# Pricing and Reimbursement of Biopharmaceuticals and Medical Devices in the USA

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## Introduction

The US is the largest market for pharmaceuticals in the world. It is also one of the few countries in the industrialized world that does not regulate pharmaceutical prices. This largely reflects the predominance in the US of competing private health insurance plans. Although the public insurance programs, mainly Medicare and Medicaid, now account for more than 40% of total health expenditures in the US, their design has historically been influenced by the design of the private insurance sector. In particular, Medicare Part D, which covers outpatient drugs for seniors, was designed to be run by competing private sector prescription drug plans (PDPs) and the enabling legislation explicitly bars the government from negotiating drug prices.

In the US, as in every other country, insurance that provides financial protection to consumers thereby also tends to make consumers insensitive to prices. For patented biopharmaceuticals, this enables producers to charge higher prices than they would in the absence of insurance. In countries with either national health insurance or regulated social insurance, government payers respond to this effect of insurance by constraining prices either directly, through price controls, or indirectly by making reimbursement contingent on cost-effectiveness. In the US no single private payer has sufficient market power to control pharmaceutical prices. Rather, the negotiation of prices with producers and the design of cost-sharing and other access controls are dimensions of competition between health plans. Fundamentally, health plans that are more restrictive on price to suppliers can offer consumers lower cost plans but with restricted access to services.

In practice, most private health plans and Medicare use similar approaches to negotiating prices and/or setting reimbursement rules for pharmaceuticals. This article describes the predominant reimbursement rules used by these US payers and the effects of these rules on manufacturer pricing, highlighting the important differences based on where a drug is dispensed and between onpatent brands and generics.

## Overview of the Drug Distribution System and Price Levels

In the US pharmaceutical market there are multiple prices, corresponding broadly to different levels of the distribution chain and whether the price is a list price or a transactions price (that reflects discounts or rebates off the list price). The main price levels and types are outlined here in summary, and the following sections describe the system and its effects in more detail.

Pharmaceutical manufacturers typically sell drugs to wholesalers at a list price, the wholesale acquisition cost (WAC), sometimes with modest discounts (1–2%) for prompt payment. Wholesalers distribute drugs to retail pharmacies (including mail-order pharmacies) and hospital pharmacies, adding a competitively determined mark-up to cover their distribution costs. Traditionally, an estimate of the average price at which wholesalers sold to pharmacies was published by pricing agencies as a list price called average wholesale price (AWP). This list price was widely used by payers as a basis for their reimbursement to pharmacies. However, AWP became an increasingly unreliable (usually inflated) measure of the actual average transaction price at which wholesalers sell to pharmacies. Although AWP and other list prices have remained the basis for payer reimbursement to pharmacies, there is usually a significant discount. For example, a payer may set pharmacy reimbursement at AWP-18%, where the discount off AWP is negotiated between the payer and the pharmacy chain. This reimbursement price is intended to allow the pharmacy to cover the cost of drug acquisition plus a competitive dispensing fee. The payer reimburses the pharmacy at this price, net of any patient cost-sharing that the pharmacy must collect from the patient, depending on the payer's plan design.

Private payers also negotiate discounts from manufacturers of patented drugs directly. These negotiated discounts are usually paid by electronic transfer from the manufacturer to the payer, thus bypassing the wholesaler/retailer system. This preserves confidentiality of the payer-specific discount amounts and prevents price arbitrage, that is, the manufacturer transfers the discount directly to the payer for whom it is intended. The ability of payers to extract these discounts from manufacturers depends on the payer's ability to influence drug use through its formulary design. The average price received by manufacturers, taking into account these discounts given to private payers, is called the average manufacturer price (AMP). Medicaid and some other public payers by statute get mandatory rebates off AMP.

This system of a manufacturer list price, combined with negotiated discounts to private payers and mandatory rebates to government payers, is similar for generics, except that the negotiated discounts given by generic manufacturers are targeted at dispensing pharmacies, rather than at health plans/payers, because the pharmacies are the ultimate decision-makers for multisource drugs (off-patent products with originator and generic suppliers). This is described below.

