disproportionate affordability challenges. Utilizing social determinants of health measures, such as the **social vulnerability index**, may be a valuable tool for such assessment.⁶⁴

Health Insurance Coverage

Patient access to prescription drugs depends on a patient's health insurance coverage and the specific prescription drug benefit plan. The major sources of health insurance coverage include private insurance (49%) through employers, Medicaid (21%), Medicare (14%), private insurance purchased by individuals directly through an insurance company (6%), and the US military (1%).⁶⁵ Approximately 1 in 12 Americans, or 27 million people, are uninsured.⁶⁶

Prescription drug benefits vary between insurance plans, and there are important differences for PDABs to understand between those with private insurance, Medicaid, and Medicare.

Private Insurance

Most adults with private health insurance obtain it through their employers as an employment benefit. For prescription drug coverage, the out-of-pocket costs associated with private health plans vary. The vast majority (90%) of workers have a health plan that uses a tiered cost-sharing model for prescription drugs, with many plans using three or more formulary tiers to drive patients toward preferred drugs.⁶⁷ Coinsurance maximums can also vary widely across private plans.

In addition, 4 in 10 working adults elected to enroll in **high-deductible health plans**.⁶⁸ In these plans, patients pay the full cost of many health care services, sometimes using health savings accounts that employers can partially fund. Although high-deductible health plans apply to more than just prescription drugs, they can impact out-of-pocket drug costs because patients pay the full retail price of a drug until they meet their deductible.

Medicaid

As of April 2023, 94 million Americans were enrolled in **Medicaid**, including 7 million in the Children's Health Insurance Program.⁶⁹ Although prescription drug coverage is not required, all state Medicaid programs offer some coverage. In general, patients in Medicaid pay very few out-of-pocket costs for drugs, with a maximum of \$4 per each medicine on the state's preferred drug list and a maximum of \$8 for non-preferred medicines.⁷⁰ In addition, states must cover essentially all FDA-approved drugs to receive statutory rebates from drug manufacturers. However, they can impose prior authorization or step therapy requirements for drugs not on a preferred drug list.

In addition, 13 state Medicaid programs have monthly prescription drug quantity limits, in which the program only pays for a set number of prescription drugs per month, ranging from three to six

⁶⁴ Spielman SE, Tuccillo J, Folch DC, et al. Evaluating social vulnerability indicators: criteria and their application to the Social Vulnerability Index. *Nat Hazards*. 2020;100(1):417-436. doi:[10.1007/s11069-019-03820-z](https://doi.org/10.1007/s11069-019-03820-z)

⁶⁵ KFF. Health Insurance Coverage of the Total Population. 2021. <https://www.kff.org/other/state-indicator/total-population/>

⁶⁶ CDC National Center for Health Statistics. Health Insurance Coverage. 2022. <https://www.cdc.gov/nchs/fastats/health-insurance.htm>

⁶⁷ KFF. 2022 Employer Health Benefits Survey - Section 9: Prescription Drug Benefits. <https://www.kff.org/report-section/ehbs-2022-section-9-prescription-drug-benefits/>

⁶⁸ Cohen RA, Zammit EP. High-deductible Health Plan Enrollment Among Adults Aged 18–64 With Employment-based Insurance Coverage. *NCHS Data Brief*. 2018;(317). <https://www.cdc.gov/nchs/data/databriefs/db317.pdf>

⁶⁹ CMS Center for Medicaid and CHIP Services. April 2023 Medicaid and CHIP Enrollment Trends

Snapshot. <https://www.medicaid.gov/sites/default/files/2023-07/april-2023-medicaid-chip-enrollment-trend-snapshot.pdf>

⁷⁰ CMS. Medicaid Cost Sharing Out of Pocket Costs. <https://www.medicaid.gov/medicaid/cost-sharing/cost-sharing-out-pocket-costs/index.html>

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prescriptions.⁷¹ However, most states have exemptions available for quantity limits, and in most cases, limits do not apply to patients with managed care plans.⁷²

Medicare

In 2022, 49 million Americans were enrolled in **Medicare Part D** prescription plans, split approximately evenly between Medicare Advantage plans and stand-alone Part D plans.⁷³ At a minimum, Medicare Part D plans must offer the Standard Benefit package of prescription drug benefits. They can also offer a more generous plan that is actuarially equivalent or improved over the standard benefit.

