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Reimbursement Knowledge Guide for Drugs

NIH SEED Innovator Support Team

Introduction

In 2021, U.S. healthcare spending totaled $4.3 trillion. This reflects steady growth in healthcare expenditures across the board: Medicare spending rose 8%, Medicaid rose 9%, and private health insurance rose 6% while patients' out-of-pocket spending increased 10%.[1] As costs continue to go up, it is important to understand what health insurance may—or may not—pay for, and the extent to which patients are willing to pay out-of-pocket, as a new drug enters the market.

This guide has been developed to help innovators developing new drugs (for simplicity, drugs and biologics are referred to as drugs) gain a basic understanding of the drug reimbursement landscape. It describes how health insurers pay for new drugs, criteria they may use to make decisions, and the types of evidence needed to influence payers' decisions. It also includes reimbursement topics (e.g., coverage, coding, payment) for U.S. Food and Drug Administration (FDA)-approved drugs.

Although the authors have done their best to explain these topics in plain language, implementation of knowledge can be challenging. Therefore, a series of reimbursement case studies have also been created to help innovators understand how and when to develop a reimbursement plan.

Link to Small Molecule Reimbursement Case Study #1
Link to Physician-Administered Drug Reimbursement Case Study #2
Link to Self-Administered Drug Reimbursement Case Study #3

[1] https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet

The goal of receiving FDA approval for a new drug is often considered the primary endpoint that leads to commercial success. However, if it does not receive the desired level of reimbursement or, even worse, is not covered by payers, physicians are unlikely to recommend and prescribe the new drug. Therefore, ensuring reimbursement for a new drug is as important as obtaining regulatory approval. It is wise to initiate reimbursement research and develop a strategic reimbursement plan at least 24 months prior to the anticipated Market Authorization and launch of a new drug.

Understanding what health insurance may—and may not—pay for, and how much patients are willing to pay out-of-pocket, is a critical component of bringing a new drug to the market.

If you have questions about the material in this guide, or want to connect with a subject matter expert to discuss your specific situation, contact the SEED Innovator Support Team.

Please use the Word navigation panel to jump to relevant sections for your specific needs. Bolded terms within the text are defined in the Glossary.

After reading this Reimbursement Knowledge Guide, you should have a better understanding of the drug reimbursement landscape and how it can impact new drug development. Specific topics that will be covered are listed below:

- An overview of the drug reimbursement landscape and how public and private stakeholders are involved in the reimbursement of drug products.
- Why it's important for early-stage researchers to conduct necessary research, develop a reimbursement strategy, and align reimbursement activities with clinical trials and regulatory approval.
- How to articulate to payers the value proposition of your new drug and show the comparative value of a new drug over existing products or treatments.
- What data should be collected during drug development and testing to support the questions that regulators and payers will likely ask.
- Specific considerations about how Medicare, Medicaid, and commercial insurers evaluate coverage of new drugs.

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1 Understand the Landscape

The U.S. healthcare system includes both public and private health insurance coverage for drugs (this guide refers to both drugs and biologics as drugs). Coverage of a drug and the amount of its reimbursement are determined by each payer's coverage policies. The two largest public insurance programs are Medicare and Medicaid, which must meet unique federal and state requirements. Private plans and commercial insurers have more flexibility to set coverage and reimbursement determinations, this means the **out-of-pocket** costs to patients can vary significantly if they have private insurance.

Medicare, national program policies for Medicaid and the Children's Health Insurance Program (CHIP), and implementation of major provisions of the **Affordable Care Act** (ACA) are all administered by a single federal agency, the **Centers for Medicare & Medicaid Services** (CMS). As a critical stakeholder in payer decisions in all three programs, CMS also influences private sector coverage and reimbursement decisions, as commercial insurers often follow Medicare's lead.

1.1 Basic Tenets of Reimbursement Policies

Coverage, coding, and payment are the building blocks of healthcare reimbursement. Payers make coverage decisions based upon the premise they should pay only for the drugs, procedures, and devices which positively affect the health of the lives they insure. Payers make these decisions by reviewing detailed information about the item or service rendered. If an item or service is determined to be of benefit, it will be described using a standard, specific identifier—known as a code. The same code will be used by all payers.

Coverage, coding, and payment are the building blocks of healthcare reimbursement policies.

