



Identifying Drugs for Affordability Review

Guidance for State Prescription Drug Affordability Boards

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Executive Summary

This memo outlines how drugs are defined and categorized within the U.S. regulatory framework and provides insight into how the definition of a drug may influence the actions of state Prescription Drug Affordability Boards (PDABs). In deciding what constitutes a drug, it may be advantageous for PDABs to define a drug broadly to include all dosage forms so as to be able to review the affordability of an entire product family. However, this memo describes technical, legal, and political barriers to implementing such a broad definition.

Background

Several state Prescription Drug Affordability Boards (PDABs) have been tasked with selecting and reviewing the affordability of certain prescription drugs. Defining a “drug” for the purposes of these assessments has important consequences for determining which and how many drugs will be included; how each state will measure affordability; and the implementation of cost-reduction tools. Though authorizing statutes in specific jurisdictions may provide foundational definitions by which PDABs must abide, this memo describes additional considerations for states in determining rules and regulations to implement PDABs.

What is a Drug?

At the broadest level, the Food, Drug, and Cosmetic (FD&C) Act of 1938 defines a **drug** as a substance, other than food, that is intended to affect the structure or function of the body for the purpose of diagnosis, cure, mitigation, treatment, or prevention of disease.^{1,2}

Active Ingredients v. Active Moieties

Drugs contain one or more **active ingredients**, the component(s) of the product that provide the pharmacological activity for the drug’s intended use.³ In many cases, a molecule that is pharmacologically active may be chemically bound to non-active components, such as salts or chelates.

¹ [21 U.S.C. § 321](#)

² FDA Center for Drug Evaluation and Research (CDER). [Drug – Glossary of Terms](#). *Drugs@FDA*. Published online February 3, 2022.

³ [21 CFR 314.3 “Active ingredient.”](#)

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An **active moiety** refers to the core molecule “responsible for the physiological or pharmacological action of the drug substance,” excluding these non-active components.⁴ The FDA uses a drug’s active moiety to determine whether new drugs qualify as a “new chemical entity” (which comes with five years of guaranteed market exclusivity).⁵ Each active ingredient and active moiety is assigned a **Unique Ingredient Identifier (UNII)**, a database of which is available in the FDA Global Substance Registration System.⁶

Example: Nexium, a medication for chronic acid reflux and other conditions, derives its pharmacological activity from its active *moiety* of esomeprazole. However, forms of the drug are marketed with different active *ingredients*, including Nexium (esomeprazole magnesium), Nexium 24Hr (esomeprazole sodium), and esomeprazole strontium.

Drug Products v. Biological Products

A small molecule **drug product** constitutes the **dosage form** of a drug’s active ingredient along with any inactive ingredients.⁷ Each dosage form can generally be segmented into two components – the **strength** of the active ingredient (e.g., 10mg, 100mg) and its **formulation** (e.g., oral tablet, capsule, solution). For the purposes of FDA regulation, each dosage form is considered a separate drug product.

Example: The diuretic hydrochlorothiazide is manufactured in strengths of 12.5mg, 25mg, and 50mg, respectively, as both a tablet and a capsule. This means that the FDA considers a 12.5mg capsule of hydrochlorothiazide a distinct drug product from a 25mg tablet or a 50mg capsule of the drug.

A **biological product**, or **biologic**, is a complex molecule (e.g., a protein or antibody) that is commonly derived from living material and used for therapeutic purposes.⁸ Biologics can also vary in strength and dosage form and are accordingly considered separate products.

Example: Neupogen (active ingredient: filgrastim), a recombinant glycoprotein hormone used to treat neutropenia, is offered in vial form at strengths of 300mcg/1mL and 400mcg/1.6mL and in syringe form at 300mcg/0.5mL and 480mcg/0.8mL. Therefore, a 300mcg/1mL vial of the biologic is considered a distinct biological product from the 300mcg/0.5mL syringe by the FDA.

FDA Regulation

Regulation of drugs in the US through the FDA is a complex and nuanced process. In general, though, authorization to market a drug proceeds through one of two pathways.

Small molecule drugs receive marketing authorization after FDA review of a **New Drug Application (NDA)**.⁹ Biologics are similarly licensed for marketing after filing a **Biologics License Application (BLA)**.¹⁰ Each NDA or BLA is assigned an identification number that is affiliated with a drug throughout its life cycle. Information on approved products is typically available in various FDA

⁴ [21 CFR 314.3 “Active moiety.”](#)

⁵ [21 CFR 314.108\(a\) “New chemical entity.”](#)

⁶ FDA. [Global Substance Registration System](#). 2023.

⁷ [21 CFR 314.3 “Drug product.”](#)

⁸ [21 CFR 600.3\(h\)](#)

⁹ FDA. [New Drug Application \(NDA\)](#). Updated online January 21, 2022.