Currently, coverage for prescription drugs varies throughout the year as patients move through four phases of spending, and patients pay unlimited 5% coinsurance even once they reach the catastrophic phase. This will change following the passage of the Inflation Reduction Act of 2022, with caps beneficiary out-of-pocket costs at \$2000/year starting in 2025, along with several other changes.⁷⁴

Insurer Formulary Tools

Most health insurers hire **pharmacy benefit managers (PBMs)** to manage their prescription drug formulary. Insurers and PBMs use formularies to restrict coverage of higher-cost medications by dividing the formulary into “tiers” and requiring higher patient out-of-pocket costs for more expensive medications. Most generic drugs are placed on the lowest tier with the smallest cost sharing, and subsequent tiers include preferred brand-name drugs, non-preferred brand name drugs, and in some cases, specialty drugs. A drug’s tier typically determines patient cost-sharing via **copayments** (a flat fee per prescription) or **coinsurance** (a percentage of the drug’s cost).

Another strategy by PBMs and insurers is to employ **utilization management** strategies, making it more difficult for patients to access expensive non-preferred medications. One of the most common utilization management strategies is **prior authorization**, which requires prescribers to obtain insurance permission before a medication will be reimbursed. Prior authorizations can impose clinical prerequisites, such as limiting the use of drugs to certain patient populations. In some cases, insurers require patients to try a less expensive medication before a more expensive drug will be covered, a strategy known as **step therapy**. Insurers also frequently limit the quantity of a drug patients can get each month.

Formulary tiering and utilization management tools are also used as leverage to negotiate prices with drug manufacturers. For example, PBMs will offer drug manufacturers preferred formulary placement or remove utilization management for their drugs in exchange for larger rebates.

As part of the affordability review, we recommend that PDABs consider a drug’s formulary placement for insured individuals in the state, including its implications for access and out-of-pocket costs. However, an individual drug’s coverage can vary greatly between insurance plans, meaning that such formulary data should be analyzed separately for those with private insurance, Medicare, and Medicaid.

⁷¹ KFF. State Medicaid Prescription Limits. <https://www.kff.org/other/state-indicator/state-medicare-prescription-limits/>

⁷² Hinton E and Raphael J. 10 Things to Know About Medicaid Managed Care. *KFF*. 2023. <https://www.kff.org/medicaid/issue-brief/10-things-to-know-about-medicare-managed-care/>

⁷³ KFF. An Overview of the Medicare Prescription Drug Benefit. 2022. <https://www.kff.org/medicare/fact-sheet/an-overview-of-the-medicare-part-d-prescription-drug-benefit/>

⁷⁴ Cubanski J, Neuman T, Freed M, Damico A. How Will the Prescription Drug Provisions in the Inflation Reduction Act Affect Medicare Beneficiaries? *KFF*. 2023. <https://www.kff.org/medicare/issue-brief/how-will-the-prescription-drug-provisions-in-the-inflation-reduction-act-affect-medicare-beneficiaries/>

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Companies like MMIT collate formulary data from insurers and provide other coverage analytics that may be valuable to PDAB operations.⁷⁵ A free or low-cost version of MMIT data is available via the Coverage Search smartphone app, providing a summary-level view of a drug's coverage by state and insurance type.⁷⁶