How much a specific item or service will receive (payment) is calculated based on the treatment inputs (time and materials related to the service, including physician, nurse, staff, and other healthcare provider compensation, capital equipment, medical supplies, utilities, and administrative overhead) combined with some outputs (such as improving quality of care, patient safety, accelerated hospital discharge, or the cost avoidance of treating a worsening condition).

Resource:
NIH SEED: Drug Reimbursement Strategy Workshop

2 Medicare, Medicaid, and Commercial Insurers

The largest and most influential categories of health insurers in the U.S. are:

- Medicare: The federal (national) **health insurance** program for individuals over age 65 and those with a long-term disability
- Medicaid and CHIP: The joint federal and state programs that provide medical assistance to low-income individuals who meet certain criteria that depend on their age, income, and health status
- Private commercial health insurance: Provided by employers or purchased in the "individual market" through the **Affordable Care Act**'s Marketplace

2.1 Medicare Coverage and Payment for New Drugs

With 64 million enrollees, Medicare's coverage, coding, and payment for new drugs are important considerations. Understanding what is covered, and why, can significantly impact the research, manufacturing, and marketing of new drugs. This section provides information on drugs covered under Medicare. This includes parts A, B, C, and/or D, each of which provides different insurance:

Medicare Part A (Hospital Insurance): Part A helps cover inpatient care in hospitals, including critical access hospitals, and skilled nursing facilities (not custodial or long-term care). Part A covers the drugs during a Medicare-covered stay in a hospital or skilled nursing facility. If the stay is not covered by Medicare Part A, the drug may be covered under Medicare Part D.
Medicare Part B (Medical Insurance): Part B helps cover doctors' services and outpatient care. Part B covers most drugs administered by a provider as part of a service provided, or at a dialysis facility, but the provider or facility must purchase and supply the drugs. Part B also covers some outpatient prescription drugs; Part D cannot pay for any of the drugs that are covered by Part B.
Medicare Part C: A Medicare Advantage Plan (like an HMO or PPO) is an optional additional Medicare health plan paid for directly by the individual recipient.
Medicare Part D (Prescription Drug Coverage): Medicare prescription drug coverage is available to anyone with Medicare, but not all plans offer Medicare drug coverage. Part C and Part D cover most outpatient (i.e., self-administered) prescription drugs. Part D is a voluntary prescription benefit. Beneficiaries can enroll in either a stand-alone prescription drug plan to supplement traditional Medicare or a Medicare Advantage prescription drug plan under Part C.

Medicare Part D plans are not required to cover all other prescription drugs rather, they are required to cover only a fixed number of drugs in different therapeutic drug classes.

A formulary is an official list of medicines that will be covered (to some extent) if prescribed. The Medicare Part D plan formulary lists what drugs are covered. The Medicare Part D formulary is not required to include all prescription drugs, rather, it is required to include only a fixed number of drugs in different therapeutic drug classes. The drugs covered by a Medicare Part D plan formulary must include at least two drugs in each of the six protected classes on their formularies: antidepressants,

antipsychotics, anticonvulsants, antiretrovirals, immunosuppressants, and antineoplastics.

Other Medicare programs may include coverage and reimbursement for drugs, such as:

Inpatient Prospective Payment System: Makes payments to acute care hospitals for each Medicare patient, or case, treated. Physicians and hospital staff determine the appropriate course of treatment. Hospitals receive a single payment—called a bundled payment—for the covered services provided to the Medicare patient, this payment may include the cost of drugs.

New Technology Add-On Payment (NTAP): Provides an additional payment to hospitals above the standard **Medicare Severity-Diagnosis Related Group** if CMS determines certain criteria are met. NTAP approval is not guaranteed, and relatively few new drugs receive add-on payments. CMS assesses these payments on an annual basis for up to three years.

Hospital Outpatient Pass-Through Status for Drugs: Is intended to encourage the use of newly FDA-approved drugs across all fields of medicine and to improve Medicare patients' access to these innovative therapies by temporarily paying more than the established facility fees. There is no guarantee that a drug will be approved for pass-through status as only a subset of new FDA-approved drugs are eligible to apply. CMS establishes the initial payment for the new drug based on a **formula**, which establishes a floor price above which the product must be priced. Reimbursement is then based on this price.