Discussion of pharmaceutical pricing in the US tends to focus on prices charged by manufacturers, including both the list prices and the discounts/rebates, because these exmanufacturer prices form the basis for prices paid by final payers, with the addition of wholesaler and pharmacy margins that are competitively determined. The wholesale segment in the US is highly concentrated with three firms accounting for more than 80% of the national market, reflecting large economies of scale. It is nevertheless highly competitive, partly due

to increasing concentration and strong competition at the retail pharmacy (including mail order) level, where the top six chains now account for more than 60% of dispensing sales. Pharmacy regulation in the US requires that retail pharmacies employ a licensed pharmacist, but there are no requirements that pharmacies be owned by pharmacists and no restrictions on chain pharmacies, in contrast to restrictive pharmacy ownership regulations in many other industrialized countries. Over the last two decades, the large chain pharmacies, such as Walgreens, RiteAid, and CVS, have grown by increasing their number of outlets and the range of products and services they offer, besides drugs. Conversely, some large supermarkets and department stores like Walmart operate pharmacies within their stores. These large, chain retailers take advantage of economies of scale and scope, and play a major role in driving competition in the wholesale and the generics sector, as described below. Within each geographic market multiple chains compete and competitive pressure on pharmacy margins is enhanced by the bargaining power of large health plans and pharmacy benefit managers (PBMs) such as Express Scripts and Caremark, including competition from their mail order pharmacies that compete with bricks and mortar pharmacies. Similarly, for inpatient drugs, hospitals purchase through large group purchasing organizations that negotiate with wholesalers and put competitive pressure on distribution margins.

Thus in the US, the exmanufacturer list price and discounts, the wholesale mark-ups, retail mark-ups, and final prices to payers/consumers are freely determined, constrained by market competition, in contrast to most other countries where prices and mark-ups at each of these levels are set by regulation. In this article 'price' refers to the exmanufacturer price, before discounts, unless otherwise noted. The term 'cost-sharing' is used to refer to the component of the final price paid by the consumer.

## Why Biopharmaceuticals Markets are Different

Although US biopharmaceutical markets are structurally competitive, as described above, several important factors differentiate biopharmaceutical markets and pricing from those for most goods. For most goods that are sold in reasonably competitive markets to reasonably informed consumers, standard economic theory implies that competition will align prices with value to consumers and marginal cost to producers, yielding outcomes that are broadly consistent with economic efficiency. Achieving efficient pricing for pharmaceuticals is complicated by several factors. First, R&D is roughly 17% of sales for the US-based originator pharmaceutical industry, compared to 4% for other US industries. Marginal cost-pricing, which is the expected outcome in competitive markets, would achieve first best static efficiency but would fail to cover total costs and would violate the requirement for dynamic efficiency that producers capture the full social surplus produced by innovation. To address the need for R&D incentives, patents (and other exclusivities) bar generic competitors for a limited term. Patents intentionally enable originator firms to price onpatent products above marginal cost and thus potentially recoup R&D expenses. Although patent-induced pricing above marginal cost may lead to only 'second best efficient' utilization of patented products, patents are the generally accepted way to pay for R&D, as reflected in the World Trade Organization's Trade-Related Intellectual Property (TRIPS) provisions. Thus, patents and the resulting temporary market power are not intrinsically a cause for concern over pharmaceutical prices.

Second and more problematic is the effect of comprehensive insurance coverage on pricing. Insurance protects consumers from financial risk and, through cross-subsidies, makes health services more affordable to low-income consumers. However, because such insurance makes patient demand highly price-inelastic, insurance creates the potential and incentives for manufacturers to charge prices that exceed the level that would result from patents alone. Public and private insurers may use various strategies to constrain this 'producer moral hazard.' In most industrialized countries payers either control prices directly, through price or reimbursement regulation, or require evidence that the drug is cost-effective, which indirectly limits the manufacturer's price based on the drug's incremental effectiveness. Third, patients, payers, and even physicians often lack good information about effectiveness of medical goods and services, which may undermine price-sensitivity. For biopharmaceuticals and devices, this uncertainty is mitigated by regulation of safety, efficacy, manufacturing quality, and promotion. Thus the effect of insurance is the main cause for concern over pharmaceutical prices.