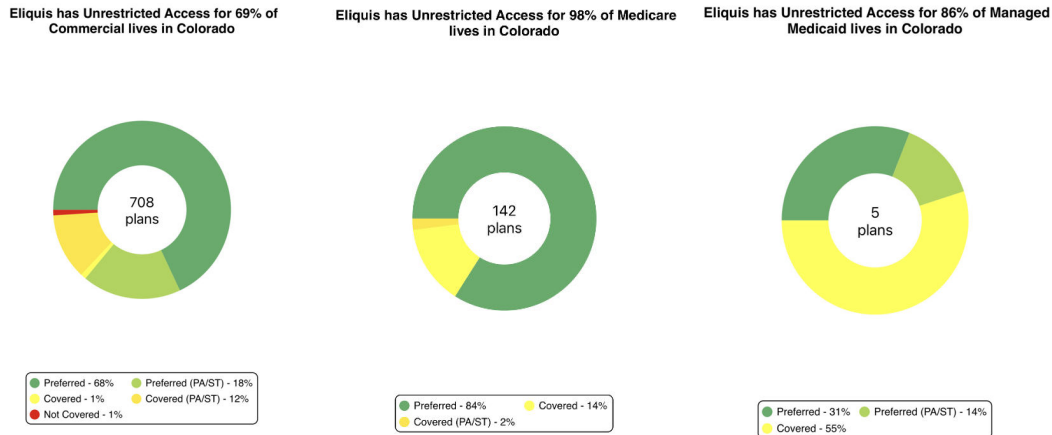


Figure 2. Coverage of Eliquis by Colorado Insurers in 2023. Data and images were obtained from the MMIT free Coverage Search tool.

However, even if drugs are well-covered, it is important to remember that patients with deductibles (e.g., those in high-deductible health plans) and those without insurance may still be responsible for a drug's full cost.

Patient Affordability Tools

When insured patients face high-out-of-pocket costs for prescription drugs, several tools may be available to lower patient costs. These tools' availability and utility vary by drug and insurer. As such, PDABs are encouraged to consider the role these tools play in patient drug spending, should a selected drug have such affordability tools available.

Copayment Cards

Brand-name manufacturers often offer **copayment cards** to offset high out-of-pocket costs set by insurers and PBMs. These cards can reduce a patient's out-of-pocket costs for a drug to less than \$30 per month, but the benefits vary by drug and manufacturer. There are also typically limits on copay cards' monthly or annual value.

Patients with private health insurance are eligible to use copayment cards, while patients with public coverage through Medicare, Medicaid, or the VA are excluded. Obtaining a coupon is usually straightforward: patients can sign up on the manufacturer's website without income restrictions. For example, as of August 2023, Eliquis (apixaban) had a copayment card that could be used by those with private insurance to lower out-of-pocket costs to \$10 per month for 24 months, with maximum savings during this time of \$6400.⁷⁷ The use of copayment coupon cards has increased dramatically in recent years, with coupon use for eligible drugs increasing from 2.1% in 2012 to 15.1% in 2018 in Massachusetts.⁷⁸

⁷⁵ MMIT. Payer Data Intelligence Solutions - Analytics. <https://www.mmitnetwork.com/analytics/>

⁷⁶ MMIT. Coverage Search. <https://www.mmitnetwork.com/coverage-search/>

⁷⁷ Bristol Myers Squibb. Eliquis Savings & Support Information. https://www.eliquis.bmscustomerconnect.com/afib/savings-and-support?cid=v_1357031

⁷⁸ Massachusetts Health Policy Commission. Prescription Drug Coupon Study. 2020. <https://www.mass.gov/doc/prescription-drug-coupon-study/download>

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Though copayment cards can provide financial relief for patients with high copayments, they have been criticized as a mechanism for manufacturers to lure patients into using expensive medications when less expensive options are available.^{79,80} Indeed, manufacturer-sponsored coupons have been found to be more closely tied to market competition rather than out-of-pocket costs.⁸¹

Patient Assistance Programs

Drug companies and non-profit organizations may provide free or low-cost, brand-name prescription drugs to low-income patients who meet strict financial eligibility criteria. These **patient assistance programs (PAPs)** often involve a lengthy application process for patients and their clinicians, requiring proof of income and a clinician signature. As a result, PAPs are typically far more limited in use than copayment cards.

