

Prescription Drug Supply Chains

An Overview of Stakeholders and Relationships

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About This Report

Many stakeholders and steps are involved in the life cycle of a prescription drug as it moves from chemical synthesis and formulation through dispensing or administration to patients. The specific steps involved in prescription drug supply chains often differ depending on the type of drug, the channel of distribution, and the patient's source of prescription drug coverage. The authors describe the stakeholders involved in prescription drug supply chains and the flows of products, payments, and information between stakeholders. Although we present a typical supply chain for retail pharmacy drugs, we also highlight the important supply chain distinctions for specific distribution channels and for specific types of drugs. This report is intended to be a reference for those interested in the prescription drug industry and pharmaceutical policy and economics.

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Summary

Patients, policymakers, researchers, reporters, and others often refer to prescription drugs collectively. All prescription drugs dispensed in the United States are used to treat or prevent disease and are regulated by the U.S. Food and Drug Administration (FDA). Beyond these similarities, there are key differences in how specific drugs are manufactured, distributed, dispensed to patients, and paid for. Relatedly, different stakeholders and economic incentives come into play depending on the category of drug, the distribution channel, and the patient population in question.

Understanding differences in supply chains across types of drugs and distribution channels is increasingly important in ongoing policy discussion and debate around approaches to address high drug prices, ensure optimal investment in drug research and development, and secure supplies of drugs needed to address the coronavirus disease 2019 (COVID-19) pandemic and other public health emergencies. Policy solutions that recognize and address differences in supply chains between categories of drugs and distribution channels are more likely to achieve these goals than those that do not.

This report provides an overview of prescription drug supply chains, first describing typical stakeholders and flows of information, product, and payment between stakeholders, and then detailing deviations from the typical case for different categories of drugs and distribution channels. We intend for the report to be a reference for those interested in the prescription drug industry and pharmaceutical policy and economics.

Approach

We collected information via a literature review, a stakeholder-focused environmental scan, and eight phone conversations with stakeholders of different types. We conducted a total of eight phone conversations with representatives from groups representing drug manufacturers, distributors, group purchasing organizations (GPOs), hospitals, pharmacies, and pharmacy benefit managers (PBMs).

Findings

We found that the typical stakeholders, relationships, and financial incentives involved in prescription drug supply chains vary depending on the characteristics of a drug and how it reaches patients. Even within a specific type of drug and a particular distribution channel, differences in business practices complicate a universal description of drug supply chains. Despite this complexity and variation, we identified four common core components of drug

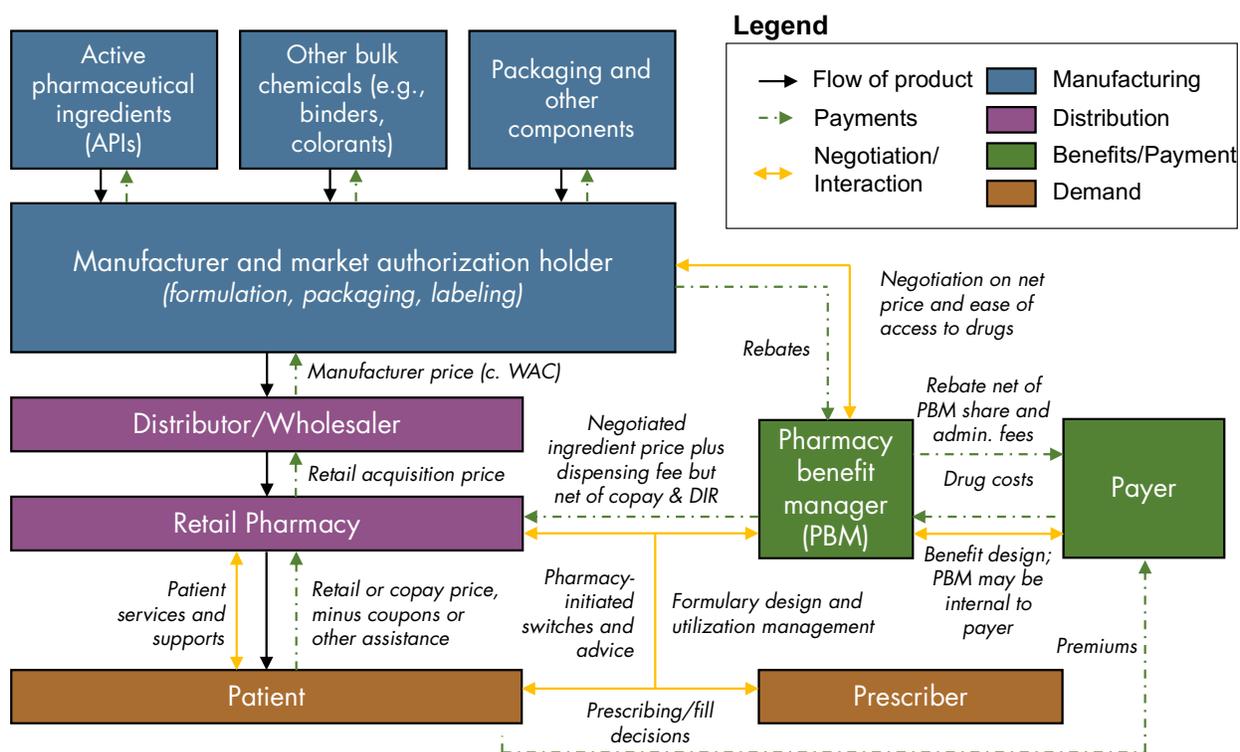
supply chains across all cases: manufacturing, distribution, coverage and payment, and prescribing and demand.¹

See Figure S.1 for an illustration of a typical supply chain for brand-name drugs dispensed via retail pharmacies. In brief, a market authorization holder has FDA approval to sell a given prescription drug. Key steps in manufacturing, including formulation, packaging, and labeling, can be either in house or under contract. These steps rely on many different inputs, including active pharmaceutical ingredients and glass vials, which are often sourced globally and sometimes have applications outside pharmaceutical manufacturing. Finished drug products often reach pharmacies and other points of dispensing via a handful of national distributors, but there are many other distribution models. In general, payers and their PBMs seek more direct control over the route drugs take to get to patients for more expensive drugs.

There are complex flows of information and payments between payers, pharmacy benefit managers, patients, drug manufacturers, and sometimes providers, all of which can vary considerably depending on the drug, patient, and distribution channel. Several large retail pharmacy chains and groups negotiating on behalf of independent pharmacies negotiate both with PBMs and with distributors. For drugs dispensed in hospitals and physician offices, GPOs negotiate prices and other contractual terms on behalf of providers.

¹ Although coverage and payment are not always included in descriptions of prescription drug supply chains, we considered stakeholders involved in coverage and payment to be in scope because of the important linkages between these and other stakeholders.

Figure S.1. Typical Supply Chain for Brand-Name Drugs Dispensed Through Retail Pharmacies



NOTES: c. = circa; DIR = direct and indirect remuneration; WAC = wholesale acquisition cost. Arrows denote relationships involving the flow of product (black arrows), information or negotiation (yellow arrows), and payments (green dashed arrows).

Discussion

Our analysis highlights the complexity of prescription drug supply chains and the important variation in stakeholders and relationships across different categories of drugs, distribution channels, and patient subgroups. As is often the case in U.S. health policy, discussion and proposals must recognize and address these differences rather than apply a one-size-fits-all approach; otherwise, the risk of unanticipated consequences is substantial.

Our analysis excluded supply chains for several categories of drugs, including vaccines, that warrant separate consideration and analysis. Our analysis also excluded narrow but important distribution channels, such as home health and long-term care facilities, that could also be the target of future study. Furthermore, we recommend further analysis on margins for different stakeholders (including study of variation in margins across products and firms), in-depth analysis of drug shortages related to supply chain issues, and the effects of horizontal and vertical integration on supply chains. Finally, given the pace of change in the prescription drug industry, including new arrangements and adaptations in response to the COVID-19 pandemic, we expect the need to revisit this overview of prescription drug supply chains in the future.

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Abbreviations

AMP	average manufacturer price
API	active pharmaceutical ingredient
ASP	average sales price
AWP	average wholesale price
BER	brand effective rate
CGMP	current good manufacturing practice
CMO	contract manufacturing organization
COVID-19	coronavirus disease 2019
CPO	contract packaging organization
CSC	consolidated service center
DIR	direct and indirect remuneration
DMF	drug master file
FDA	U.S. Food and Drug Administration
FSS	federal supply schedule
FUL	federal upper limit
GER	generic effective rate
GPO	group purchasing organization
MAC	maximum allowable cost
NADAC	National Average Drug Acquisition Cost
P&T	pharmacy and therapeutics
PBM	pharmacy benefit manager
PSAO	pharmacy services administrative organization
WAC	wholesale acquisition cost

1. Introduction and Approach

Prescription drugs are used to prevent and treat a wide range of health conditions and diseases. Patients require a prescription from an authorized practitioner to receive prescription drugs, and the manufacture and sale of all prescription drugs sold in the United States is regulated by the U.S. Food and Drug Administration (FDA). Beyond these commonalities, prescription drugs encompass a broad, heterogeneous set of products varying in their chemical composition and complexity, manufacturing processes, distribution channels to reach patients, and uses.

Although a precise accounting is difficult for reasons that will be discussed in this report, recent estimates of the total annual spending on prescription drugs in the United States range from \$450 billion to \$477 billion (Yu, Atteberry, and Bach, 2018; Keehan et al., 2020), or about 12 to 13 percent of total U.S. health care spending in 2018.²

Like other sectors in the U.S. health care system, prescription drugs involve multiple stakeholders and many financial and other relationships. An understanding of the stakeholders and relationships in prescription drug supply chains—which we define broadly to include not just the physical flow of drugs but also flows of information and payment—is an important foundation for both policymaking and analysis in this area.

As in other industries and parts of the U.S. health care system, it is likely that financial incentives drive both the structure of prescription drug supply chains and the behavior of stakeholders. As we will describe, some of these economic incentives likely evolved through business practices and policy changes over decades, while others are the result of more recent innovation on the part of certain participants in the supply chain. Regardless of their origin, the financial incentives in drug supply chains have important implications for the drugs patients receive and at what cost, the resiliency of the market to deal with disruptions in supply and demand, and investment in innovation for new drugs.

There is an important imbalance in the relative contributions of drugs marketed under a brand name versus unbranded generic drugs to total U.S. prescription drug spending and volume. Most brand-name drugs are protected by patents and other forms of market protections granted by the government and, as a result, face limited competition and have high prices.³ After these barriers to competition expire or are successfully challenged by potential competitors, therapeutically

² The percentages are the two estimates of drug spending relative to 2018 total health care spending from the National Health Expenditure data (Keehan et al., 2020).