¹⁰ FDA. [Therapeutic Biologics Applications \(BLA\)](#). Updated online February 24, 2020.

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databases, including Drugs@FDA, the Orange Book (for small molecule drugs), and the Purple Book (for biologics).^{11,12,13} Information on a drug's approved indications and other clinical information can be found in the FDALabel database.¹⁴

Any drug that includes a never-before-approved active moiety must typically be approved via a new NDA or BLA.¹⁵ In some cases, however, an NDA or BLA may include approval for multiple strengths and formulations of a single active moiety.

Companies can also seek approval for new dosage forms of an existing drug by submitting **supplements to an approved NDA or BLA**, which typically undergo an expedited review process.

Example: A new, more concentrated version of Humira (active ingredient: adalimumab) that did not contain a citrate buffer was approved by the FDA in 2018 as a supplement to the original adalimumab BLA approved in 2002.

Alternatively, manufacturers may seek approval for new dosage forms through a new NDA or BLA, though doing so carries an additional user fee.¹⁶ In other cases, manufacturers may submit separate NDAs or BLAs for drugs that share an active ingredient but have different uses or indications.

Example: Ozempic and Wegovy share an active ingredient (semaglutide) and formulation (injectable solution), yet were approved for the treatment of diabetes and obesity, respectively, through separate NDAs.

PORTAL Recommendation

Because manufacturers have discretion whether to bundle products into a single NDA/BLA or submit separate applications, we advise PDABs to avoid defining a drug based on a unique NDA or BLA; doing so may be prone to gaming by manufacturers by filing separate NDA/BLAs for different versions of their drug so that each must be considered separately by the PDAB.

The National Drug Code (NDC) Identification System

For approved drugs, manufacturers are required to regularly submit to the FDA a list of all drugs currently manufactured, processed, compounded, or otherwise produced for commercial distribution.^{17,18} Each drug product on this list is subsequently assigned a **National Drug Code (NDC)**.

¹¹ FDA CDER. [Drugs@FDA](#).

¹² FDA CDER. [Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations](#).

¹³ FDA. [Purple Book: Database of Licensed Biological Products](#).

¹⁴ FDA. [FDALabel: Full-Text Search of Drug Product Labeling](#).

¹⁵ FDA CDER. [New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products](#). Updated online May 22, 2023.

¹⁶ FDA. [FDA User Fee Programs](#). Updated online March 30, 2023.

¹⁷ [21 CFR 207.33](#)

¹⁸ FDA. [National Drug Code Directory – Background Information](#). Updated online July 22, 2022.

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An active list of NDCs that are currently marketed is available in the FDA’s NDC Directory.¹⁹ More comprehensive NDC lists, including those for products that are no longer marketed, are available from proprietary databases, including First Databank, Red Book, and Medi-Span.^{20,21,22}

NDCs are 11-digit numbers* that are segmented into three codes:^{23,24}

1. Labeler (5 digits) - Identifies the firm that manufactures, repackages, or distributes the drug; these codes are assigned by the FDA. This is often the drug’s manufacturer, but in some cases, drugs are re-packaged by third-party labelers (e.g., 1000 tablet containers re-packaged to 30 tablet bottles). In these cases, the code reflects the third-party labeler.
2. Product (4 digits) - The product code identifies the specific strength, dosage form, and formulation of the product. This is supplied by the manufacturer.
3. Package (2 digits) - Identifies package size and type. This is supplied by the manufacturer.

** In some cases, NDCs are displayed in a 10-digit format because a leading zero is left off one of the three components.*

Pharmacy claims reimbursed by insurers always identify the dispensed drug using its NDC. As a result, **the NDC is the most specific way to identify a drug product used in the US.** Clinician-administered drugs (e.g., intravenous infusions) can also be identified using the Healthcare Common Procedure Coding System (HCPCS) codes, or “J-codes,” used to bill insurance. These J-codes are assigned by CMS and may cover the use of one or more NDC. CMS provides crosswalk files to identify this NDC-J-code relationship.²⁵

PDAB Considerations for Defining a Drug

In defining what constitutes a drug, PDABs face the challenge of balancing a combination of strategic and practical considerations.

Definition Breadth

Technically, the easiest solution is to **narrowly define each NDC as a separate drug.** For the purposes of PDABs, the package code is irrelevant, so the **first nine digits of the NDC (i.e., NDC-9) are the most informative.** However, treating NDCs separately results in treating each dosage form separately, which could pose some problems. For example, if a PDAB chooses to select drugs with the highest spending or use in the state, drugs with multiple dosage forms may have their total spending and utilization diluted across these forms, compared to a drug with a single dosage form.

PORTAL Recommendation

If PDABs decide to define a drug as each distinct NDC, we recommend utilizing the first nine digits of the NDC. However, this approach will result in different dosage forms and/or brands of the same active ingredient being treated separately, which may complicate the overall evaluation of a drug’s affordability.