Pharmacy Coupons

Another option for patients with high out-of-pocket costs is using pharmacy coupons from companies like GoodRx.⁸² These coupons offer medications at prices negotiated by PBMs to patients and can be used in place of insurance. The discounts vary by pharmacy and ZIP code and can change frequently, with the largest discounts often available for expensive generic prescription drugs or generics not covered by insurance. These coupons are less useful for expensive brand-name drugs, which are typically very expensive even at discounted prices. For insured patients who use a coupon, the amount paid does not count towards their insurance deductible or annual out-of-pocket maximum. Insurers do not track the use of these coupons in claims data, so information about how frequently they are used is difficult to obtain.

Direct-to-Consumer Pharmacies

Some pharmacies purchase prescription drugs directly from drug manufacturers or wholesalers, allowing patients to obtain them outside their insurance arrangements at affordable prices. The most prominent examples of this model include Costco, the Walmart \$4 list (although some drugs are now more than \$4), and the Mark Cuban Cost Plus Drug Company.^{83,84,85} Other companies sell drugs for specific clinical areas (e.g., men's health). Most of these pharmacies' formularies are limited to generic drugs. Prices vary; to take advantage, patients must shop around for the lowest price. These costs do not count towards the patient's insurance deductible or annual out-of-pocket maximum.

Overall, the affordability tools available to patients who face high out-of-pocket costs for their prescription drugs are an important consideration for PDABs. However, Boards may face challenges in collecting accurate information on these tools. As such, considering patient assistance should serve as another element of the broader review that, paired with direct patient engagement, could help clarify affordability.

⁷⁹ Dafny L, Ho K, Kong E. How Do Copayment Coupons Affect Branded Drug Prices and Quantities Purchased? *National Bureau of Economic Research*. Published online February 2022. doi:[10.3386/w29735](https://doi.org/10.3386/w29735)

⁸⁰ Ross JS, Kesselheim AS. Prescription-Drug Coupons — No Such Thing as a Free Lunch. *N Engl J Med*. 2013;369(13):1188-1189. doi:[10.1056/NEJMp1301993](https://doi.org/10.1056/NEJMp1301993)

⁸¹ Kang SY, Liu A, Anderson G, Alexander GC. Patterns of Manufacturer Coupon Use for Prescription Drugs in the US, 2017-2019. *JAMA Network Open*. 2023;6(5):e2313578. doi:[10.1001/jamanetworkopen.2023.13578](https://doi.org/10.1001/jamanetworkopen.2023.13578)

⁸² GoodRx. <https://www.goodrx.com/>

⁸³ Costco Wholesale Corporation. Member Prescription Program. <https://www.costco.com/cmpp>

⁸⁴ Walmart. Retail Prescription Drug Program List. <https://www.walmart.com/cp/4-prescriptions/1078664>

⁸⁵ Mark Cuban Cost Plus Drug Company. <https://costplusdrugs.com/>

Market Dynamics

In assessing a drug's affordability, it is also important to consider a drug in the context of the broader market in which it is sold. This includes understanding the investments into the drug's development, the current state of competition in the market, and the patents and regulatory exclusivities that prevent competition for brand-name drugs.

It is also critical to note that assessing these market elements may necessitate a review of manufacturer-submitted data, which may present a different landscape than that depicted in the other information PDABs consider. Keeping the source of this information (and that of any materials reviewed by the PDAB) in mind throughout the affordability review process is important to maintain an objective process.

Research and Development Costs

Industry advocates often suggest that high drug prices are justified given the research and development costs of bringing a drug to market.⁸⁶ High prices during the period of market monopoly allow drug manufacturers to recoup their investments in the development of the approved drug and that of failed drug candidates. In addition, manufacturers argue that these high prices and lucrative revenues are necessary to invest in risky new treatments, which leads to claims that lower drug prices will restrict pharmaceutical innovation.