Private and public payers in the US use neither direct price regulation nor indirect price control through incremental cost-effectiveness thresholds as a requirement for reimbursement. Rather, US payers influence the prices charged by manufacturers primarily through use of tiered formularies that offer preferred formulary position and therefore larger market share to drugs that are favorably priced (or give larger discounts), relative to therapeutically similar drugs. Medicaid and other smaller public programs receive mandatory rebates off the manufacturer's price. These approaches leave list prices unconstrained but do achieve significant discounts on onpatent drugs in crowded drug classes with several close therapeutic substitutes. However, these approaches provide little constraint on prices of drugs that are more unique, including most specialty drugs and biologics. By contrast, reimbursement and substitution rules for generics result in highly price competitive generic markets and very low generic prices in the US. The following sections describe in detail these reimbursement rules and their effects on pricing in the US.

## Reimbursement Rules for Onpatent Brands

In the US, payer rules and approaches to pharmaceutical reimbursement differ, depending on where the drug is dispensed – retail pharmacy, physician office, or hospital inpatient (Table 1). Reimbursement differences largely reflect the historical evolution of insurance coverage. Retail pharmacy (54% of prescription sales) and mail order pharmacy (17% of sales) dispense self-administered drugs and are reimbursed on a fee-for-service basis by a private insurer's pharmacy benefit or by Medicare's Part D benefit for seniors. Drugs dispensed as part of an inpatient hospital admission (approximately 10% of sales) are covered by the patient's inpatient benefit

**Table 1** US: Reimbursement rules depend on product type and distribution channel

| *Channel* | *Retail pharmacy* | *Physician office* | *Hospital inpatient* |
|---|---|---|---|
| Medicine type | Orals, creams, and self-injectibles | Biologics, infusions, and vaccines | All types |
| Benefit | Pharmacy/Medicare D | Medical/Medicare B | Hospital/Medicare A |
| Reimbursement | Tiered formularies with access controls | Buy-and-bill with ASP + 6% | Hospital is paid DRG per admission |

(Medicare Part A for seniors). Inpatient drugs are reimbursed, along with all other inpatient costs, in a single bundled payment for the hospital admission. Drugs that are dispensed in physicians' clinics (approximately 12% of sales), including infusions and vaccines, are covered by the patient's medical benefit (Medicare Part B) which pays for physicians' services. Because many new, expensive biologics are physician-dispensed, including many oncologics, the reimbursement rules for this category are critical to pricing of biologics in the US.

## Pharmacy-Dispensed Drugs

### *Primary care drugs*

Private health plans use PBMs to manage drugs that are dispensed through retail pharmacies. PBMs developed in the 1990s as stand-alone, independent contractors that managed drug benefits on behalf of self-insured employers and other health insurers. Since then, some large insurers have developed their own in-house PBMs that compete with the stand-alone PBMs. When Medicare Part D was created in 2003 to provide outpatient drug coverage for seniors, administration of the Part D benefit was assigned to competing, private entities called prescription drug plans (PDPs), which are similar to PBMs, with important differences noted below. Many private health insurers and PBMs also serve as PDPs.

Private PBMs and Medicare PDPs use similar strategies to manage drug costs. Specifically, a pharmacy and therapeutics (P&T) committee, which includes physicians and pharmacists, evaluates alternative drugs and designs the formulary, that is, the list of drugs that are covered, with associated patient cost-sharing levels and any other controls. Most plans use a formulary with three or more tiers with corresponding copayments. The first tier is for generics and has a US$0–10 copayment per prescription (or a month's supply of a chronic medication); the second tier includes preferred onpatent brands with a modest (US$25–45) copayment; and the third or nonpreferred brand tier has significantly higher copayment, currently approximately US$45–90 per month. In addition, a fourth tier is increasingly used for expensive specialty drugs and usually has a 25–30% coinsurance of the drug's price. Additional tiers with high coinsurance rates may also apply to 'lifestyle' drugs. These tiers and associated differential copayments are designed to incentivize patients and their physicians to accept generics, if available, or choose 'preferred' brands among onpatent brands.

In addition to these differential copayments, plans increasingly also use direct controls to achieve appropriate utilization. Most common are a step edit (a computerized block that automatically rejects reimbursement of a drug unless the patient meets certain conditions, such as prior failure on a generic alternative) and prior authorization (which requires the physician to obtain prior approval from the health plan before a drug is reimbursed).