³ Some companies market older drugs under brand names after patents and exclusivity expire.

equivalent generic versions of prescription drugs introduce competition and drive down prices.⁴ Approximately 80 percent of spending but only 10 percent of prescriptions are for brand-name drugs (Association for Accessible Medicines, 2019). The remaining 20 percent of spending and 90 percent of prescriptions are primarily from generic drugs, where price competition results in lower prices.

Although many stakeholders are involved in the manufacture of, distribution of, and payment for prescription drugs broadly, the relative margins (i.e., net profit) involved often differ across categories of drugs, leading to important differences in incentives. Supply chains, costs, and incentives are likely different for *biologics*, which have large, complex active ingredients manufactured in living systems, compared with small-molecule drugs, which are synthesized chemically (FDA, 2018a). *Biosimilars*, which are drugs that are highly similar to brand-name “reference” biologics, introduce competition like generic drugs but in many respects more closely resemble brand-name than generic drugs, as we will describe (FDA, 2017). Other important differences involve drugs dispensed via mail-order pharmacies rather than retail pharmacies, drugs administered in physician offices or hospitals rather than dispensed through pharmacies, and expensive “specialty” drugs, which are treated differently by both the distribution system and payers.

The aim of this report is to summarize the stakeholders and relationships involved in prescription drug supply chains, starting first with the most common and well-understood area of drugs (those dispensed through retail pharmacies) and then comparing how supply chains vary for drugs dispensed through other channels (outpatient facilities, physician offices, and inpatient hospitals). In each section, we highlight the financial incentives in play and describe common variants on the typical supply chain case. We intend for the report to be a reference for those interested in the prescription drug industry and pharmaceutical policy and economics. Disparate sources exist describing each of the components of the supply chain, but, to our knowledge, no single document has compiled them to facilitate understanding of their interdependence and complexity. Given rapid evolution in how drugs are manufactured, distributed, and paid for, our report is an important update to prior but now dated efforts to describe the prescription drug industry (e.g., Kaiser Family Foundation, 2005). Our report adds to prior surveys of drug supply chains by describing differences between pharmacy and other distribution channels.

Approach

We collected information via a literature review, a stakeholder-focused environmental scan, and stakeholder discussions. We discuss our approach for each below. Across all three avenues

⁴ In the United States, generic drugs are approved via an abbreviated and less-expensive regulatory pathway (compared with the regulatory approval pathway for new innovator drugs). Most generics approved in the United States are determined by FDA to be therapeutically equivalent, and therefore substitutable by pharmacists, relative to an innovator reference drug.

of data collection, we excluded certain types of drug products, including over-the-counter drug products, radiopharmaceuticals, unapproved drugs, vaccines, and compounded drug products, because the supply chains for these niche markets involve additional stakeholders and idiosyncrasies that we could not address given our project resources and timeline.

Literature Review

We reviewed the peer-reviewed and gray literatures to identify papers and other resources that describe prescription drug supply chains. Our initial search terms included (“prescription drug” OR “drug”) AND (“supply chain” OR “stakeholders” OR “margins”); we later used reference mining to identify additional articles for review.

Stakeholder-Focused Environmental Scan

We identified major stakeholder groups through an initial scan of resources identified through the literature review search (suppliers of bulk chemicals and ingredients used in drug manufacture, drug manufacturers, distributors, pharmacies, hospitals and delivery systems, and insurers and pharmacy benefit managers [PBMs]). We then searched for national groups representing these stakeholder groups and identified relevant white papers and reports posted on the websites of these organizations.

Stakeholder Discussions

Separately, we invited several individuals to discuss specific stakeholder groups and relationships with our project team to confirm our understanding of drug supply chains from the literature review. These individuals were often but not always from national associations representing the specific stakeholder categories listed above. We conducted a total of eight phone conversations with representatives from groups representing drug manufacturers, distributors, group purchasing organizations (GPOs), hospitals, pharmacies, and PBMs. A note-taker recorded key points from each phone conversation.

Report Overview

Chapter 2 introduces a typical supply chain for drugs dispensed through retail pharmacies and discusses variants on this initial case. Chapter 3 elaborates on differences between retail pharmacy supply chains and outpatient facility, physician office, and inpatient hospital supply chains. Chapter 4 is a brief discussion of our main findings and directions for future research.

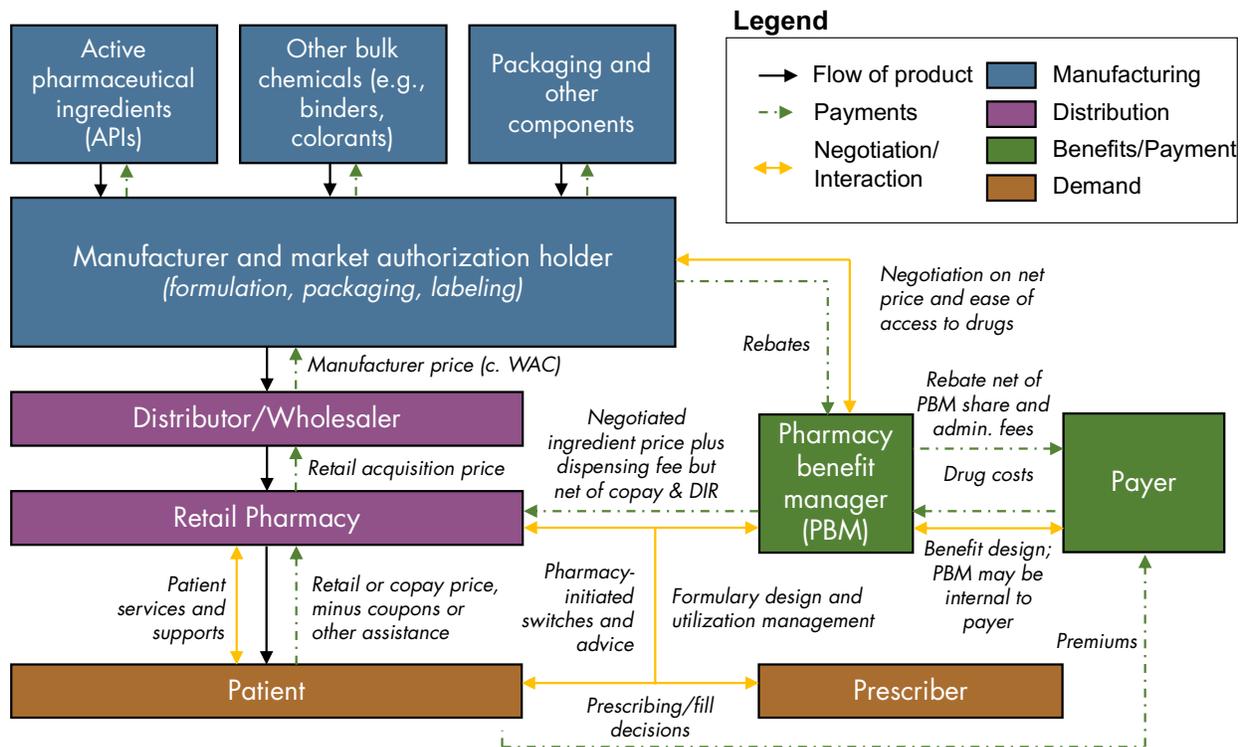
2. Retail Pharmacy Supply Chain Stakeholders and Relationships

This chapter introduces a schematic illustrating the stakeholders and relationships involved in a model supply chain for drugs dispensed through retail pharmacies. We describe how supply chain stakeholders and relationships can vary under different business practices, for different types of drugs, and for patients with different sources of coverage.

Model Retail Pharmacy Supply Chain

A typical supply chain for brand-name drugs dispensed through retail pharmacies (Figure 2.1) involves many stakeholders, which we represent as boxes in Figure 2.1, and many relationships between stakeholders, which we represent using arrows differentiating between relationships involving the flow of product (black arrows), information or negotiation (yellow arrows), and payments (green dashed arrows). The payments illustrated in Figure 2.1 can vary dramatically in terms of magnitude and whether margins for different stakeholders are included. The appendix includes a glossary of pricing terms, and many are discussed in detail later in the report.

Figure 2.1. Typical Supply Chain for Brand-Name Drugs Dispensed Through Retail Pharmacies



NOTES: c. = circa; DIR = direct and indirect remuneration; WAC = wholesale acquisition cost.

The colors of the stakeholder boxes in Figure 2.1 are organized by broad activity and are described in detail in the following sections: blue for manufacture, purple for distribution, green for benefits and payment, and brown for the stakeholders who ultimately prescribe or use drugs. The key stakeholders in each of the boxes in Figure 2.1 are defined briefly below; the following sections explore each of the stakeholders and relationships in more detail.

- A **market authorization holder** has approval from FDA to sell a prescription drug. In the simplest case, the market authorization holder is also the manufacturer, packager, and labeler of a finished drug product. The manufacturer sources **chemicals, including APIs, and other inputs** from other companies to produce finished drug products.
- Finished drug products are shipped to **distributors** that in turn ship drugs to points of dispensing, such as pharmacies and hospitals.
- **Pharmacies** purchase drugs from distributors and, when drugs are dispensed to patients with prescriptions, receive payments from payers or PBMs hired to administer prescription drug benefits.
- For patients with prescription drug coverage, **payers**, which can be health insurers, large employers, or government programs, weigh the generosity of the pharmacy benefit they want to offer (in terms of coverage, cost-sharing, etc.) against the cost.
- Based on payer specifications, **PBMs** design and maintain drug formularies to encourage patients and prescribers to use certain drugs in exchange for discounts from market authorization holders paid to PBMs via rebates, a share of which are passed back to payers, and which ultimately could result in lower premiums or other benefits for insured patients. Separately, PBMs maintain networks of pharmacies, including some preferred pharmacies where dispensing fees are lower.
- **Patients** and **prescribers** ideally make joint decisions on which drugs patients should be prescribed. For patients with prescription coverage, these decisions are influenced by the placement of different treatment options on formularies, with typically lower out-of-pocket costs and fewer utilization management requirements applied to alternatives that are more preferred by payers and PBMs. Patients pay some or all of the cost of the drug when filling prescriptions at pharmacies depending on whether they have coverage or other sources of support.

Manufacturing

Drug manufacturing involves a number of different types of operations, including

1. sourcing and/or synthesizing chemical ingredients
2. combining ingredients into finished dosage forms, such as capsules or pills
3. packaging and labeling finished drug products, such as bottles of pills for distribution.

The company holding the authorization from FDA to sell the drug product is the key coordinator of all these activities, even if they outsource some or even all of the individual steps to other firms. We refer to this company as the *market authorization holder*.⁵

In our model supply chain, the market authorization holder purchases ingredients necessary to manufacture the drug from other companies and then performs all other manufacturing steps internally. In this case, the market authorization holder could also be described as the manufacturer of the drug. In other cases, a company other than the market authorization holder actually manufactures the drug. We discuss several common manufacturing outsourcing scenarios below.