There is no evidence that manufacturers set prices based on research and development investments – prices are set based on a company's expected profit margins and market conditions for the drug.⁸⁷ In addition, much of the seminal innovation leading to drug discovery is publicly funded by the National Institutes of Health,⁸⁸ and there is no evidence that higher prices drive meaningful innovation for drugs that benefit patients.⁸⁹

Nonetheless, PDABs may need to consider manufacturer research and development as part of an affordability review. To do so requires first determining what constitutes a research and development cost for PDAB purposes. Guidance issued by CMS in operationalizing the Medicare drug price negotiation program may serve as a template for defining these costs.⁹⁰ The agency has proposed five cost categories to determine the research and development costs to manufacturers for indications of its drug:

- **Acquisition Costs:** costs directly tied to the manufacturer's purchasing of the rights to a drug from another entity, including the patents on the selected drug.
- **Pre-Clinical Research Costs:** direct and indirect research costs to the manufacturer from the date of discovery of the drug through the date at which the drug started human clinical trials.

⁸⁶ CBO. Research and Development in the Pharmaceutical Industry. <https://www.cbo.gov/publication/57126>

⁸⁷ Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. *JAMA*. 2016;316(8):858-871. doi:[10.1001/jama.2016.11237](https://doi.org/10.1001/jama.2016.11237)

⁸⁸ Galkina Cleary E, Jackson MJ, Zhou EW, Ledley FD. Comparison of Research Spending on New Drug Approvals by the National Institutes of Health vs the Pharmaceutical Industry, 2010-2019. *JAMA Health Forum*. 2023;4(4):e230511. doi:[10.1001/jamahealthforum.2023.0511](https://doi.org/10.1001/jamahealthforum.2023.0511)

⁸⁹ Kesselheim AS, Avorn J. Letting the government negotiate drug prices won't hurt innovation. *Washington Post*. <https://www.washingtonpost.com/outlook/2021/09/22/drug-pricing-negotiation-biden-bill/>. Published September 30, 2021.

⁹⁰ CMS. Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026. 2023. <https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf>

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- **Post-IND Application Costs:** direct costs associated with the evaluation of the drug through clinical trials, preparation for regulatory review, and any completed post-marketing studies.
- **Abandoned and Failed Drug Costs:** direct pre-clinical research costs of drug candidates with the same active moiety or active ingredient that failed to reach clinical trials, as well as a portion of the post-IND costs of drugs in the same therapeutic class that did not obtain FDA approval.
- **All Other R&D Direct Costs:** any allowed direct research and development costs that do not fall into the other categories (e.g., costs of ongoing post-marketing studies).

Under the CMS proposal, these costs would then be compared with the manufacturer's global and US lifetime net revenue for the selected drug to determine whether a selected drug has recouped its research costs. State PDABs may consider adopting a similar framework to CMS. Drugs shown to have adequately recouped research and development costs may be more likely to be deemed unaffordable at high prices. By contrast, those who have not recouped research and development costs may be allowed an affordability designation at higher prices.

It is important, however, to ensure that the review of a selected drug's research and development costs is limited to that particular drug and its derivatives rather than the manufacturer's broader portfolio, as too broad a review may shroud the economic reality of a selected drug. Relatedly, PDABs may consider reviewing the manufacturing and distribution costs associated with an eligible drug, as complex therapeutics (e.g., biologics and biosimilars) may have higher barriers to market entry that would influence the product's price.

Overall, though, **research and development costs alone do not provide a comprehensive picture of a drug's market position**, meaning that such a factor may be better suited as a secondary consideration for PDABs. Other criteria, including the presence of generic competition for a selected drug and its existing market exclusivities, have been shown to be better price indicators and may promote greater attention.

Public Funding

In addition to the private investment supporting a selected drug's development and approval, many innovative pharmaceutical products have benefitted from substantial public investment. These investments can be tax credits, grants, contracts, and other funding mechanisms that support basic and applied research attributed to a drug. For example, of the more than 350 drugs approved by the FDA between 2010 and 2019, 99.4% could be traced back to federal funding.⁹¹ Such funding often occurs as innovations are discovered in federally-funded academic laboratories and later transferred to the private sector for further development. In some cases, public funding may persist into later stages of development; in one study, about one in four new drugs was found to have public funding connected to late-stage development.⁹²