Resource:
Website: Medicare Drug Coverage (Part D)

2.2 Medicaid Drug Coverage Considerations

Medicaid plans can vary significantly from one state to another. It's important to understand the extent to which each states program uses managed care versus **fee-for-service** (FFS) payment, and how that can influence the localized adoption of your drug. In addition, some aspects of Medicaid may be covered by the Medicaid **managed care organization** (MCO), while the drug benefit may continue to be managed by the state. This is commonly referred to as a **pharmacy** carve-out.

A good starting point to understanding the unique features of each state's Medicaid program is the CMS-provided State Overviews, which includes the percentage of the population covered in Medicaid managed care plans. Other considerations include understanding your drug's applicability to programs for populations that are dually eligible for Medicare and Medicaid (in which case Medicare is the primary payer), or other programs operating under Medicaid waiver programs.

The Medicaid Drug Utilization Board requires each state to develop a drug utilization review (DUR) program targeted at reducing clinical abuse and misuse of outpatient prescription drugs covered under the state's Medicaid program. CMS requires any MCO that includes covered outpatient drugs to operate a DUR program.

State Medicaid **preferred drug lists** (PDLs) aim to ensure that Medicaid beneficiaries have access to prescription drugs that are of known quality, safe, and will provide optimal results. When a prescriber is considering medications from a class included on a state PDL for Medicaid beneficiaries, they are encouraged to choose drugs designated as preferred. Drugs on PDLs are grouped into therapeutic classes based on how they work or the disease states they are intended to treat. The state Pharmacy and Therapeutics (P&T) Committee recommends therapeutic classes to include on the PDL, preferred or non-preferred status for the drugs in each class, and prior authorization guidelines for each class.

Adding a new FDA-approved drug to a state Medicaid PDL: The state PDL is updated at least annually, but new drugs that come to market will still be covered if they meet the state's criteria for coverage. Difference between a PDL and a formulary: A state PDL is not the same as Medicare or commercial payers' formularies. In Medicaid, the list of covered drugs is determined by each state and is based on whether the manufacturer agrees to pay the federally mandated Medicaid drug rebate. Medicaid agencies must make payment for all Medicaid-covered drugs when they are medically necessary.

2.2.1 Medicaid Drug Rebate Program

New drug innovators should understand the Medicaid Drug Rebate Program (MDRP) and its rebate agreements, drug rebate formulas, and reporting requirements. The MDRP is a program that includes CMS, state Medicaid agencies, and participating drug manufacturers. It helps offset the federal and state costs of most outpatient prescription drugs dispensed to Medicaid patients. All 50 states and the District of Columbia cover prescription drugs under the MDRP.

The program requires a drug manufacturer to have a national rebate agreement with the Secretary of the Department of Health and Human Services in exchange for state Medicaid coverage of most of the manufacturer's drugs. When a manufacturer markets a new drug, it must also submit product and pricing data concerning the drug to CMS via the Drug Data Reporting for Medicaid system. This ensures that states are aware of the newly marketed drug, and it meets the definition of a Covered Outpatient Drug, as defined in section 1927 of the Social Security Act (the Act) and required by the Medicaid Drug Rebate Program (MDRP). Manufacturers are required to report all covered outpatient drugs under their labeler code to the MDRP within 60 days at the end of each quarter.

Manufacturers may not be selective in reporting their national drug codes (NDCs) to the program. Manufacturers are not required to include NDCs that represent samples that will not be sold (e.g., products marked as "sample" and provided to a physician at no charge), or NDCs that do not have a specific marketing start date. You can verify that the drugs are listed (or de-listed if any have been discontinued) with FDA on their comprehensive NDC SPL Data Elements File. Manufacturers are then responsible for paying a rebate on those drugs the state plan paid for. Drug manufacturers pay these rebates quarterly to states. The rebates are shared between the states and the federal government to offset the overall cost of prescription drugs under Medicaid.

Resource:
Website: Medicaid Drug Rebate Program

2.3 Commercial Insurers New Drug Coverage

As noted earlier, CMS influences private sector coverage and reimbursement decisions, as commercial insurers often follow Medicare's lead. But private plans and commercial insurers do have more flexibility to set coverage and reimbursement determinations that may impact the marketability of your new drug. For example, commercial insurers generally have specific policies regarding drug coverage. These policies can include:

Formulary controls: Utilization (also known as formulary) controls may include, but are not limited to, differential cost sharing, generic substitution, therapeutic substitution, prior authorization, step therapy edits, quantity limits, dose limits, and day's supply limits.