Inputs in Drug Manufacturing

APIs are parts of any drug that produce the intended effect. Prescription drugs are often referred to by their API (e.g., atorvastatin, penicillin, or ibuprofen) even though finished dosage forms, such as tablets and capsules, are composed primarily of other ingredients in terms of volume or weight. Finished dosage form manufacturers sometimes synthesize APIs from chemical precursors internally, particularly for the most important drugs in the manufacturer's portfolios. But they more often buy APIs from specialized chemical companies. Many of the APIs used in the manufacture of drug products sold in the United States come from countries outside the United States—and in particular from China and India.⁶ When a drug product or input is manufactured in a foreign country, an importer is responsible for meeting FDA requirements for entry into the country. An importer is registered and listed with each manufacturing facility that they import from, and multiple importers can be listed with one facility. Importers can be the input manufacturer, the market authorization holder, or a third party.

Other inactive bulk chemicals, including binders, coatings, flavorings, and colorants, are also needed to manufacture drug products. Both APIs and other bulk chemicals tend to be purchased by drug manufacturers in large batches that are then used over relatively long periods of time (e.g., six months or longer). Batches of bulk chemicals are typically shipped by sea or air and stored at the manufacturing site for the finished dosage form.

Manufacturers of APIs and other chemicals can submit a drug master file (DMF) to FDA describing the ingredients, manufacturing steps, stability, purity, and other characteristics of the

⁵ FDA grants marketing authorization after review of new drug applications for small-molecule drugs and some types of biologics under the Food, Drug, and Cosmetic Act (21 U.S.C. § 355) or biologic license applications for other types of biologics per the Public Health Service Act (Pub. L. 78–410).

⁶ Exact shares of the amount of API sourced by country are not available. FDA tracks the number of approved API manufacturing facilities but not the volume or sales from specific facilities. A recent FDA report details that 88 percent of API manufacturing sites are foreign (FDA, 2019). According to an older U.S. Government Accountability Office report, “FDA estimates that nearly 40 percent of finished drugs and approximately 80 percent of active pharmaceutical ingredients (API) are manufactured in registered establishments in more than 150 countries” (U.S. Government Accountability Office, 2016).

chemical (FDA, 2020; FDA, 1987).⁷ FDA reviews the submitted DMFs for completeness but never formally approves or disapproves them; it does, however, consider the content of DMFs when reviewing new drug applications.⁸ Drug manufacturers looking to source an API would know that FDA has a complete DMF on record for the API but could not review the DMF unless it was provided by the API manufacturer. Although DMFs are not required, having one can help manufacturers of inputs in drug manufacturing describe their products to potential buyers (such as drug manufacturers) and avoid litigation risk through disclosure of technical details.

All APIs and other chemical ingredients of drugs must be manufactured, processed, packed, and held in accordance with current good manufacturing practices (CGMPs).⁹ According to CGMPs, manufacturers of APIs and other bulk chemicals are required to test their products to ensure the identity, strength, quality, and purity of chemicals during production.¹⁰ Drug manufacturers must examine the ingredients they use for damage and contamination and ensure that they meet standards—for example, standards laid out in a DMF—for purity, strength, and quality, either through internal testing or, in cases when a supplier’s testing reliability is validated at appropriate intervals, by accepting the supplier’s own certificate of testing.¹¹

In general, the API and bulk chemical industry is highly competitive, with many competing manufacturers offering broad catalogues of products. Suppliers typically sell on a per-batch basis, and drug manufacturers routinely switch suppliers to secure lower input costs. There are some niche firms focusing on ingredients used in specialized formulations (e.g., certain extended-release formulations). In these cases, manufacturers and suppliers might have longer-term relationships because there are fewer competing suppliers.

Formulation

Manufacturers of finished dosage forms *formulate*—or combine—API and other chemical ingredients into a drug product, such as a pill or liquid. The processes, equipment, and manufacturing facilities necessary for formulation vary depending on the form of the drug (e.g., oral solid tablets or capsules versus liquids). Drug manufacturers often have facilities that specialize in the formulation and packaging of a single product category, such as sterile injectable drugs or tablets. The companies that actually formulate drugs—whether the market authorization holder or a contract manufacturer—vary widely in terms of product portfolio scope. Several large pharmaceutical companies (e.g., Pfizer) manufacture brand-name drugs of

⁷ *Stability* refers to how the chemical degrades over time. *Purity* refers to the concentration of the desired chemical relative to other chemicals or contaminants.

⁸ DMFs are also filed for packaging and finished dosage forms.

⁹ 21 CFR 210 and 211.

¹⁰ The *identity* of a chemical refers to its molecular structure. *Strength* refers to the concentration of a chemical per unit volume. *Quality* and *purity* refer to the extent to which other chemicals or contaminants are present in a product.

¹¹ 21 CFR 210 and 211.

many different forms and uses. Other companies specialize in manufacturing drugs of a specific type (e.g., sterile injectables or infused biologics) or drugs that treat a narrow set of conditions (e.g., oncology).

CGMPs similarly govern the manufacture, processing, packing, and holding of drug products and require a manufacturing system that ensures the identity, strength, quality, and purity of the drug product. Specifically, CGMPs set forth requirements for the facilities and equipment used, as well as for production, testing, packing, labeling, warehousing, and distribution procedures and conditions.¹²

Packaging and Labeling

Finished dosage forms, such as pills and liquids, must be packaged and then labeled before they can be distributed for sale as drug products. Packaging involves several steps, including primary packaging, when the dosage form is enclosed in a bottle, vial, or other container, and secondary packaging, which groups together primary-packaged products (e.g., packaging several vials in a box). Packaging involves a separate set of inputs, including glass vials, cardboard, syringes and injector parts, many of which are inputs into the manufacture of a wide range of products outside the pharmaceutical industry.

Regulatory bodies in different countries impose different requirements in terms of how these packaged drug products are labeled. In the United States, under the Drug Supply Chain Security Act, FDA requires serialization of labeling such that serial numbers on individual final drug products (e.g., vials) match serial numbers on cartons and boxes of the product for tracking purposes (FDA, 2018b). Packaged and labeled drug products are stored at market authorization holder or third-party storage and distribution centers until they are shipped to pharmacies, hospitals, or other purchasers.

Manufacturing Outsourcing Scenarios

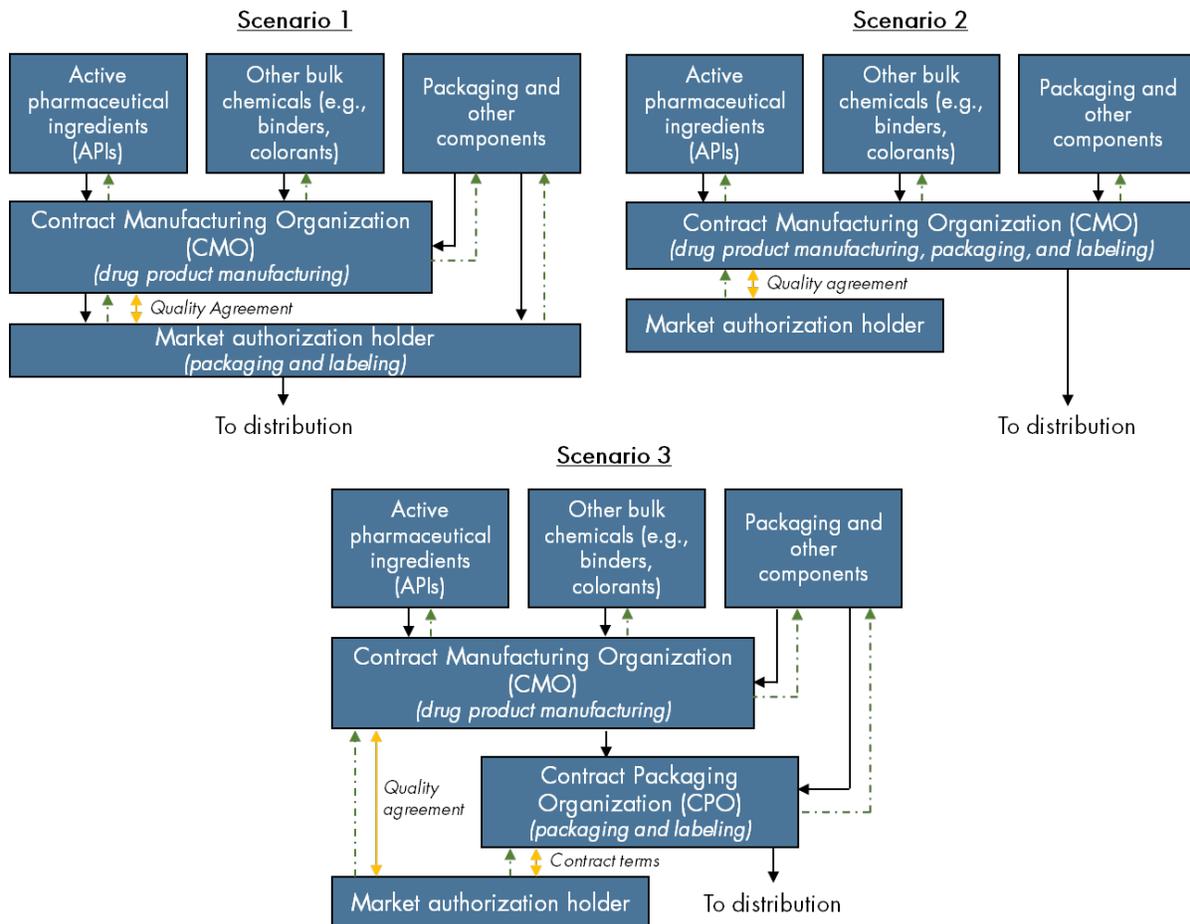
Market authorization holders outsource manufacturing to contract manufacturing organizations (CMOs) to varying extents. The extent of the CMO's role in the overall manufacturing process varies with CMO capabilities and the market authorization holder's needs. Start-up and other relatively small market authorization holders without adequate manufacturing facilities or capabilities might have no option other than outsourcing the entirety of their manufacturing processes. There are several reasons why larger pharmaceutical companies might also routinely use CMOs. For example, high fixed and opportunity costs could preclude larger companies from investing in certain technologies for a small number of products with specialized forms or manufacturing requirements, so they might engage CMOs to manufacture those drugs. In other cases, companies transfer the manufacturing of older products

¹² 21 CFR 210 and 211.

to CMOs to free up internal capacity for newer, higher-margin products. Additionally, sometimes, to divest manufacturing capabilities without laying off workers, companies might decide to transfer ownership of their facilities while continuing to source products from them.

The development and implementation of contract manufacturing relationships—from initial contact to the actual transfer of product manufacturing—usually takes up to two years and can take even longer. A significant share of this time is spent establishing processes to ensure manufacturing quality (e.g., testing the drug product for stability and producing commercial-scale batches called *validation batches* to validate manufacturing processes; Contract Pharma, 2012). Depending on the customer agreement, CMOs might be responsible for sourcing all of the necessary ingredients for manufacturing a finished drug product, including APIs, other bulk chemicals, and, if applicable, packaging. The different actors involved in contract manufacturing are subject to CGMPs by FDA. The buyer is required to approve the quality of drug products using written quality control procedures; buyers and contractors use FDA-recommended quality agreements specifying each party’s responsibilities in complying with these requirements (FDA, 2016). See Figure 2.2 for an overview of some manufacturing outsourcing scenarios.