In considering a selected drug's affordability, it may be in the interest of PDABs to consider the public investments made in the drug's development. Drugs that relied on substantial public funding for their

⁹¹Galkina Cleary E, Jackson MJ, Zhou EW, Ledley FD. Comparison of Research Spending on New Drug Approvals by the National Institutes of Health vs the Pharmaceutical Industry, 2010-2019. *JAMA Health Forum*. 2023;4(4):e230511. doi:[10.1001/jamahealthforum.2023.0511](https://doi.org/10.1001/jamahealthforum.2023.0511)

⁹²Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. *BMJ*. 2019;367:l5766. doi:[10.1136/bmj.l5766](https://doi.org/10.1136/bmj.l5766)

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success may warrant greater scrutiny of their affordability. In such cases, high prices mean the public is being asked to pay “twice” for the drug. In assessing the public contributions, it is important to weigh these contributions relative to the broader research and development costs of the drug and the budgets of the public entity that provided funding.

Life Cycle Management

New brand-name drugs are granted a period of monopoly protection before generic or biosimilar competition begins, obtained through a combination of patent protection and other statutory exclusivity periods. PDABs may consider reviewing these extended protections for a selected drug to evaluate the drug’s competitive landscape. The information may be particularly relevant in circumstances when limited therapeutic alternatives are available, as they point toward the degree to which the drug addresses an unmet need. Such data can also highlight manufacturers’ strategies to maximize revenue from a given product.

Understanding such market dynamics for a selected drug is particularly important as it relates to generic competition. Typically, the entrance of three or more interchangeable generic competitors can stimulate expected reductions in drug price.⁹³ Though a similar dynamic has not been observed in the biosimilar market, the first biosimilars were approved in 2015, so many hope that biologic prices will come down as more biosimilars enter the market.

Patents

When developing a new medication, brand manufacturers nearly always protect the product’s core active ingredient with a **patent**, which lasts for 20 years. Patents that protect the primary innovation behind a product are often the strongest and most reliable protectors of market exclusivity for a company, since patents allow their holders to exclude others from making, using, or offering to sell the product described in the patent. For successful drug products, manufacturers will patent other elements of their product, such as its formulation, metabolites or intermediates, delivery mechanism, clinical uses, and manufacturing process.

The strength or validity of such additional patents beyond the primary patent may be questionable, but the resulting “**patent thicket**” can dissuade generic or biosimilar competitors from entering the market for fear of infringement. Since each patent lasts 20 years from the time of its application, a patent thicket can ensure market exclusivity persists even after a drug’s primary patent has expired. PDABs may be interested in learning how many patents manufacturers have obtained to protect their drug, or when a drug’s primary patent has expired. Manufacturers of small molecule drugs must list certain key patents with the FDA, which publishes them in the Approved Drug Products with Therapeutic Equivalents database (also called the Orange Book).⁹⁴ For biologics, some relevant patents are listed in a similar FDA compendium called the Purple Book, though it is less comprehensive and patents only appear there after they are the subject of litigation.⁹⁵ Manufacturers should also be able to provide comprehensive information on their patent portfolios.

⁹³ Darrow JJ, Kesselheim AS. Promoting Competition To Address Pharmaceutical Prices. *Health Affairs*. Published online March 15, 2018. doi:[10.1377/hpb20180116.967310](https://doi.org/10.1377/hpb20180116.967310)

⁹⁴ FDA. Approved Drug Products with Therapeutic Equivalence Evaluations - Orange Book. Updated August 11, 2023. <https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>

⁹⁵ FDA. Purple Book Database of Licensed Biological Products. Updated August 9, 2023. <https://purplebooksearch.fda.gov/>

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For competitors to enter the market, generic and biosimilar manufacturers must challenge patents, often resulting in settlements between brand and generic manufacturers on when competition can begin. The challenge process for generics was outlined in the Hatch-Waxman Act of 1984 and for biologics was detailed in the Biologics Price Competition and Innovation Act of 2009. In some cases, brand-name manufacturers offer incentives to delay generic competition, a strategy called “**pay-for-delay**” when it involves a financial payment. In recent years, the Federal Trade Commission has investigated a few of these settlements for being anti-competitive.⁹⁶