Mandatory substitution: Mandatory substitution implementation is based on specific state pharmacy laws and regulations. The substitution may involve a generic drug substituted for a brand drug of the same chemical, or a therapeutic substitution within a class of drugs.

Prior authorization: Prior authorization is a cost-containment procedure that requires a prescriber to obtain approval to prescribe a drug prior to a pharmacy dispensing it. Prior authorization is also called prior approval. Health plans require prior authorization for various reasons, including age, medical necessity, the availability of a generic alternative, or checking for drug interactions.

Step therapy: Step therapy is a type of prior authorization for drugs that is the practice of beginning drug therapy for a medical condition with the most cost-effective and safest drug therapy and progressing to other more costly or risky therapy, only if necessary. The aims are to control costs and minimize risks. Step therapy is also called step protocol.

Formulary management and tier: Health plans providing prescription drug coverage separate the drugs they cover into four or five drug formulary tiers. See Section 4.4 for examples of drug formulary tiers.

2.4 Coverage Determinations

Each type of insurer approaches the process of determining coverage of medically necessary items and services according to the legal mandates of the geographic area and the plan's business needs. All private insurers must comply with the 2010 ACA's essential benefits provision, which includes items and services in 10 benefit categories. Some states mandate additional benefits, such as treatment for

infertility and autism. Beyond these mandates, private payers can tailor benefit plans to the populations they serve. Most private payers review benefits and coverage decisions annually. Public payers, such as Medicare, Medicaid, and CHIP, rely on a mixed process to define benefits and coverage of items and services. Benefit categories for these programs are either spelled out in statute or defined

through notice and comment rulemaking. The coverage of medically necessary items and services in the benefit categories is either decided by the government (following a prescribed process) or delegated to a government contractor.

In recent years, CMS has increased transparency about the processes used to determine **National Coverage Determinations** (NCDs) for Medicare. In the absence of an NCD, coverage decisions are left to the Medicare Administrative Contractors (MACs). MACs are private healthcare insurers that have been awarded a geographic jurisdiction to administer Medicare Part A and Part B medical claims or **durable medical equipment** (DME) claims for Medicare FFS beneficiaries. CMS relies on a network of MACs to be the primary operational contact between the Medicare FFS program and the healthcare providers enrolled in the program. MACs perform many activities, including:

- Process Medicare FFS claims
- Make and account for Medicare FFS payments
- Enroll providers in the Medicare FFS program
- Handle provider reimbursement services and audit institutional provider cost reports
- Handle redetermination requests (first-stage appeals process)
- Respond to provider inquiries
- Educate providers about Medicare FFS billing requirements
- Establish local coverage determinations
- Review medical records for selected claims
- Coordinate with CMS and other FFS contractors

Currently there are 12 Part A/Part B MACs and four DME MACs in the program. They process Medicare FFS claims for nearly 60 percent of the total Medicare beneficiary population, or 37.5 million Medicare FFS beneficiaries.

CMS also sets national guidelines for state Medicaid programs, but most coverage decisions (including the drug lists) are left to the states and the District of Columbia. It is important to note that CMS is not the single point of contact that sets coverage policy. Both Medicare and Medicaid are decentralized, and only NCDs are done centrally. Consequently, new drug innovators may need to include state-specific considerations when they develop a reimbursement strategy.

3 Define a Drug Reimbursement Strategy

Bringing a drug product to market requires many skill sets. You need to have a basic understanding of the entire commercialization process and manage multiple tasks related to early-stage research and development, clinical trials, regulations, reimbursement, and post-market surveillance. The goal of receiving FDA Market Authorization is often considered the primary endpoint that leads a new drug to commercial success. However, if a new drug does not obtain the desired amount of reimbursement or, even worse, is not covered by payers, physicians are unlikely to recommend and prescribe the new

drug. Therefore, from an innovator's perspective, ensuring reimbursement for a new drug can be as important as obtaining regulatory approval.

The foundation of a strong drug reimbursement strategy is research. Initially, you need to define your drug type and establish a plan for gaining regulatory approval (see the Regulatory Knowledge Guide for Small Molecules and Regulatory Knowledge Guide for Biological Products for a regulatory process overview). You will then need to formulate a **target product profile** (TPP), identify an appropriate comparator(s), collect evidence across the drug lifecycle, identify potential providers and payers, and determine the target patient population.