Figure 2.2. Manufacturing Outsourcing Scenarios



Given the long lead time in qualifying a CMO and developing quality agreements, market authorization holders tend to continue to work with CMOs that they have worked well with in the past, and, in some cases, market authorization holders can help finance a CMO's expansion into new manufacturing lines. However, market authorization holders and CMOs generally have transactional relationships as opposed to partnerships. Some interviewees noted that CMOs shoulder much of the risk in manufacturing for relatively slim profit margins compared with the margins accrued to market authorization holders. Although the CMO market is generally fragmented, with the largest five CMOs accounting for only 15 percent of the CMO market, there has been increasing merger and acquisition activity among CMOs in recent years (PricewaterhouseCoopers, 2019).

The role of CMOs in packaging and shipping finished drug products varies. In some cases, CMOs ship bulk-packaged finished drug product (e.g., containers of pills or liquids) back to the market authorization holder, which would then package and label the drug (Figure 2.2, Scenario 1). In other cases, the CMOs perform these roles themselves (Figure 2.2, Scenario 2) or ship finished drug product to another specialized contract packaging organization (CPO; Figure 2.2, Scenario 3).

Market authorization holders (and, if applicable, contract manufacturers) might outsource packaging and labeling to a specialized company, particularly if they are selling in a country where they themselves do not have a manufacturing presence to ensure compliance with regulations. If a CPO is used, the CPO typically performs all of the packaging and labeling steps (rather than just a subset of the steps) because of serialization requirements. When drugs are packaged and labeled by a CMO or CPO, the CMO or CPO ships the packaged and labeled product to market authorization holder distribution centers, to a third-party logistics company (such as UPS), or directly to distributors.

Distribution

Although distribution logistics can vary widely, most drugs are sold by drug manufacturers to distributors (sometimes referred to as *wholesalers*) that then sell and transport drugs to their final point of dispensing, such as retail pharmacies.

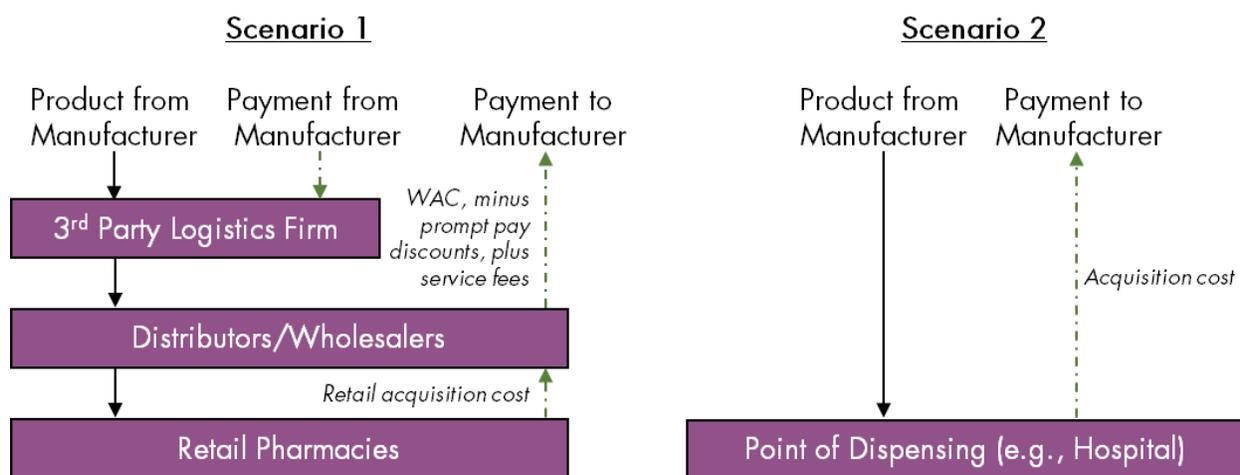
Distributors

The core functions of distributors are to manage inventory, to ship products to customers, and to manage financial risk. In the typical case, manufacturers hold inventory of drugs directly and sell product to a range of national and regional distributors. Manufacturers sometimes send inventory to third-party logistics companies that handle shipping to distributors and other customers (Figure 2.3, Scenario 1). Distributors take ownership of the drug and usually retain enough inventory to supply their customers for 30 days, which is sufficient stock to smooth over shocks in supply and demand. Distributors serve retail pharmacies primarily through a direct-to-

store model (Deloitte, 2019). Under this model, distributors send shipments direct to a pharmacy rather than to, for example, a separate distribution center operated by a chain pharmacy. There are important variations in this typical distribution model that apply to specific types of drugs and buyers. For example, specialty drugs, including biologics and other typically high-cost drugs, are sometimes distributed directly from manufacturers to the point of dispensing, which could be hospitals or specialty pharmacies (Figure 2.3, Scenario 2).¹³

There are three major health care distributors in the United States—AmerisourceBergen, Cardinal Health, and McKesson—that together account for 92 percent of the overall market (Deloitte, 2019). These large distributors all supply a full range of prescription drugs, over-the-counter products, medical devices, and other goods. There are smaller distributors serving regional markets, specific types of products (such as dermatological drugs), or specific categories of buyers (such as specialty pharmacies or physician offices). Individual customers, which could be a large pharmacy chain, independent pharmacy, physician office, or hospital system, often have a primary distributor covering all of their needs, while some have secondary distributors for certain types of products.

Figure 2.3. Additional Distribution Scenarios



Health care distribution is a high-revenue but low-margin industry. Distributors typically buy drugs from manufacturers at a price around a benchmark called wholesale acquisition cost (WAC), minus a small amount (e.g., 1 or 2 percent) for prompt payment and other discounts. For brand-name drugs, distributors then sell drugs to buyers (such as retail pharmacies) at around, and often just below, WAC, leaving only a small per-unit margin in percentage terms, although this amount can be substantial in dollar terms given the high cost of brand-name drugs. Although

¹³ Specialty pharmacies typically offer a wide range of prescription drugs, including specialty drug products, as well as additional services related to specialty drugs, such as patient counseling and adherence management programs.

distributor margins can be considerably higher on generic drugs in percentage terms, lower unit prices for generic drugs limit the magnitude of return from distributing these drugs. Distributors often purchase broad portfolios of many generic products from a single generic manufacturer, likely leading to lower acquisition prices compared with sourcing individual generic drugs from different manufacturers.

Separately, distributors realize revenue from service fees paid by their drug manufacturer suppliers in exchange for access to markets (i.e., stocking fees); from business intelligence data sold to manufacturers, pharmacies, and data aggregators; and from services (e.g., logistics management consulting) sold to their pharmacy customers and other customers.

Beyond managing the logistics of moving prescription drugs from manufacturers to points of dispensing, distributors must manage security (particularly for controlled substances with a risk of misuse and abuse, such as opioids); ensure that temperature and environmental requirements are maintained, which in some cases involves cold-chain management;¹⁴ and collect and supply data to manufacturers and retail pharmacies. Some distributors repackage and relabel drugs acquired from manufacturers—for example, repackaging pills sold in bulk thousand-pill bottles into blister packs—although this is more common for drugs dispensed in facility and institutional settings rather than through retail pharmacies. Repackaging and relabeling can also be done by specialized firms, either before or after drugs are shipped to distributors.

Pharmacies

Most drugs are dispensed to patients via retail pharmacies, including large national and regional pharmacy chains (e.g., CVS and Walgreens), pharmacies in grocery stores and “big box” stores (e.g., Target and Walmart), and independent pharmacies. Pharmacies have contractual relationships with typically one main distributor governing prices, payment terms, delivery logistics, and financial incentives tied to meeting thresholds of distribution through the distributor (e.g., 90 percent of generics dispensed must be purchased through the primary distributor). Although chain pharmacies negotiate prices with distributors directly, most independent pharmacies negotiate prices through buying groups that bid members’ distribution needs to distributors. Buying groups set prices with preferred distributors (usually one per buying group, although some buying groups have multiple preferred distributors; Fein, 2017). The relationships between manufacturers and distributors often contractually prohibit manufacturers from negotiating separately with buying groups. As is generally the case, buying groups have limited leverage when negotiating for brand-name drug products. In some cases, independent pharmacies source drug products outside of their buying group’s ties with distributors (Fein, 2017).

¹⁴ *Cold-chain management* refers to equipment and procedures to ensure that products remain within temperature thresholds through distribution.

In some cases, pharmacies play an important role in decisionmaking regarding which drug is dispensed to patients. For brand-name drugs, pharmacists interact with patients and prescribers when an initially prescribed drug is not on a preferred tier of a patient’s formulary and therefore has high cost sharing (as discussed below). For most generic drugs, pharmacists are free to substitute any of a set of drugs considered by FDA to be therapeutically equivalent to a reference product.¹⁵ As a result, in cases where there are many generic manufacturers of a specific drug, pharmacies generally carry product from only one or a small number of generic manufacturers—and, more specifically, they carry the generic manufactured by the company offering the lowest price (and therefore highest margin) to the pharmacy’s distributor.

Pharmacies generally carry a relatively short-term inventory of prescription drugs and receive frequent shipments from distributors.¹⁶ They ship unused product and overstock back to distributors when it can be resold if their contractual arrangements with distributors allow return privileges. As described above, pharmacies’ contractual arrangements with distributors can also govern how information is shared and aggregated.

For brand-name drugs, pharmacies purchase drugs primarily from distributors at prices at or around WAC, given the small markups at the distributor level. For generic drugs, pharmacies acquire drugs from distributors with a larger distributor markup, albeit off of a typically smaller basis than for brand-name drugs (see the discussion on payments to pharmacies below; Association for Accessible Medicines, 2017).¹⁷ Pharmacies typically pay distributors one to two weeks after delivery.

Pharmacies dispense drugs to patients and receive payments from two main sources described in detail in the next section: patients and PBMs.¹⁸ Pharmacies have substantial leeway in setting retail prices, which are prices paid by patients without coverage and by patients with coverage buying a non-covered drug or choosing to pay cash for a covered drug.¹⁹ The revenue realized by pharmacies for drugs covered by insurance is determined by contracts between PBMs and retail pharmacies.

¹⁵ State laws governing substitution vary—for example, in the exact conditions under which pharmacists must dispense a brand-name version of a drug if noted by the physician on the prescription. The therapeutically equivalent versions of a reference drug (often a brand-name drug) are listed in FDA’s Orange Book, which records listed patents and therapeutic equivalence codes for individual drug products regulated by FDA’s Center for Drug Evaluation and Research (FDA, 2021).

¹⁶ Some independent pharmacies might carry more inventory and have slower turnover because of lower prescription volume and the absence of centralized control over distribution compared with chain pharmacies.