Formulary design with tiered cost-sharing, step edits, and prior authorizations enables PBMs/PDPs to shift drug utilization toward preferred drugs. This ability to 'shift share' within a therapeutic class gives plans leverage to negotiate price discounts from manufacturers in return for preferred formulary positioning. For example, a plan that is willing to severely limit the number of preferred brands and impose a large copay differential for nonpreferred brands creates leverage in price negotiations, because a drug manufacturer may be willing to give a large discount to be the only brand on the preferred tier, whereas they may give little or no discount if they share the preferred tier with all competitor products in the class.

Thus, this tiered formulary approach enables PBMs to gain significant leverage over manufacturer prices provided that there are several clinically similar drugs in a class and the PBM is able/willing to limit patient choice of drugs. More restrictive PBM plans that limit patient choice and impose high cost-sharing on nonpreferred drugs can get lower prices and offer lower premiums. Essentially, this process structures patient cost-sharing and utilization controls to increase the cross-price demand elasticity facing manufacturers. It gives payers and patients a trade-off between drug choice and cost of coverage. It has worked reasonably well for large, primary care therapeutic classes, such as statins or antiulcerants, where the availability of several, therapeutically similar drugs has enabled PBMs to drive deep discounts, particularly once generics become available in a crowded class. Because these discounts are confidential, comprehensive data are not available and conclusions here are based on anecdotal and the limited, publicly available data.

Discounting has been challenged by retail pharmacists in antitrust litigation alleging collusive pricing and price discrimination by drug manufacturers (Scherer, 1997). Dispensing pharmacies do not receive the discounts on onpatent drugs comparable to those given to PBMs because pharmacies cannot - and arguably should not – independently influence a physician's/patient's choice between therapeutic substitutes. This litigation conspicuously excluded off-patent drugs and generics, because for these drugs the discounts go to the pharmacies as decisionmakers in choosing between generically equivalent versions of a prescribed compound (see below). Under the settlement of this litigation, manufacturer discounts were to be made available on the same terms to all purchasers; however, because PBMs/PDPs and payers design the formularies that drive therapeutic substitution, they remain the main recipients of discounts on onpatent drugs, whereas pharmacies (including mail-order pharmacies) are the main recipients of discounts on generics.

Consistent with this theory, that the largest discounts go to payers that have greatest control over market share, the

conventional wisdom is that Kaiser gets among the deepest discounts, because Kaiser, as a staff-model health maintenance organization whose physicians work only for Kaiser, can enforce formulary adherence and steer utilization toward preferred drugs. By contrast, most private payers have limited ability to enforce their formularies and influence the prescribing practices of independent physicians because each payer's patients account for a small fraction of each physician's practice.

### Specialty drugs

The tiered formulary approach works reasonably well for large classes with several drugs that are close clinical substitutes. However, it works less well for specialty drugs and other classes with few close substitutes. 'Specialty drugs' refer to relatively high-priced drugs used to treat complex diseases for which most prescribing is done by specialist physicians, such as cancer, rheumatoid arthritis, multiple sclerosis, and all rare diseases. Even specialty drugs for the same indication often differ in efficacy and tolerability for individual patients, such that doctors and patients are unwilling to accept payer control over clinical choices. Over the past decade, biopharmaceutical innovation has increasingly shifted toward such specialty drugs, including many biologics that each has distinct risks and benefits. For such specialty drugs, PBMs' only tools to control spending are high patient cost-sharing and/or prior authorizations and step edits, to assure that the patient tries any cheaper alternatives first. These mechanisms at most control utilization, but have little direct effect on price. The limited control of payers over the price of specialty drugs is one factor making these drugs a more attractive target for pharmaceutical R&D compared to primary care therapeutic classes with close substitutes and potential genericization.