Figure 1. Key Elements of a Reimbursement Strategy

Figure 1 outlines the key elements of a drug reimbursement strategy. Refer to the NIH SEED's Drug Reimbursement case studies for an in-depth discussion and examples on managing the multiple tasks related to early-stage research and development, clinical trials, regulations, reimbursement, and post-market surveillance.

Resources:
NIH SEED: Drug Reimbursement Strategy Workshop
NIH SEED: Guidance and Considerations on Selecting a Reimbursement Consultant
NIH SEED: Drug Reimbursement Case Study 1 Small Molecule
NIH SEED: Drug Reimbursement Case Study 2 Physician Administered

3.1 Establish a TPP and Comparator

Defining a TPP for your drug is useful in strategic planning, drug development, and identifying reimbursement considerations. The TPP can also help define how the drug is different from its competition, which is a critical aspect of your reimbursement strategy. A TPP should include:

- Indications and usage (indications for the drug, target patient populations, and site of care where the drug will be used, as well as a comparison of your drug vs. the standard of care)
- Dosage and administration (site of administration, duration, and dosing)

- Contraindications (circumstances in which the drug cannot be used)
- Adverse reactions (serious and common adverse effects)
- Clinical pharmacology (includes mechanism of action)
- Non-clinical toxicology (laboratory and animal safety studies)
- Clinical studies (trials to demonstrate safety and effectiveness, healthcare economics, and outcomes research)
- Comparative effectiveness (compared with prior standard of care and other treatment alternatives, not just vs. a placebo)

Determining the appropriate comparator—defined as an investigational or marketed product that is used as a reference in a clinical trial—is a critical part of your early research. This research and analysis should be conducted 18 to 24 months prior to the estimated approval date and should also be a component of your reimbursement strategy. Once developed, it should be updated on an ongoing basis to account for any new competitive activity.

Using an appropriate comparator in your clinical trials helps ensure that they will meet FDA approval and be well situated for insurance coverage and reimbursement. The current standard of care and how well the drug addresses treatment failures (in the context of the comparator) as well as how it works in sub-populations of interest to the payer are all critical to the value proposition of the drug.

How well the drug addresses comparator treatment failures and how it works in target populations are critical to the value proposition of the drug.

It is important to identify other drug comparators and create an attribute template for pricing and payer positioning discussions as you progress toward FDA approval. The attributes that should be identified for comparison for each potential drug comparator can include patient population, payer mix, annual production cost, current market competitor, administration, acute versus chronic treatment, potential discounting, and distribution.

Resources:
Article: Defining Your Target Product Profile - Therapeutics
NIH SEED: Creating a Target Product Profile for New Drug Products
NIH SEED: Example TPP - Small Molecule Drug
NIH SEED: Example TPP - Biologic
NIH SEED: Example TPP - Vaccine

3.2 Identify Providers, Target Populations, and Payers

When developing a reimbursement strategy, new drug innovators should thoroughly research potential providers, target populations, and payers.

Providers: What types of healthcare providers would be interested in learning about the new drug product and be likely to prescribe it? In addition, consider what evidence specific providers may require prior to prescribing the new drug.

Target populations: Is your new drug applicable to specific target populations? For example, if your drug targets a geriatric condition, you need to understand how new drugs are added to **Medicare Part D** plan formulary lists. Similarly, if your drug treats a pediatric disease, you need to research coverage considerations under Medicaid and CHIP programs.

Payers: As discussed in Section 2, the three largest categories of insurers are Medicare, Medicaid and CHIP, and private commercial insurers.

Medicare is a **health insurance** program for people aged 65 or older, people under age 65 with certain disabilities, and people of all ages with end-stage renal disease (permanent kidney failure requiring dialysis or a kidney transplant).

Medicaid and CHIP also have specific eligibility criteria. Medicaid is a joint federal and state program that, together with CHIP, provides health coverage to low-income Americans, including children, pregnant women, parents, seniors, and individuals with disabilities.

Private commercial insurers enter into contracts with companies that offer insurance to their employees. Individuals can also purchase insurance through the Health Insurance Marketplace.®

3.3 Obtain a Healthcare Common Procedure Code

The **Healthcare Common Procedure Coding System** (HCPCS) is the standard code set for items and services furnished in settings such as physicians' offices, hospital outpatient departments, and patients' homes. The HCPCS includes codes for new drugs and biological products. Requests for new codes can be submitted 4 times a year, so deciding when to submit these requests is a flexible aspect of a reimbursement strategy. Note that code verification takes about 65 days.