¹⁷ The final pharmacy acquisition cost for generic drugs reflects initial payments (which are on-contract negotiated prices for purchases from a primary distributor) and rebates paid by distributors to pharmacies.

¹⁸ Although we describe the role of PBMs separately, some large insurers perform the functions of a PBM internally.

¹⁹ Pharmacies might set retail prices lower than the copay amount for patients with insurance (particularly for generic drugs).

PBMs play an important role in determining which pharmacies patients can use, as well as the net revenue per prescription realized by pharmacies. The three largest PBMs—Express Scripts, CVS/Caremark, and OptumRx—cover 76 percent of national prescription claims (Fein, 2019).²⁰ PBMs assemble networks of pharmacies that agree to the PBM’s payment terms in exchange for an increase in prescription volume from the PBM’s patients. Pharmacy networks often include a mix of chain and independent pharmacies. The largest three distributors facilitate *banner pharmacies* (e.g., Good Neighbor Pharmacy and Health Mart) that can be included in pharmacy networks. Independent pharmacies can be included in pharmacy networks in some cases, individually or, more commonly, as a block through pharmacy services administrative organizations (PSAOs), which represent independent pharmacies in negotiations with PBMs.²¹ AmerisourceBergen, Cardinal, and McKesson, the three largest distributors, each operate PSAOs, and other PSAOs are independently operated. PSAOs might offer independent pharmacies efficiencies in collectively accepting contracts and streamlining administrative processes.

Pharmacies have a financial incentive to be part of multiple PBM networks because additional networks drive additional patients and prescription fills and, therefore, revenue. The other key issues in pharmacy negotiation with PBMs typically include dispensing fees, which are a flat amount paid per prescription filled; the prices paid per drug, which, in many cases, are a negotiated ceiling on how much the PBM will pay on a per-drug basis (see discussion below); and payment timing and terms. These terms often involve pharmacy price concession and performance-related bonus clauses that tie payment rates from PBMs to performance on prespecified metrics—for example, generic substitution rates measuring the share of prescriptions filled with generics (National Community Pharmacists Association, undated).²² If pharmacies fail to meet the specified performance target, they must return a portion of payments to the PBM, and if they exceed the target, they might receive a supplemental payment, although, at least in Medicare Part D, payments *from* pharmacies are much larger in aggregate than payments *to* pharmacies (Fein, 2020a). The following section discusses specific prices paid in more detail.

Pharmacies and pharmacists provide other important health care services beyond dispensing drugs. Pharmacists can educate and advise patients on their prescription drugs and increasingly play an important role in helping to manage drug treatment regimens, with a focus on increasing adherence (Okumura, Rotta, and Correr, 2014). Although not in the scope of this report, over-

²⁰ The estimate of 76 percent includes claims from network pharmacies, claims from the PBMs’ own pharmacies, and claims involving discount cards.

²¹ PSAOs are separate from buying groups and serve different functions. PSAOs represent independent pharmacies in negotiations with PBMs. Buying groups pool independent pharmacy negotiating leverage when purchasing drugs from distributors.

²² Generic substitution rates might not apply in cases in which the PBM pays a lower net price for brand-name drugs after rebates from manufacturers.

the-counter drugs, vaccines, and medical supplies dispensed or administered at pharmacies play an important role in treating many diseases. Additionally, pharmacies are increasingly co-located with clinics providing primary care and urgent care services that can serve as a driver of prescription volume.

Mail-Order Pharmacies

One strategy that PBMs use to manage pharmacy benefits is leveraging mail order pharmacy, and most PBMs operate their own mail-order pharmacies (Danzon, 2015). Mail-order pharmacy is often required or incentivized by prescription drug plan sponsors for refills of prescriptions used to treat chronic conditions, such as diabetes, chronic heart disease, and HIV/AIDS (Khandelwal et al., 2012). Mail-order pharmacies typically dispense 90-day quantities of drugs instead of 30-day quantities, and patient cost-sharing tends to be lower than through retail pharmacies (Khandelwal et al., 2012).

Prescription drug plan sponsors and payers generally prefer that their enrollees use mail-order rather than retail pharmacies, particularly for drugs used on an ongoing basis (for example, to treat chronic conditions), for three reasons. First, mail-order services can increase adherence,²³ which, in turn, can improve health outcomes and could reduce non-drug health spending (Devine, Vlahiotis, and Sundar, 2010). Second, mail-order pharmacies benefit from economies of scale, at least to a point.²⁴ Third, PBMs generally operate their own mail-order pharmacies, which can lower per-prescription costs relative to prescriptions filled via retail pharmacies, depending on the costs involved in running the mail-order pharmacy versus retail dispensing fees (Pharmaceutical Care Management Association, 2011; Visante, 2014). Despite these benefits, the use of mail-order pharmacies reduces face-to-face interaction between patients and pharmacists on side effects, adverse events, drug-drug interactions, and dosing (Khandelwal et al., 2011). This interaction might be less important when patients fill an initial prescription in a retail pharmacy and then receive refills via mail-order pharmacy.

Specialty Pharmacies

Manufacturers tend to restrict the number of distributors for specialty drugs (e.g., self-injected biologics) because of the importance of closely managing inventory for high-unit-cost drugs and the need to monitor cold chain and other specific distribution requirements (Fein, 2018; Drug Topics, 2017; American Pharmacy News, 2016; Hagerman, Freed, and Rice, 2013;

²³ Although several studies have found that mail order programs increase adherence (Zhang et al., 2011; Schmittiel et al., 2013; Valluri et al., 2007; Devine, Vlahiotis, and Sundar, 2010), others have not (Khandelwal et al., 2011; Fernandez, McDaniel, and Carroll, 2016).

²⁴ *Economies of scale* is the extent to which costs per unit of output decrease as volume increases, often because fixed costs are spread over the higher volume.

McCain, 2012). In some cases, manufacturers might sell specialty drugs to pharmacies and other dispensing points directly without using a distributor (Fein, 2018).

PBMs and health plans might also require that patients access specialty drugs through narrow distribution channels, such as a subset of network pharmacies or specialized specialty pharmacies, both of which are often owned by PBMs themselves (Fein, 2018).²⁵ Specialty pharmacies can help manage access to and the utilization of expensive specialty drugs by providing services to patients, such as medication therapy management, patient education and engagement, clinical support services, and other services to increase adherence. Specialty pharmacies can interact with the health care delivery system in ways that are atypical for other retail pharmacies. For example, some health plans and providers will encourage patients to use *white bagging* (a patient buys the drug from the specialty pharmacy and has it delivered directly to their provider for administration) and *brown bagging* (the patient buys and receives the drug from the specialty pharmacy and then takes it to their provider) strategies (McCain, 2012).²⁶

Benefits and Payment

Beyond building and maintaining pharmacy networks, as described in the prior sections, PBMs also play a critical role in advising plan sponsors and payers on the development of their pharmacy benefit, including their formularies, and the net prices paid for covered prescription drugs. Plan sponsors and payers, which we refer to as *payers* for brevity, are a diverse group of organizations and entities offering health and/or drug coverage to individual patients. Payers include, for example, large employers offering plans to their employees, commercial insurers selling health and prescription plans to individuals, and government programs. A payer might choose to offer both medical and pharmacy benefits through a combined health insurer/PBM (such as Aetna and CVS/Caremark) or through separate companies (e.g., with Aetna providing health coverage but Express Scripts, a separate company, managing pharmacy benefits).

The design of a pharmacy benefit by a payer or plan sponsor involves many components, including

- pharmacy networks (described above) which might include differential cost-sharing
- deductibles under which the patient is responsible for 100 percent of drug costs (or combined medical and drug costs)
- out-of-pocket caps and catastrophic spending thresholds to limit total patient liability
- determining whether some drugs will not be covered at all, subject to decisions by pharmacy and therapeutics (P&T) committees operating under regulatory oversight

²⁵ In 2019, 74 percent of prescriptions dispensed via specialty pharmacies were from four specialty pharmacies owned by PBMs (Fein, 2020b).

²⁶ Although these strategies are more common for specialty drugs dispensed through retail pharmacies, they can also apply to other physician-administered drugs.

- tiered formularies in which patients face lower cost-sharing for more-preferred drugs and higher cost-sharing for less-preferred drugs
- limits on quantity or prescription frequency for specific drugs
- utilization management strategies (such as prior authorization requirements) laying out steps to ensure coverage for typically less-preferred, very expensive, and/or potentially unsafe drugs
- special provisions for specialty drugs, including narrower distribution options and coinsurance (a cost-sharing mechanism in which the patient pays a share of a drug's cost rather than a fixed dollar amount)
- varying degrees of overlap with patients' medical benefits (e.g., for physician-administered drugs).

Patients, PBMs, pharmacies, and payers all play important roles related to payment for drugs. Payments for prescription fills covered by insurance involve four main components. First, patients typically pay some share of the cost of a drug at the point of dispensing. Second, the PBM pays the pharmacy the balance of the amount owed to the pharmacy as determined by the contract between the PBM and pharmacy. Third, discounts negotiated between the market authorization holder and PBMs are paid as rebates from the market authorization holder to PBMs. Finally, health care payers compensate PBMs (under various contractual arrangements), and, again depending on contractual arrangements, PBMs pass either most or all of the rebates to payers, resulting in net prices to the payers that are often lower than the amounts paid to pharmacies.

Out-of-Pocket Payments

The type and magnitude of out-of-pocket payments vary depending on benefit design. Many prescription drug plans include an initial annual deductible phase under which patients pay 100 percent of drug costs up to a certain dollar limit. After that, patients filling a prescription covered by their insurance typically pay a fixed amount (copay) or a fixed share (coinsurance) toward the total cost of the drug out of pocket. In the case of coinsurance, the fixed share is typically based on the amount charged at the pharmacy and therefore does not reflect rebates and other discounts that ultimately result in lower net prices.²⁷ Copays and coinsurance are typically lower for drugs with low net prices relative to health benefits; PBMs and payers place these drugs on preferred formulary tiers.²⁸ Similarly, copays and coinsurance are typically higher for drugs on non-preferred formulary tiers. Very expensive specialty drugs are often placed on separate tiers

²⁷ Many plans have catastrophic limits above which patients face lower or no cost-sharing.

²⁸ Cost-sharing is often lower for generic drugs than for brand-name drugs. However, brand-name drugs with large rebates can sometimes be more preferred by PBMs and therefore have lower cost-sharing than therapeutically equivalent generics.

paired with coinsurance. Patients typically pay high copays and coinsurance at specialty pharmacies (American Pharmacy News, 2016).