Medicare PDPs have taken the lead in placing pharmacy-dispensed specialty drugs (which Medicare defines as drugs that cost US$600 or more a month) on a fourth 'specialty' tier with a 25–33% coinsurance, and PBMs are increasingly following this approach. These high coinsurance percentages applied to very expensive drugs potentially imply patient cost-sharing of hundreds of dollars per month. Simple insurance theory suggests that such high patient cost-sharing may imply inappropriately high financial risk for patients and make patients highly price sensitive (and noncompliant), which might constrain manufacturer prices. However, in practice, the majority of patients are protected from such high cost-sharing by other features of their coverage or by manufacturer assistance programs. Specifically, low income seniors are protected from most cost-sharing by Medicare Part D's low income subsidy, and all seniors are protected by the catastrophic stop-loss on Part D cost-sharing, which in 2013 is US$4750 per year, after which the patient pays at most 5% of the drug price (0 for Medicaid-eligibles). Moreover, manufacturers are required to give Medicare patients a 50% discount while they are in the coverage gap ('doughnut hole') where they must pay the full drug cost. These discounts are ignored in calculating beneficiary's out-of-pocket expenses, so effectively they reach the stop-loss after lower cost-sharing. Some private patients may also face high cost-sharing and some currently have no catastrophic stop-loss. For such patients, manufacturers increasingly provide patient assistance programs (PAPs) for low income patients and cost-sharing coupons for other patients (such coupons are illegal for Medicare patients).

Thus although patients nominally face high cost-sharing for specialty drugs, in practice actual marginal cost-sharing is often minimal due to the combination of supplementary insurance through Medicaid and other private coverage, stop-loss limits, copay coupons, and patient assistance programs. In that case, cost-sharing is ineffective at constraining manufacturer prices for specialty drugs. There is little robust evidence on effects of this recent high cost-sharing for costly, specialty drugs, and obtaining reliable estimates is difficult if those who truly do face the 25–30% coinsurance simply forego the treatment. However, it seems likely that for an increasing fraction of new drugs, patient costsharing, which is the main approach to constraining prices in the US, cannot simultaneously constrain manufacturer pricing and enable appropriate patient use.

The fact that Medicare PDPs typically have significantly higher copayments for nonpreferred brand drugs than private PBMs, and more PDPs use specialty tiers with a 25–30% coinsurance for specialty drugs, suggests that PDPs' increasing use of these cost-sharing strategies may partly reflect the greater financial and adverse selection risk born by PDPs, due to three factors. First, to incentivize PDPs to control costs, by law the PDP is at risk for 15% of a patient's cost beyond the Medicare catastrophic threshold (US$6955 in 2013). By contrast, PBMs are not directly at risk for the drug spending of their enrollees, rather, they are reimbursed a fee per script and retain a fraction of the discounts they negotiate. Second, PDPs face greater adverse selection risk because most Medicare beneficiaries can choose between several stand-alone PDPs. If one PDP in an area were to offer more generous coverage of specialty drugs, it might attract a disproportionate share of the patients who need these and other drugs. By contrast, each private employer offers their employees only one PBM, hence that PBM does not face adverse selection within the employee pool. Third, by law Medicare PDPs are exempt from tier exemption requests for drugs on a specialty tier, hence use of a specialty tier may reduce the administrative cost burden of exemption requests for PDPs, which would likely be significant if the PDP were to place some specialty drugs on a preferred tier while putting others on a nonpreferred tier with very high cost-sharing.

### Medicaid

Unlike the Medicare Part D drug benefit, which is operated by private sector entities that use similar tiered formularies and negotiated discount strategies to private PBMs, the federal-state Medicaid program uses mandatory rebates. Because Medicaid beneficiaries are low income families with children, seniors and the disabled, even modest patient cost-sharing may lead to noncompliance. Rather than use tiered cost-sharing, since 1990 Medicaid has required manufacturers to give a mandatory rebate equal to the greater of 15.1% off the AMP (which is the manufacturer's average price charged to the private sector, including discounts) or the 'best price' (largest rebate) given to any private payer. For generics, the mandatory Medicaid rebate was a flat 11%, unrelated to discounts to other payers. When Medicare Part D was established in 2003, drug coverage for 'dual eligible' seniors (who are eligible for both

Medicaid and Medicare) was exempted from these Medicaid rebates, and rebates to Medicare PDPs were exempted from the definition of 'best price.' Under the Affordable Care Act of 2010 (ACA), the minimum Medicaid rebate on brand drugs was increased to 23.1% (13% for generics) and Medicaid Managed Care Organizations are required to pay this rebate on Medicaid-eligible enrollees.