¹⁹ FDA. [National Drug Code Directory](#).

²⁰ First Databank. [Analysource](#).

²¹ Merative. [Micromedex – RED BOOK](#).

²² Wolters Kluwer. [Medi-Span](#).

²³ [21 CFR 207.33\(b\)](#)

²⁴ FDA. [National Drug Code Directory – Background Information](#). Updated online July 22, 2022.

²⁵ CMS. [Medicare Part B Drug Average Sales Price – 2023 Drug Pricing Files](#). Updated online June 21, 2023.

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Alternatively, states could adopt a **broad definition** of drugs that would offer more latitude to consider affordability for an entire product family. For example, states could **aggregate all dosage forms of a given active moiety**. Such consolidation would be straightforward in many cases. This approach also mirrors that proposed by CMS to identify eligible single-source drugs in its Medicare price negotiation program.²⁶

In addition, aggregation prevents the ability of manufacturers to game PDAB regulations by launching new dosage forms of an existing drug that are treated separately from the original. Such “product hopping” is already a common strategy to extend exclusive brand-name sales, and PDABs may not wish to allow this tactic to affect their drug selection.²⁷

However, **there are also limitations to consider** when aggregating drugs by active moiety:

1. The same active moiety may be used in multiple branded drugs made by different manufacturers.

Example: There are three branded versions of albuterol inhalers (Ventolin, Proair, Proventil), all of which have the same active moiety.

2. Even when made by the same manufacturer, there may be instances in which different dosage forms have entirely different clinical uses that merit separate consideration.

Example: Fluticasone is the active moiety in both an inhaled nasal product (Flonase) and a respiratory inhaler (Flovent). These products are produced by the same manufacturer yet have different clinical uses. The nasal version is also available over-the-counter and has generic alternatives, while the inhaler does not have generics as of June 2023.

3. Fixed-dose combination products, which contain two or more active ingredients, may make aggregation difficult. In these cases, PDABs must decide whether to treat the combination product as a separate drug or to aggregate it with drug products containing only one of its active ingredients.

Example: The diabetes drug Synjardy is a combination product consisting of both empagliflozin and metformin, while Jardiance includes only empagliflozin. The eligibility of these two drugs could be considered together if it was determined that all products containing empagliflozin should be aggregated.

4. Different dosage forms may carry different prices. This could result in situations in which one dosage form of a drug is deemed eligible for selection (e.g., if it meets a PDAB’s statutory threshold of a wholesale acquisition cost above \$30,000/year) while another is not.
5. Aggregating by active moiety may, in some circumstances, overlook meaningful clinical differences between drug products. In these cases, PDABs may consider excluding a particular NDC from an affordability review, provided that doing so would not undermine the overall review.

²⁶ Seshamani M. [Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments](#). CMS. Published online March 15, 2023.

²⁷ Gowda V, Beall RF, Kesselheim AS, Sarpatwari A. [Identifying potential prescription drug product hopping](#). *Nature Biotechnology*. 2021;39(4):414-417.

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PORTAL Recommendation

Where statutorily possible, we recommend maintaining a broad definition of a drug for the purposes of eligibility to prevent gaming by manufacturers and to ensure a comprehensive affordability assessment of an entire drug family. However, PDABs must consider the limitations of such an approach and accordingly enable flexibility to consider the nuances of each drug under their review.

Aggregation Timing

It is also important to consider **the point at which NDC aggregation occurs**. Aggregating early in the process (e.g., when creating a list of eligible drugs) is ideal because it ensures a consistent definition throughout the process.

However, aggregating at the onset can pose challenges, as certain statutory eligibility criteria (e.g., WAC per annual course of treatment) may vary between a drug's dosage forms. To address this, PDABs may consider aggregating all information (e.g., calculating a weighted average WAC per annual course of treatment) or determining eligibility if *any* formulations of a drug meet the eligibility criteria.

Alternatively, states could initially identify eligible drugs using a narrower definition (e.g., NDC-9) and then broaden the definition when selecting drugs for affordability review (i.e., the board could select all formulations of a drug and decide to review them together). However, this poses a problem if one or more formulations of a drug do not independently meet the statutory eligibility criteria.

PORTAL Recommendation

We recommend aggregating drug products as early in the PDAB procedure as is technically and statutorily feasible to ease the review of eligibility criteria. Nonetheless, individual PDAB priorities and available resources will influence such timing decisions.

Implications for Next Steps

States must also consider how a broad or narrow definition of a drug will affect the affordability review process and, when relevant, the setting of an upper payment limit. For example, if the price of a drug varies by dosage form, the PDAB should maintain the ability to make different determinations of whether each version is unaffordable. Furthermore, PDABs should preserve the ability to determine different upper payment limits for different dosage forms of a drug.