In general, high cost-sharing is an effective deterrent to patients filling prescriptions (Goldman, Joyce, and Zheng, 2007; Gibson, Ozminkowski, and Goetzel, 2005). Manufacturers might work to increase utilization of their drugs by offering copay coupons to cover part or all of the patient's out-of-pocket liability (Dafny, Ody, and Schmitt, 2016). Some states, including Massachusetts and California, and federal health care programs, including Medicare and Medicare Part D, ban manufacturer coupons. In the case of federal programs, manufacturer coupons are prohibited because the anti-kickback statute (42 U.S.C. § 1320a–7b[b]) prohibits payments or incentives to induce the purchase of drugs paid for by federal health care programs. Besides coupons, vouchers, and similar offers, patients with and without coverage might also have sources of other support, such as patient assistance programs, to cover part or all of the patient's out-of-pocket liability.²⁹

In response to manufacturer coupons and other forms of patient assistance, PBMs and payers are increasingly implementing *copay accumulator* programs, which estimate contributions from coupons and third-party sources and exclude these from contributing toward patients' deductibles or out-of-pocket caps, and *copay maximizer* programs which adjust cost-sharing (upward) to match available coupons and other sources of support from manufacturers. Some states and Medicare Part D prohibit copay accumulator programs because of concerns that they result in higher out-of-pocket spending (compared with alternative programs in which manufacturer contributions do contribute toward deductibles and out-of-pocket caps).³⁰

Cost-sharing is typically lower to steer patients to relatively higher-value (i.e., lower-cost and/or higher-benefit) treatment alternatives. Insurers and PBMs covering both pharmacy and medical benefits (such as Medicare Advantage plans) are increasingly using value-based insurance design in which the out-of-pocket costs for certain maintenance medications to treat chronic conditions—such as statins to treat high cholesterol or insulin for patients with diabetes—are eliminated in an effort to increase uptake and adherence and to lower downstream medical costs associated with untreated conditions (Agarwal, Gupta, and Fendrick, 2018).

Payments to Pharmacies

PBMs typically pay the balance of a negotiated amount owed to the pharmacy (net of patient cost-sharing contributions) within one month of the drug being dispensed. The contractual arrangements between PBMs and pharmacies specify dispensing fees and a cap on the price for the drug itself that pharmacies can charge the PBM. For single-source brand-name drugs, most

²⁹ Patient assistance programs are often financed by drug manufacturers to increase access to expensive specialty drugs.

³⁰ See 85 FR 29164 (Centers for Medicare and Medicaid Services, U.S. Department of Health and Human Services, 2020).

contracts between PBMs and pharmacies specify payment at or around WAC. For multisource drugs, many contracts use maximum allowable cost (MAC) schedules to set payment rates. MAC schedules list maximum prices for all therapeutically equivalent generics and multisource brands (Danzon, 2014; Danzon, 2015). Some contracts use generic effective rate (GER) and brand effective rate (BER) schedules instead of MAC schedules that list prices for drugs that are a fixed percentage of average wholesale price (AWP). For example, PBMs might pay at most 88 percent of AWP. Unlike the case with brand-name drugs, MACs or effective rates do not vary with the pharmacy's acquisition cost. Either of these approaches sets a ceiling for the maximum amount a pharmacy can charge a PBM and, for generic drugs in particular, incentivizes pharmacies to source the lowest-cost version of therapeutic substitutes.

Rebates

PBMs also negotiate on price with market authorization holders. This negotiation boils down to the extent to which PBMs work to shift volume to a specific drug versus potential alternatives in exchange for discounts paid to the PBM by the manufacturer as a rebate. PBMs can shift volume to a specific market authorization holder's drug using tools targeted to both patients and to prescribers. In terms of patients, PBMs use tiered formularies with lower patient cost-sharing for preferred drugs and higher cost-sharing for alternatives. In terms of prescribers, PBMs use a set of utilization management tools that require prescribers to invest time to secure coverage of non-preferred drugs for their patients. One common utilization management tool, prior authorization, requires prescribers to justify the medical necessity of a drug before the payer will cover it for the patient.³¹

The magnitude of discounts that a PBM can negotiate from market authorization holders hinges on both the PBM's ability to shift patients and prescribers to specific drugs and on the availability of close substitutes. If there are no close substitutes available—for example, when there is only one drug to treat a condition—then PBMs have little leverage to negotiate discounts. Discounts might be relatively large in relation to the price initially paid to pharmacies in cases in which there are multiple similar brand-name drugs to treat the same condition (Roehrig, 2018).³²

Payers cover PBMs' initial payments to pharmacies, either with a pass-through model or a spread model under which payments might exceed PBMs' actual costs. PBMs might receive additional fees for services. Depending on contractual provisions, PBMs pass some or all of the negotiated rebates on to payers, lowering payers' overall spending on health benefits, which could lead to lower premiums.

³¹ Prior authorization and other utilization management tools are also used to prevent unsafe or low-value utilization of even preferred drugs.

³² One recent study (Roehrig, 2018) estimated that rebates and coupons combined account for a 23-percent reduction from retail payments for drugs.

Payment in Medicaid

Payment for prescription drugs is different in the Medicaid program than under commercial insurance or Medicare Part D. State Medicaid programs pay pharmacies at rates equal to acquisition cost plus a dispensing fee. States then receive rebates from manufacturers covering the difference between these rates and either (1) the best price available to any other buyer (with a few exceptions) or 23.1 percent of the average price paid to manufacturers for most brand-name drugs or (2) 13 percent for generic drugs (42 U.S.C. § 1396r-8).³³ State Medicaid programs might negotiate supplemental rebates via PBMs in exchange for placement on preferred drug lists, although, in general, Medicaid programs are limited in their ability to apply tiered formularies and utilization management as commercial insurers do, and Medicaid beneficiaries usually face relatively low out-of-pocket cost.³⁴

Payment Without Insurance

PBMs are not involved at all when a patient does not have prescription drug coverage or when the patient has coverage but is buying a non-covered drug or chooses to pay cash for a covered drug (for example, when the cash price is less than the copay). Pharmacies can apply any markup to the drug, and the patient is responsible for paying the entire cost upon receipt. Pharmacy list prices for both brand and generic drugs vary widely. Some discount card programs—such as GoodRx—offer prices at participating pharmacies that can be significantly below the pharmacies' list prices, as well as price comparison tools to help patients find the lowest-cost pharmacy. Some pharmacies, including those in big box stores, offer low or no-cost cash prices for certain generic drugs, likely as a strategy to draw customers to their stores.³⁵

Patients and Prescribers

Patients can receive prescription drugs only with a prescription from an authorized practitioner, who is often a physician. One or more payments (typically two, one from the patient to the pharmacy and the other from the PBM to the pharmacy) are triggered when a patient actually fills a prescription or is administered a drug. As described above, patients' and prescribers' choices between therapeutic alternatives can be influenced by both pharmacies and PBMs. Pharmacies can switch patients to therapeutically equivalent generics on their own authority and can contact physicians to initiate switches from non-preferred to preferred brand

³³ There is a separate inflationary rebate component to cover price increases that exceed inflation. Manufacturer participation in the Medicaid Drug Rebate Program is optional. However, most manufacturers do participate because Medicaid programs are required to cover all drugs offered by participating manufacturers.

³⁴ Medicaid copays vary based on beneficiary income, with very modest copays for beneficiaries with incomes under 150 percent of the federal poverty level.

³⁵ See, e.g., Walmart, undated.

drugs in response to out-of-pocket cost, safety, or other concerns raised at the point of dispensing. PBMs use tiered formularies and cost sharing to influence patient decisionmaking and utilization management tools, such as prior authorization, to shift prescribing patterns toward preferred drugs.

Market authorization holders also influence prescribing decisionmaking with the hope of increasing demand for—and, therefore, revenue from—their products. They market directly to consumers via direct-to-consumer advertising, which can be targeted to specific drugs or to informational ads on specific diseases or conditions for which the company manufactures a drug. Drug companies send sales representatives to physician offices and hospitals to “detail” a company’s drugs and use other strategies, including sampling, to encourage prescribing of their products.

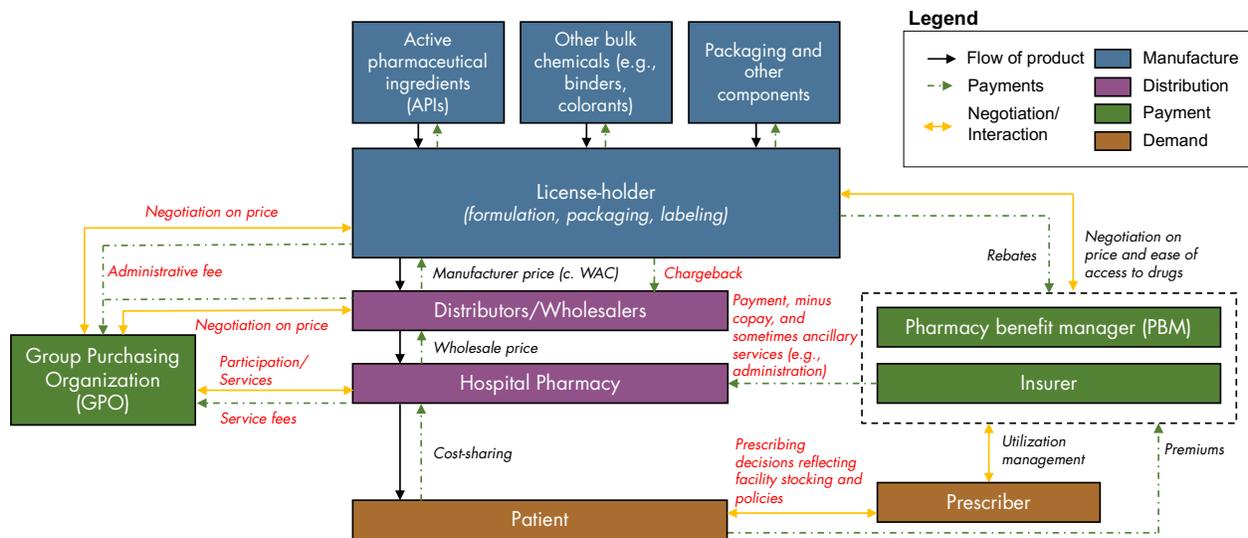
3. Outpatient Facility, Inpatient Hospital, and Physician Office Supply Chains

This chapter describes the differences in drug supply chains when distribution occurs through hospitals or physician offices rather than in retail pharmacies. Our description focuses on differences in supply chains when drugs are dispensed in these other channels relative to the model retail pharmacy supply chain illustrated in Figure 2.1. The figures in this chapter mirror Figure 2.1 with differences emphasized in red.

Drugs Administered in Outpatient Facility Settings

Some oncology, rheumatology, and other drugs are administered to patients by physicians or other practitioners in an outpatient facility setting like hospital outpatient departments (Figure 3.1). In Medicare, these drugs are covered by Medicare Part B rather than the Part D retail pharmacy benefit. In commercial insurance, physician-administered drugs are often covered under the medical benefit rather than the pharmacy benefit.