By requiring that manufacturers of brand drugs give to Medicaid the largest discount they give to any private purchaser, Medicaid's 'best price' rule effectively raised the cost of giving discounts that exceed the mandatory minimum Medicaid rebate (15.1% before 2010, now 23.1%) to private payers. Manufacturers rationally give discounts to customers who use formularies to create elastic demand. But paying the government a rebate for Medicaid usage has no effect on drug utilization by Medicaid patients, as the rebate is unrelated to preferred formulary status or incentives of patients or prescribers. Therefore, from the perspective of manufacturers, tying a mandatory rebate to Medicaid to a discount given to private payers reduces the overall elasticity of response to private rebates beyond the mandatory minimum, which is now the weighted average of the (presumably elastic) response of the private enrollees and the totally inelastic response of Medicaid enrollees. Thus, the Medicaid best price requirement reduced manufacturer willingness to give discounts to private payers in excess of the mandatory minimum Medicaid rebate, particularly for drugs with relatively high usage by Medicaid patients.

Empirical studies have confirmed that private sector rebates declined in response to this Medicaid best price. When Congress established Medicare Part D, discounts given to Medicare PDPs were explicitly excluded from the Medicaid best price calculations, in order to encourage manufacturers to give deep discounts to PDPs. The 2010 increase in the mandatory minimum Medicaid rebate to 23.1% means that the 'best price tax' now only applies to private sector discounts larger than 23.1%, hence increased discounting up to this 23.1% threshold is expected, ceteris paribus.

Mandatory Medicaid rebates may also create an incentive for manufacturers to raise the price from which the rebate is calculated. Anticipating this effect, Medicaid requires an additional rebate equal to the cumulative excess increase in a drug's price over the consumer price index (CPI), since the drug's launch. This 'excess-CPI rebate' has not been sufficient to eliminate increases in manufacturer prices for onpatent drugs faster than the CPI in recent years. Thus, the Medicaid mandatory rebate provisions have probably contributed to both higher list prices and smaller discounts for private sector payers. Consistent with this, Duggan and Scott Morton (2006) found that drugs with a higher Medicaid share experienced larger increases in prices (including discounts) to private payers.

## Physician-Dispensed Drugs

Drugs that require infusion or injection, including many cancer drugs and other biologics, are dispensed in physician clinics. For Medicare patients, physician-dispensed drugs are covered under Medicare Part B (which covers physician services) rather than Medicare Part D (which covers pharmacy-dispensed outpatient drugs). Before 2005, Medicare reimbursed dispensing physicians at 95% of AWP, an unregulated list price, and most private payers followed suite. This reimbursement rule created incentives for manufacturers to compete for market share by offering discounts off AWP to physician practices, in order to increase the margin between their acquisition cost and the reimbursement. Evidence has confirmed that financial incentives influenced physician prescribing choices (Epstein and Johnon, 2012). Lawsuits have also alleged that some manufacturers raised AWP in order to increase the physicians' margin. The margin accrued to dispensing physicians because Medicare and other payers did not attempt to reduce their reimbursement price to capture the discounts. This contrasts to payer response to a similar incentive system for generics in the US (see below) or in Japan. In Japan, manufacturers similarly offer discounts below the reimbursement price to physicians who dispense drugs, as an inducement to use their drugs. However, the Japanese payers (partially) capture these competitive discounts by reducing their reimbursement price paid to dispensing physicians, based on a biennial audit of actual acquisition prices.

Following substantial litigation over the alleged manipulation of AWP and large margins given to dispensing physicians, in 2005 Medicare changed its Part B reimbursement, intending to align reimbursement more closely to actual acquisition prices. Under the new rules, Medicare Part B reimburses dispensing physicians at the manufacturer's Average Selling Price (ASP) plus a six percent margin. Manufacturers are required to report each drug's ASP quarterly, which is defined as the volume-weighted average manufacturer selling price, including all discounts, lagged two quarters. In the short run, this shift to ASP + 6% reimbursement reduced the prices that Medicare Part B pays for drugs. But in the longer run, the ASP + 6% formula eliminates incentives for manufacturers to compete on price, because any discounts offered to physicians in quarter T reduce the ASP and hence reduce the reimbursement price and the 6% margin for all physicians in period T + 2. Moreover, the ASP + 6% reimbursement rule creates perverse incentives for manufacturers to compete by charging high rather than low prices, because a higher price offers a larger margin to the dispensing physician. The main impact of the perverse ASP + 6% incentives is for higher launch prices. Raising prices postlaunch by more than one or 2% a quarter risks squeezing physicians' margins because their reimbursement only rises after a two quarter lag. Because many private payers follow Medicare reimbursement, this Part B reimbursement rule and its perverse incentives have probably contributed to higher prices for oncologics and other biologics in the US.