The HCPCS code set is divided into two principal subsystems, referred to as Level I and Level II:

- Level I is the **Current Procedural Terminology** (CPT®) coding system maintained by the American Medical Association to identify medical services and procedures furnished by physicians and other healthcare professionals
- Level II is a standardized coding system that is used primarily to identify products, supplies, and services not included in the CPT codes

Because Medicare and other insurers cover a variety of services, supplies, and equipment that are not identified by CPT codes, the Level II HCPCS codes were established so that providers could submit claims for these items.

Drugs are generally assigned a "J" code that will represent the drug for billing purposes. CMS maintains the HCPCS code set and the process to obtain a code. It's important to note that these codes are used by all payers.

For innovators, it is important to know that public meetings are held to provide a forum for the general public to present information regarding specific HCPCS coding requests for new products, supplies, and services. The meeting also discusses any preliminary coding recommendations of the CMS HCPCS Workgroup, as well as CMS's preliminary recommendations regarding payment methodology. Note that coding decisions related to the Medicare and Medicaid programs internal operating procedures are reviewed internally and not included in this forum.

Resource:
CMS: HCPCS - General Information
NIH SEED: All About CPT Codes
NIH SEED: Drug Reimbursement Strategy Workshop

3.4 Set a Drug Price

Drug pricing is a key factor in marketing a new drug. Innovators should understand that pricing models and terminology vary across payers. The pricing terms most frequently used by commercial and government payers are:

Average Wholesale Price (AWP): Most frequently listed official price that was previously used as a reference for reimbursement (i.e., sticker/list price).
Average Manufacturer Price: Benchmark used for Medicaid rebates, defined as the average price paid to manufacturers by **wholesalers** and retail **pharmacies**.
Average Sales Price (ASP): Weighted average price of all non-federal sales to wholesalers, net of discounts, and rebates. Note that the ASP determines the reimbursement for **Medicare Part B** drugs administered by physicians.
Medicaid Best Price: Lowest price paid to a manufacturer for a brand name drug, accounting for rebates, discounts, and other price adjustments.
Average Acquisition Cost: Current Medicaid benchmark to pay for drug ingredients that reflects pharmacy provider prices paid for drugs.

Most payers use multiple prices in an algorithm to determine what they pay for a specific drug.

In addition to pricing terminology, also understand that there are different pricing strategies to consider:

- Competitor-based pricing is usually a component of value-based pricing and benchmarked against current competitors to test a new product's perceived value.

- Skim pricing is a pricing strategy that sets new product prices high and subsequently lowers them as competitors enter the market. This pricing is easier to apply in a small market (e.g., orphan drug) with little or no competition or where the volume of prescriptions is limited.
- Value-based pricing is based on product attributes, costs, profit targets, and customer cost tolerance.

Resources:
FDA: FDA Takes Actions to Help Lower U.S. Prescription Drug Prices
CMS: Medicare Part B Drug Average Sales Price
CMS: Medicaid Drug Pricing Regulation: A Summary

4 Develop Evidence and Engage Stakeholders

As part of your reimbursement strategy, you will need to develop evidence to meet both regulatory (see the Regulatory Knowledge Guide for Small Molecules) and payer requirements. For example, CMS requires evidence of safety, effectiveness, appropriateness, and comparative benefit *in the Medicare population*. You should also engage stakeholders (e.g., CMS, private payers, patient advocates) to get feedback on your plan and advocate for your product's inclusion on formularies. Finally, learning about the pharmaceutical ecosystem can help you move efficiently to manufacturing and distribution.

4.1 Clinical Evidence Requirements

The FDA determines if a drug provides substantial evidence of efficacy and safety and decides if the benefits of the drug outweigh the risks for the intended use of the drug (and if specialized drug safety programs are needed to manage serious risks of harm). This evaluation is generally based on clinical trial data that may not completely represent the patients who will ultimately take the drug once it is approved. The FDA's standard of evidence for approval is evidence consisting of at least two adequate and well-controlled studies (one may be acceptable in some cases) demonstrating safety and efficacy.