Figure 3.1. Typical Supply Chain for Drugs Dispensed in Outpatient Facility Settings



Some hospital and health system buyers of prescription drugs negotiate lower prices directly with manufacturers or via GPOs. GPOs combine the negotiating power of their member hospitals to secure favorable prices and terms for drugs from manufacturers (O'Brien, Leibowitz, and

Anello, 2017; Burns and Briggs, 2018).³⁶ There are several large, national GPOs (e.g., Catalent and Vizient) with membership that includes primarily hospital-based health care delivery systems and independent hospitals. Members sign agreements detailing access to negotiated prices and terms as well as additional services (such as supply chain support) that they will receive from the GPO. Although there typically is not a membership fee for access to negotiated prices per se, members often purchase at least some services from GPOs. Most hospitals belong to at least one GPO; some belong to several.

GPOs negotiate with both manufacturers and distributors to secure national contracts detailing prices and other terms. The collective negotiation on the part of many (potentially competing) hospitals is possible due to an anti-kickback “safe harbor” provision.³⁷ Although price negotiation is the major GPO function, negotiating standard terms is also important and can cut down on transaction costs and risk for members. Manufacturers compete with one another to secure contracts from large GPOs; for drugs with significant competition between close substitutes, negotiated discounts tend to be large; for drugs without close substitutes, negotiated discounts might be more modest. Specialty pharmaceuticals are less likely to be purchased via GPO channels because they are typically marketed by one market authorization holder who, therefore, is not incentivized to offer discounts (Burns and Briggs, 2018). Importantly, manufacturers pay an administrative fee to the GPO when they are selected for a national contract. Separately, GPOs form agreements with distributors to provide these negotiated prices to their members.

The members of a specific GPO might use a wide range of distributors. These distributors play an important role in implementing discounted prices for drugs bought by health systems. Buyers pay distributors the GPO-negotiated price even though the distributor paid manufacturers a flat WAC-based price. For example, the distributor might pay manufacturers \$100 per unit of a drug while a pharmacy buyer negotiates and pays distributors a lower price of \$80 (Figure 2.3, Scenario 3). In this case, the distributor bills the manufacturer for the difference (a “chargeback”; \$20 in this case). In contrast with rebates, which apply primarily for drugs dispensed through retail pharmacies (where distributors are not aware of the net price negotiated between manufacturers and PBMs), in the case of chargebacks, distributors are aware of the price

³⁶ GPOs play a similar role in negotiating prices and terms for the purchase of medical devices and other supplies and input used by hospitals.

³⁷ The Anti-Kickback statute (42 U.S.C. § 1320a-7b[b]) prohibits the purchase of goods or services in exchange for payment under a federal health care program. Under the Omnibus Budget Reconciliation Act of 1986, Congress amended the statute to add a “safe harbor” provision making an exemption for vendors’ payment to GPOs. In 1991, directed by the 1987 Medicare and Medicaid Patient Protection Action, the U.S. Department of Health and Human Services implemented a regulation specifying requirements for GPOs to qualify for safe harbor. In addition to other requirements under the regulation, a GPO must have a written agreement with its customers stating that the maximum contract administrative fees it can receive from vendors is 3 percent of the purchase or establishing a maximum payment amount for each vendor.

negotiated between manufacturers and the distributors' customers, which might limit manufacturer's willingness to offer large discounts via this mechanism.

Although hospitals generally have flexibility to purchase drugs through GPOs or other channels, some GPO membership agreements include financial incentives for hospitals to purchase an amount of product that is above a threshold through preferred manufacturers. Some large hospital or broader health care delivery systems might be able to negotiate prices directly from manufacturers that are even lower than GPO-negotiated prices. These larger systems might set up their own consolidated service centers (CSCs), which function as system-owned distributors, buying directly from manufacturers and storing and distributing products to hospitals and other components of the delivery system. Health care delivery systems operating CSCs often use the CSC to procure certain higher-priced or differentiated drugs, devices, and other supplies while working through distributors and GPO-negotiated prices for commodity inputs.

There are other important differences in outpatient hospital versus retail pharmacy supply chains for drugs. Hospitals develop and maintain their own formularies and policies to steer prescribers and patients receiving drugs at the hospital to therapeutic alternatives where they earn the largest margin or have the lowest cost. As a result, prescriber and patient decisionmaking is constrained by both hospital pharmacy policy and prescription drug benefit design considerations.

Hospital P&T committees determine policies regarding medication use, such as formularies of drugs approved for use in the hospital, based on clinical considerations as well as cost (Vogenberg and Gomes, 2014; Zellmer, 2017). A 2019 survey of hospital pharmacy directors found that hospitals are increasingly using relatively restricted formularies: Approximately 73 percent reported having "a limited, strict formulary with tight restrictions on nonformulary medication use" (Pedersen et al., 2020). Pharmacists are generally involved in managing medication therapies, which can include "writing medication orders, selecting doses, ordering appropriate laboratory tests, and monitoring patient response to therapy" (Pedersen et al., 2020). However, they are more likely to manage certain therapy types over others: For example, 97 percent of hospitals have pharmacists manage vancomycin therapy, and 77 percent of hospitals have them manage anticoagulation therapy, while 8.3 percent of hospitals make pharmacists responsible for pain and palliative care medication management. Most hospitals permit pharmacists to initiate or modify medication orders according to protocols (Pedersen et al., 2020).

Another important difference is that hospital outpatient departments, unlike pharmacies in most cases, can bill patients and their insurers for services in addition to the drug itself. For example, hospitals might, depending on the coverage policies of insurers, bill for services related to the administration of the drug. Insurer payment rates for drugs dispensed in outpatient facility

settings are often based on Medicare’s average sales price–based (ASP-based) payment rates.³⁸ Medicare pays ASP plus 4.3 percent (typically ASP plus 6 percent but adjusted downward for sequestration³⁹) for most Part B drugs. Payment for biosimilars is based on the ASP for individual biosimilar products plus the margin calculated on the reference biologic. ASP rates are lagged by two quarters but over time reflect the prices paid to manufacturers after rebates and chargebacks. In general, providers might have an incentive to choose more-expensive Part B drugs because the margin on a drug with a higher ASP is greater than the margin on a drug with a lower ASP. Payments for new drugs, blood products, and vaccines are based on WAC and AWP. Payment rates for other services are often based on Medicare’s physician fee schedule and outpatient hospital prospective payment system, although payment approaches vary widely.⁴⁰

The 340B Drug Pricing Program

The 340B Drug Pricing Program is intended to help safety net providers “stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services” (U.S. House of Representatives, Committee on Veterans Affairs, 1992). The program does so by providing covered entities with access to lower prices for outpatient drugs, in general without regard to whether the patients receiving the drugs do or do not have access to outpatient pharmacy coverage. Eligible hospitals and clinics (called *covered entities* for the purposes of the program) qualify either through their status under other programs and designations (e.g., federally qualified health centers and critical access hospitals) or, for hospitals, by meeting a threshold of care provided to Medicaid patients (called *disproportionate share hospitals*).

The 340B program sets ceiling prices that are approximately equal to Medicaid Prescription Drug Rebate Program prices. Participating covered entities can voluntarily purchase drugs through the 340B prime vendor, which can negotiate additional discounts. Drugs are dispensed either directly by the covered entity (typically a hospital or clinic) or, increasingly, through community pharmacies under contract with the covered entities. Contract pharmacies must maintain separate accounting for drugs dispensed to patients of 340B covered entities for accounting purposes. Participating covered entities and their contract pharmacies bill patients and, if applicable, their sources of pharmacy coverage for the outpatient drugs they receive.

Participation in the 340B program is voluntary, and not all eligible entities choose to participate. Participating covered entities in some categories—including disproportionate share

³⁸ Under Medicare’s Outpatient Prospective Payment System, certain drugs are bundled into the payment for broader outpatient hospital services.

³⁹ *Sequestration* refers to federal government spending cuts implemented in the Budget Control Act of 2011. These cuts apply to certain Medicare payments to providers.

⁴⁰ Some low-cost drugs are packaged into payments for outpatient hospital services under Medicare’s payment policies.

hospitals—are prohibited from purchasing covered outpatient drugs through GPOs if they participate in the 340B program. Providers that choose not to participate might be able to negotiate favorable prices through GPOs or, for the largest buyers, on their own.

The Physician Office Supply Chain

The stakeholders, relationships, and flows of money supporting drugs administered in physician offices are broadly similar to those discussed above for drugs administered in outpatient facility settings (Figure 3.1). The main “buy and bill” model applies to both physician office and outpatient facility settings.

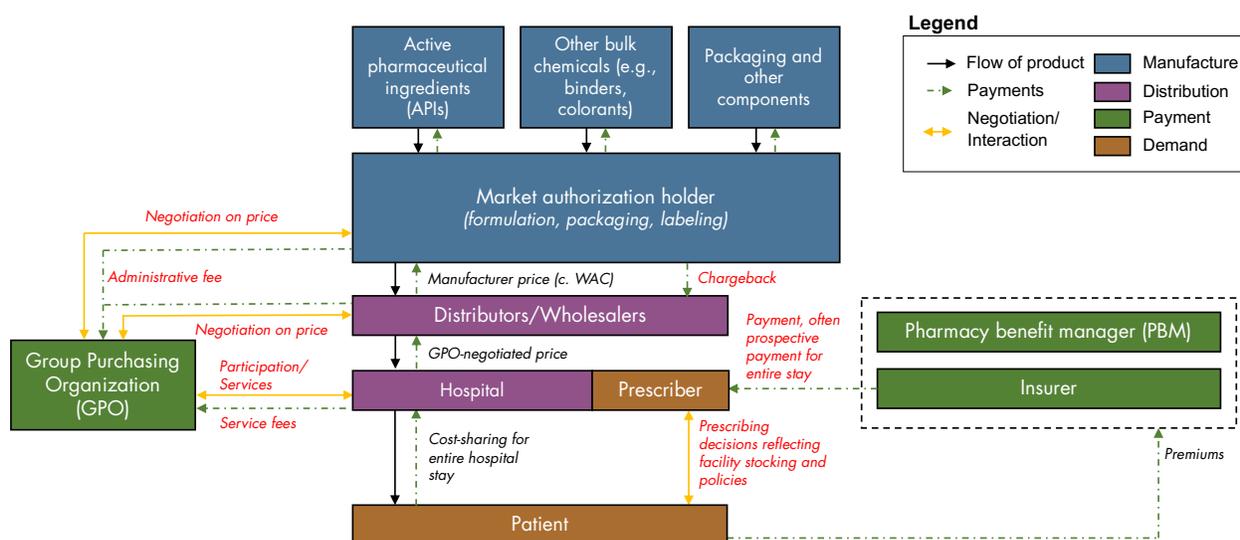
There are, however, some differences in how physician offices not owned by hospital-based delivery systems acquire drugs. Like hospital-based delivery systems, physician practices are often members of GPOs and rely on GPOs to negotiate discounts off of wholesale prices. Several of the largest hospital delivery system–focused GPOs have smaller membership among physician practices. There are also more-specialized GPOs focusing on physician practice customers, and in some cases GPOs subspecialize in specific types of drugs administered in physician offices (such as dermatological drugs).