Another strategy manufacturers can use to undermine competition is “**product hopping**,” which is a term that describes when a manufacturer releases and markets a new version of a drug with additional patent protection just as the original one nears the end of its exclusivity period.⁹⁷ Manufacturers heavily market the new version to help shift patients to it and away from the original formulation that is nearing generic competition. The new formulation may have some advantages over the original version, but it is invariably much more expensive than the old version, particularly after generic competition begins. Some prominent examples have included the multiple sclerosis drug glatiramer, which was switched from a daily to 3-times-weekly injection, delaying competition by more than two years and costing \$4-\$6 billion in excess spending.⁹⁸ Another example is esomeprazole (Nexium), which was the chemical enantiomer (mirror image) of the original drug omeprazole (Prilosec).

As part of an affordability review, it will be important for PDABs to consider whether there is any evidence that the drug’s manufacturer has launched updated versions late in the exclusivity period to avoid competition, as this could have a major impact on the drug’s affordability to patients.

Market Exclusivity

In addition to patents, manufacturers receive other statutory **market exclusivities** upon FDA approval. Developers of novel small molecules are typically granted a minimum of five years of exclusivity, during which time no generic competitor may submit an application to the FDA to enter the market. Drugs with a designation under the Orphan Drug Act are protected from competition for a minimum of 7 years.⁹⁹ Three years of market protection may be provided for a drug that is a new formulation if new clinical studies were conducted to secure FDA approval. Some antibiotics and treatments evaluated in pediatric patients can get additional exclusivities beyond those initially granted.¹⁰⁰ Similarly, biologics are guaranteed 12 years of exclusivity before biosimilars may enter.

Such incentives can also be gamed to maximize manufacturer control and delay generic entry. These non-patent statutory protections are listed in the FDA Orange Book or Purple Book. However, patents often extend beyond the expiration of these statutory protections and are the most common reason preventing or delaying generic or biosimilar competition and would, therefore, likely warrant greater attention by PDABs.

⁹⁶ FTC. Pay-for-Delay: When Drug Companies Agree Not to Compete. <https://www.ftc.gov/news-events/topics/competition-enforcement/pay-delay>

⁹⁷ Carrier M, Shadowen S. Product Hopping: A New Framework. *Notre Dame Law Review*. 2016;92(1). <https://scholarship.law.nd.edu/ndlr/vol92/iss1/4>

⁹⁸ Rome BN, Tessema FA, Kesselheim AS. US Spending Associated With Transition From Daily to 3-Times-Weekly Glatiramer Acetate. *JAMA Intern Med*. 2020;180(9):1165. doi:10.1001/jamainternmed.2020.2771

⁹⁹ FDA. Designating an Orphan Product: Drugs and Biological Products. Updated July 8, 2022. <https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products>

¹⁰⁰ FDA. Frequently Asked Questions on Patents and Exclusivities. Updated February 5, 2020. <https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#howlongexclusivity>

Final Considerations

The above sections provide guidance states can use in identifying information to inform whether a drug is affordable or unaffordable. The list is not exhaustive; states may be required to consider additional factors that may reflect the unique circumstances of the PDABs' purview through statute, policy, and regulation.

These factors can be used to assess affordability from various perspectives, including affordability to the health care system, affordability to patients, and affordability relative to other comparable treatments. We recommend that PDABs consider all of these vantage points when conducting an affordability review, holistically considering the interplay between factors that may influence Board determinations of affordability and access. Determining whether a drug is affordable can hold many highly context-dependent meanings. Boards may need to balance and weigh competing information, and how this is done will vary based on the context of individual drugs.

Conducting affordability reviews that are as inclusive as is legally and technically possible, with ample opportunity for stakeholder engagement and feedback, will be instrumental in ensuring that PDABs can adequately fulfill their statutory mandates and have positive impacts on prescription drug spending and patient benefit in their states.