Payers focus on evidence of safety and effectiveness in their covered populations, which may be different from the clinical trial population (e.g., the population may be older than the population in the trials that led to approval). Additional evidence may be required if the clinical trial participants do not represent the patient population likely to use the drug in the open market. This may necessitate real-world data-based studies to demonstrate effectiveness and safety in the relevant populations of interest for payers.

Payers focus on evidence of safety and effectiveness in their covered populations, which may be different from the patients who participated in the clinical trial.

CMS uses evaluation criterion of "reasonable and necessary" to inform coverage and reimbursement decisions. This includes a requirement of evidence in the Medicare population of safety, effectiveness, appropriateness, and comparative benefit with the standard of care. Approval for sale by FDA does not

automatically mean CMS, or other payers, will cover or reimburse a given drug. In fact, many private payers will not even consider a new drug for coverage until six to 12 months after FDA approval. Based on the applicability (or lack thereof) of a clinical trial protocol to both the patient population and standard of care they cover, some may still consider an FDA-approved drug "experimental."

FDA Market Authorization does not automatically mean that CMS or other payers will consider a given drug covered and eligible for reimbursement.

4.2 Evidence across the Drug Lifecycle

Post-market safety evidence can include spontaneous adverse event reports submitted to the **FDA Adverse Event Reporting System**, observational studies, meta-analyses, and in some cases post-approval clinical trials. If a drug was approved under accelerated approval based on a surrogate endpoint, additional evidence may be required to confirm its impact on clinical outcomes of interest. It is important to note that payers, both public and private, will continue to review evidence and may adjust reimbursement for a drug throughout its lifecycle.

Reimbursement policy for a drug may change throughout its lifecycle. Payers focus on evidence of safety and effectiveness in their covered populations both during and after Market Authorization.

Refer to the Regulatory Knowledge Guide for Biological Products and the Regulatory Knowledge Guide for Small Molecules for the premarket and post-market evidentiary requirements.

Resource:
FDA: FDA Adverse Event Reporting System (FAERS)

4.3 U.S. Pharmacopeia's Role in Formulary Development

Pharmaceutical science expertise is the foundation of the U.S. Pharmacopeia's (USP's) work to help advance public health and ensure the quality and safety of medicines, dietary supplements, and foods. From a reimbursement perspective, where a new drug falls within the USP classification systems can provide insight into how it will be viewed by insurers.

The quality standards developed by USP help manufacturers deliver safe products to billions of people worldwide. The most widely used USP classification systems are:

- The U.S. Pharmacopeia-National Formulary includes over 6,800 quality standards for medicines, both chemical and biologic, active pharmaceutical ingredients, and excipients. It is the most comprehensive source for quality standards and is utilized in over 150 countries worldwide and integrated into the laws of more than 40 countries, including the U.S.
- USP Medicare Model Guidelines (USP MMG) is a comprehensive list of categories and classes of **Medicare Part D** drugs.

- USP Drug Classification (USP DC) is an independent drug classification system.

The USP DC is intended for use by any stakeholder interested in a classification of drugs for use in formulary development or review. The classification system has many uses for formulary support including, but not limited to:

- Building and mapping formularies
- Reviewing formulary adequacy for a minimum baseline of drugs
- Identifying drugs in a particular pharmacologic grouping
- Reviewing formularies and comparing formulary design and benefits

USP DC may be helpful as part of a comprehensive formulary review process but is not intended to replace the final review provided by the local P&T Committees. USP DC is not intended for review of medical benefit drug coverage, since USP DC does not include all drugs administered in a clinical setting. It is separate from the USP MMG and is not endorsed or funded by CMS. The USP DC is not designed for CMS Part D Formulary Submissions. Part D stakeholders would use the USP MMG. Drugs included in the USP DC are identified through various sources, including Drugs@FDA, RxNorm Current Prescribable Content, Purple Book: Lists of Licensed Biological Products, stakeholder feedback, and publicly available prescription formularies.

Resources:
Website: USP Drug Classification
Website: USP Medicare Model Guidelines v6.0
Website: Stakeholder Engagement Forums

4.4 Pharmacy and Therapeutics Committees

As a new drug innovator, you will want your drug to be included on payers' drug formularies. A drug formulary is list of drugs that are covered by a payer, and some drugs are excluded from coverage. A P&T Committee—usually composed of external physicians, pharmacists, consumer representatives, and voting members—recommends therapeutic classes/drugs to include on a **preferred drug list** or formulary. The P&T Committee also establishes a preferred or non-preferred status for the drugs in each class, and corresponding prior authorization guidelines for each drug if applicable.