In terms of payment, the Medicare allowed amount for physician-administered drugs covered under Medicare Part B is ASP plus a margin (typically 6 percent, although now 4.3 percent due to sequestration) in most cases (with exceptions discussed above). Physicians are in some cases able to bill for a separate administration service, although not for drugs administered on the same day that the patient receives any other Medicare service (like an evaluation and management office visit). Rates from commercial insurers are typically ASP- or AWP-based and also include an administration fee (National Academies of Sciences, Engineering, and Medicine, 2018).

Inpatient Hospital

The boundaries between separate supply chains for inpatient hospitals and ambulatory care (such as in an outpatient hospital and physician office setting) are increasingly blurred as delivery shifts to more-integrated delivery systems. Still, there are some important differences in financial incentives for drugs administered in these settings driven primarily by payment considerations (Figure 3.2).

Figure 3.2. Typical Supply Chain for Drugs Dispensed During Inpatient Hospital Stays



Although much of the inpatient hospital pharmacy model is similar to that of the outpatient hospital pharmacy model, one main difference lies in insurer payments. Medicare pays a single amount for inpatient stays based on diagnoses, with only some allowances for high-cost outliers. These prospective payment rates include all care provided during the stay, including drugs administered during the stay.⁴¹ Many commercial and other payers adapt some version of Medicare’s inpatient payment approach and rates (NORC at the University of Chicago, 2016). The single bundled per-stay payment means that hospitals’ margins are dependent not only on the acquisition cost for drugs but also on which drugs are used and whether drugs are used at all. This is a key difference between drugs administered in ambulatory facility settings (such as hospital outpatient departments) where the typical “buy and bill” payment model might incentivize the use of drugs. Given the financial stake of the hospital, hospital pharmacies, formularies, and pharmacy and therapeutics committees might more actively manage prescription drug utilization for patients in the inpatient setting compared with the outpatient hospital setting.

⁴¹ There are some exceptions. Medicare and most other payers have special provisions for separate payment of extremely expensive and/or new drugs administered in inpatient settings—for example, with a temporary new technology add-on payment, hospitals receive approximately \$250,000 for chimeric antigen receptor T-cell therapy for blood cancers.

4. Discussion and Conclusion

Prescription drug supply chains are continually evolving in response to changes in the mix of drugs used by patients, use of new drug and insurance benefit design features, consolidation in health care delivery systems, and shifting negotiating leverage between key stakeholders. This report is intended as an update on prior efforts that are now dated (Kaiser Family Foundation, 2005), focusing on differences in stakeholders and incentives for different categories of drugs and in different distribution channels. Because of the pace of change in the pharmaceutical industry and in the U.S. health care system, we expect that an update to the current document will be necessary in another decade.

We found that the typical stakeholders, relationships, and financial incentives involved in prescription drug supply chains vary depending on the characteristics of a drug and how it reaches patients. For example, GPOs play a significant role in nonpharmacy distribution channels, and their role has evolved from providing price negotiation to include provision of other services, such as supply chain data analytics, to members. Even within a specific type of drug and a particular distribution channel, differences in business practices complicate a universal description of drug supply chains. Despite this complexity and variation, we identified four common core components of drug supply chains across all cases: manufacturing, distribution, coverage and payment, and prescribing and demand.

Separate analysis of relationships is needed for specific categories of drugs that we did not consider in our analysis and are often excluded in other research, including vaccines, radiopharmaceuticals, and compounded drugs. These product categories have additional steps and stakeholders involved. In addition, separate analysis of relationships is also needed for the specific distribution channels we did not consider in our analysis, such as home health care, long-term care facilities, nuclear medicine, and federal health systems.

More research is also needed to understand how the evolving industrial organization of stakeholders in prescription drug supply chains—particularly vertical and horizontal integration—affect margins, financial incentives, and, ultimately, patients. One prominent example of vertical integration is CVS's 2006 acquisition of Caremark, a major PBM, and its subsequent 2018 merger with the health insurer Aetna. Vertical integration could facilitate the sharing of information and elimination of some duplicative costs but at the potential cost of less choice for patients and more-concentrated market power. In terms of horizontal integration, there are now just three major national PBMs and three distributors. It is unclear whether the balance between cost-cutting and pricing power with three firms is optimal for these stakeholder groups.

Although prescription drugs are generally available to dispense when prescribed in the United States, there are important exceptions that warrant further investigation and scrutiny. Shortages of drugs—in particular, sterile injectable drugs—persist, even if they are not

widespread (FDA, 2019). The coronavirus disease 2019 (COVID-19) pandemic has increased attention on the extent to which inputs of raw materials and APIs used in the manufacture of prescription drugs are sourced from China and other countries. Although there were at least some disruptions in prescription drug supply attributed to the pandemic (Rowland and Slater, 2020), most of these appear to be due to buyers aggressively stocking drugs used to treat patients with COVID-19 rather than to disruptions in manufacturing or supply.

The ability of policymakers to identify, assess, and respond to shortages and other disruptions in supply chains, regardless of the cause, is hampered by incomplete data. FDA does maintain databases listing the facilities and companies registered to manufacture and import APIs and finished drug products. FDA does not, however, have the regulatory authority to collect data on the volume of drugs or their constituent ingredients manufactured at different sites or on the flow of products between stakeholders. At present, policymakers' ability to identify disruptions in drug supply chains is largely through self-report by industry stakeholders and from third-party crowdsourcing data collection efforts, such as the American Society of Health-System Pharmacists' Drug Shortages Database (American Society of Health-System Pharmacists, undated). Although mandating drug manufacturers to report additional data would impose additional burden, richer data would allow for a more accurate assessment of drug supply chains and analysis of potential and actual disruptions.

More broadly, recent policy proposals aim to tackle a range of perceived issues in prescription drug markets, including high prescription drug prices, safety and quality concerns (Byrd, Chertow, and Bhalla, 2019), and the need to ramp up the manufacture and distribution of potential new drugs to treat COVID-19. Assessing how policy proposals affect stakeholders and how they will likely respond is necessary to assess unanticipated consequences of these proposals. In particular, the need to test, manufacture, and distribute millions of doses of COVID-19-specific therapies and vaccines will be a major undertaking that will utilize the supply chain components described in this report but likely in new ways and configurations.

Appendix: Pricing Term Glossary

This appendix includes definitions of several pricing terms referenced throughout the report. The terms are listed in alphabetical order. An asterisk preceding the term indicates that the prices are publicly available, although in some cases a payment is required to access the data.

340B ceiling price: The 340B program determines a maximum (ceiling) price using reductions off of AMP, like the Medicaid drug rebate program. The 340B prime vendor can negotiate additional 340B discounts beneath this ceiling price.

The **average manufacturer price (AMP)** is the average price paid to the manufacturer by distributors for distribution to retail pharmacies and retail pharmacies purchasing from manufacturers directly after accounting for rebates and most other manufacturer price concessions. AMP is defined at 42 CFR § 447.504 and is used by Medicaid to calculate rebates under the Medicaid drug rebate program. Prices for sales to hospitals and delivery systems other than retail pharmacies, 340B prices, rebates under the Medicaid drug rebate program, and prices paid by various federal purchasers do not contribute to AMP. Medicare bases payment on AMP rather than ASP in the relatively rare case where AMP is lower (U.S. Department of Health and Human Services, Office of Inspector General, 2018).

* The **average sales price (ASP)** is the average net price paid across all purchasers (not just retail purchasers, as in AMP) after accounting for most discounts, rebates, and other price concessions. 340B prices and rebates under the Medicaid drug rebate program do not contribute to ASP. ASP is defined at 42 CFR § 414.904 and is used by Medicare as the basis of payment for most Medicare Part B drugs. Medicare payments for non-biosimilar Part B drugs are a fixed amount (typically 6 percent, now 4.3 percent due to sequestration) above ASP per billing unit of a drug. Payment for biosimilars is based on the biosimilar ASP plus the markup calculated using the reference biologic's ASP.

* The **average wholesale price (AWP)** is a price available from third-party data vendors estimating the average amount paid by distributors to purchase drugs from manufacturers. Some narrow categories of drugs (e.g., Part B drugs infused through durable medical equipment) are paid at 95 percent of AWP. AWP is by convention approximately 1.2 times WAC.

The **“Big 4” price** is a price set at the minimum of FSS prices or 76 percent of AMP available to the four largest federal purchasers of prescription drugs (the Coast Guard, the Department of Defense, the Department of Veterans Affairs, and the Public Health Service).

The **brand effective rate (BER)** is a rate describing the amount received by a pharmacy for a brand drug relative to a benchmark, such as AWP. BERs apply over a period of time. Differences between BER and actual rates might result in reconciliation between and pharmacies and PBMs.

The **cash price** is the price charged by pharmacies, for example, to those without prescription drug coverage.

* **Federal supply schedule (FSS) price:** The Department of Veterans Affairs, on behalf of the federal government, maintains a database of prices contractually negotiated between federal buyers and drug companies. These prices are generally available to all federal buyers of drugs.

The **federal upper limit (FUL)** is equal to 175 percent of AMP. State Medicaid plans pay at FUL-based rates for brand-name drugs with three or more generic competitors.

The **generic effective rate (GER)** is a rate describing the amount received by a pharmacy for a set of therapeutically equivalent generic drugs relative to a benchmark, such as AWP. GERs apply over a period of time. Differences between GER and actual rates can result in reconciliation between and pharmacies and PBMs.

The **maximum allowable cost (MAC)** is a single price set by payers that applies to all therapeutically equivalent versions of a drug—for example, to a brand-name drug and therapeutically equivalent generics.

The **Medicaid best price** is the lowest net price paid by any non-federal buyer or Medicare Part D plan sponsors for a drug (42 CFR § 447.505). State Medicaid programs are guaranteed access to this price if it is lower than the rebates that would otherwise apply under the Medicaid drug rebate program (42 CFR § 447.509).

* The **National Average Drug Acquisition Cost (NADAC)** is the average acquisition cost for a drug as determined by a nationally representative sample of pharmacies.

Net price (seller): The net price from the market authorization holder's ("seller's") perspective is the amount received after all rebates, discounts, and other price concessions are applied. Several of the other prices listed in this glossary are the net price from the seller's perspective (e.g., AMP and ASP) from certain buyers. The overall net price from the seller perspective is a volume-weighted average of these buyer-specific net prices.

The **net price (payer)** is the net price from the payer's perspective after all rebates and other price concessions are applied. The net price from the payer perspective includes margins retained by each stakeholder along the supply chain, including the manufacturer, market authorization holder (if different than the manufacturer), distributor, and pharmacy.

The **wholesale acquisition cost (WAC)** is a list price set by manufacturers. WAC does not include rebates or other discounts. New Part B drugs are paid on a WAC basis until ASP data are available.

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