Despite the perverse price-increasing incentives created by Medicare's ASP + 6% reimbursement rule, two factors may provide some constraint. First, as prices for these drugs rise and increasingly exceed $40 000 or even $100 000 per treatment course, physicians that 'buy-and-bill' face significant cash flow cost and even risk, if reimbursement is uncertain. Thus, uptake of some very costly drugs has initially been slower than expected, at least until payer reimbursement is assured. Second, the 20% Medicare Part B patient cost-sharing should in theory act as some constraint on manufacturer

prices. However, in practice most seniors are protected from this cost-sharing by supplementary insurance through either Medicaid (for low income seniors) or Medigap (employer-sponsored or privately purchased). Similarly, although private insurance plans usually have cost-sharing, most private patients have a stop-loss limit on annual out-of-pocket costs and such limits become mandatory under the PPACA. Further, for uninsured or privately-insured patients who face significant out-of-pocket costs, most manufacturers offer copay coupons or patient assistance programs (copay coupons are illegal for Medicare patients). As a last resort, although physicians cannot waive copayments without risk of violating antikickback statutes, they can refer patients to a hospital outpatient department, which may waive copayments. Thus similar to the situation for pharmacy-dispensed specialty drugs, most patients are protected from the nominally high cost-sharing on physician-dispensed drugs. If so, manufacturers face highly inelastic demand and little if any constraint on pricing.

## Hospital Inpatient Drugs

Drugs that are dispensed as part of an inpatient episode are generally not reimbursed separately but are included in the bundled diagnosis-related group (DRG) payment for the hospital admission. Medicare updates its DRG payment rates over time, based on national average costs, by DRG, as reported in hospital cost reports. Private payers negotiate various forms of bundled payment for inpatient hospital care, with private rates generally above Medicare rates but also no separate reimbursement for inpatient drugs. Thus in the short run the cost of new inpatient drugs (or price increases for existing drugs) are borne by hospitals, with pass-through to payers with a lag, if/when the drug becomes standard of care and reflected in average cost for the DRG. In exceptional circumstances, a very high-priced new drug may be reimbursed separately from the DRG temporarily, until its cost is included in an increased DRG payment.

This system of bundled payment for inpatient admissions puts hospitals at risk for inpatient drug costs in the short run. Hospitals therefore have incentives to be price sensitive in designing their formularies and negotiate price discounts with manufacturers in return for preferred formulary placement. Larger hospital systems that negotiate on their own behalf and can enforce formularies have greater bargaining power and get larger discounts than smaller hospitals and those that bargain indirectly through group purchasing organizations (GPOs). However, as with PBMs/PDPs, hospitals have little or no leverage to negotiate discounts for drugs that have few or no close substitutes, which includes many specialty drugs.

## Generics

In 2011, 80% of all prescriptions were dispensed as generics in the US, and for compounds with a generic available the generic share of scripts was 94%. By contrast, generics account for only 27% of dollar value of sales (IMS, Health Informatics Institute, April 2012). This high generic share by volume reflects both the large percentage of drugs for which patents have expired (or been successfully challenged) and the rapid conversion to generics once they become available. The much lower generic share of sales by value reflects the low generic prices, relative to originator prices. Compared to most other high income and some middle income countries, generic penetration is more rapid and generic prices are lower absolutely in the US (Danzon and Furukawa, 2006).

The high-generic volume share and low generic prices in the US relative to most other industrialized countries reflects several institutional features that interact to produce a highly price-competitive generic market in the US. First, the statutory rules governing generic entry are designed to reduce costs of entry and encourage patent challenges. Under the 1984 Hatch Waxman Act, generic versions of chemical drugs can file an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA). By demonstrating bioequivalence to the originator drug, generics can be approved as substitutable for the originator, while simply referencing the originator's clinical trials to establish safety and efficacy, rather than doing new clinical trials. This dramatically reduced the cost and time required for generic approval. The Hatch-Waxman Act also incentivized generics to challenge patents, by offering a 180-day market exclusivity to the first completed ANDA that successfully challenges the originator's patents (a Paragraph IV filing). This FDA requirement, that generics demonstrate bioequivalence to the originator, is the basis for confidence on the part of physicians, consumers, and payers that generic substitution by pharmacists is safe. Although bioequivalence and substitutability apply to the great majority of small molecule drugs, certain compounds are considered too high risk or too difficult to characterize to permit safe substitutability.