You will likely need to submit drug information in a different format for each P&T Committee and may have an opportunity to present the information at a public meeting. This will vary among plan sponsors and state Medicaid programs.

Adding a new FDA-approved drug to a formulary requires a review by the plan sponsor's P&T Committee.

Most plans providing prescription drug coverage separate the medications they cover into four or five drug formulary tiers. The tiers range from least expensive cost sharing for beneficiaries to the most expensive (see Table 1).

Tier	Type of Drug
Tier 1	Preferred generic drugs, lowest cost sharing
Tier 2	Non-preferred generic drugs
Tier 3	Preferred brand name drugs
Tier 4	Non-preferred brand name drugs
Tier 5	Specialty drugs, highest cost sharing

Table 1. Example of a Plan with Five Drug Formulary Tiers

Each plan sponsor and health system will have its own P&T Committee to review and continually manage drugs for inclusion or exclusion on their formularies. A state Medicaid program may also have a P&T Committee along with the mandatory **Drug Utilization Review Board** (DURB). These two groups are often combined into one or may exist as separate entities depending on state regulations. The DURB is responsible for the establishment and implementation of medical standards and criteria for the retrospective and prospective DUR program, in addition to the development, selection, application, and assessment of educational interventions for physicians, pharmacists, and recipients that improve care.

4.5 Drug Supply Ecosystem

New drug innovators should consider the factors discussed in this section when developing their reimbursement, marketing, and distribution strategies.

Manufacturers produce drugs and manage the distribution from manufacturers to **wholesalers**, and even directly to retail **pharmacies**, mail-order and specialty pharmacies, hospitals, clinics, or other entities. A manufacturer contracts with wholesalers and may include conditions for bulk-purchasing discounts or discounts for immediate payment, and often the discounts are negotiated on a drug-by-drug basis. In addition, manufacturers pay wholesalers a service fee to manage inventory, financial transactions, distribution, and data processing.

Wholesalers purchase drugs from manufacturers and distribute to multiple types of customers, including independent, chain, or mail-order pharmacies; hospitals; long-term care; and other medical facilities. Wholesalers typically purchase drugs at wholesale acquisition cost (WAC), adjusted for any negotiated purchase discounts (e.g., WAC – 2 percent).

Pharmacies generally purchase drugs from wholesalers, and occasionally directly from manufacturers. Pharmacies typically purchase drugs at WAC, adjusted for any purchase discounts

(e.g., WAC – 1 percent), and the negotiated percentage is often influenced by a pharmacy's volume of purchases.

Pharmacy benefit managers (PBMs) are primarily responsible for processing and paying prescription drug claims. PBMs also work closely with health plans to negotiate rebates and other discounts with manufacturers and in designing formularies. The manufacturer rebates are often negotiated as a percentage of the drug's list price. Rebates might also be in the form of **value-based contracts** or volume-based contracts that are paid if certain predetermined thresholds are met. For drugs that are dispensed, PBMs submit rebate claims to manufacturers for retrospective rebate payments. Rebates or discounts are not typically reflected in the price or copay a patient pays at the pharmacy.

PBMs then pass on a portion of negotiated manufacturer rebates to health plans. The rebate amount passed on to the health plan can vary based on contract terms. PBMs may also offer fee-based services to manufacturers, such as **drug utilization review**, disease management, consultative services, program administration, and data collection.

Pharmacies contract with PBMs for inclusion in their pharmacy network and submit claims for reimbursement at a negotiated rate. The reimbursement rate is typically based on a discount percentage from AWP plus a dispensing fee, minus any patient cost sharing (e.g., copays) collected. Pharmacy networks consist of pharmacies that have agreed to dispense prescription drugs and provide pharmacy services to a health plan's enrollees under a set of specified terms and conditions.

Patients with **health insurance** prescription coverage may be required to pay **out-of-pocket** cost sharing at the pharmacy. Cost sharing can be in the form of a copay or coinsurance, with amounts dependent on the tier placement of the drug, the drug's list price, and/or the patient's health plan benefit structure, including deductibles and out-of-pocket maximums. Alternatively, patients without health insurance would likely face the full cost of the drug at the pharmacy, based on the drug's list price, or a discounted price through a prescription coupon program (e.g., GoodRx).

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