Second, payers incentivize patients to accept generics by structuring formularies with low copayments (US$0–10) for generics, whereas the patient may have to pay the full price or a nonpreferred tier copayment for the originator. Third, the rapid uptake of generics reflects the rules and financial incentives for pharmacy substitution. The great majority of states have adopted the default rule that pharmacists may substitute any FDA-substitutable generic, even if the physician writes the script for the originator brand, unless the physician explicitly requires that the brand be dispensed. Thus the pharmacy decides which version of the compound to dispense, if substitutable generics are available and the physician does not require the brand. Payers incentivize pharmacies to prefer low-priced generics by reimbursing the same 'maximum allowable cost' (MAC) regardless of whether they dispense a generic or the brand. The MAC is similar to a reference price used in many other countries. Payers generally set the MAC at a relatively low generic price, though methodologies for setting and updating MACs vary. Because the pharmacy captures the margin between the MAC reimbursement and the acquisition cost of the drug, generic manufacturers compete by offering discounts on the acquisition cost to increase this margin. Over time, the payers revise the MACs downward to capture some of this discounting on generic prices, which leads to further price cutting by generics. Thus once multiple generics enter for a given drug, aggressive price competition and rapid generic erosion of brand sales occur, because pharmacy substitution is incentivized by MAC reimbursement and patient acceptance of generics is incentivized by low cost-sharing.

In a pharmacy-driven generics market such as the US, where generics are required by regulation to be bioequivalent and pharmacies are authorized and incentivized to substitute, generics have little incentive or possibility to use branding to create a perceived quality differential. Generics are therefore unbranded and compete on price and service to their highly-price conscious pharmacy customers. By contrast, in countries where generics are not required by regulation to be bioequivalent, which includes most middle and lower income countries, actual and perceived quality differences can play a big role in choice between supposedly similar products. In such regulatory regimes, there are often multiple 'similar' or 'copy' products that claim to have the same active ingredient as the originator brand, but there is no assurance that they in fact have exactly the same active ingredient and an equivalent therapeutic effect, quite aside from issues of substandard or counterfeit products. Given such intrinsic quality uncertainty, generic producers have strong incentives to sell branded generics, where brand becomes a proxy for quality. With quality uncertainty, physicians prescribe by brand – either the originator brand or a specific branded generic – and pharmacy substitution is not legally authorized, although it may not happen in practice. Branded generics are promoted and detailed to physicians, just like originator brands, which adds significant marketing costs. Generics also promote their brand to pharmacies in countries where pharmacies dispense without a prescription. In such branded generic markets, competition between generics focuses on brand as a proxy for quality, not price. On the contrary, branded generic prices are relatively high, compared to the originator price in that country and compared to US generic prices, in part because a low price might be interpreted as a proxy for low quality. In physician-driven, branded generic markets, originator brands usually retain a significant market share even after patent expiry, in contrast to the virtually complete originator brand erosion in the US.

Generic prices have traditionally been lower in the US than in major European markets, including Germany, France, and Italy, in contrast to onpatent brand prices which are higher in the US. But since the late 1990s most western European countries have changed their regulatory and reimbursement rules to permit and incentivize pharmacy substitution and generic price competition, which has increased savings to payers from generics. In Germany, since 2007 payers are authorized to contract directly with generic companies, using competitive tenders to drive and capture savings from price competition. So far, branded generics markets remain the norm in Latin America, Africa, and most Asian countries, including China. In such countries, generic quality is uncertain and some branded generic prices are relatively high. Some multinational originator companies are entering these relatively high-margin, branded generic markets through licensing arrangements with branded generic producers. This strategy draws on their brand selling expertise and brand image. However, because this physician-driven branded generic model delivers only modest savings to consumers and payers, compared to the pharmacy-driven unbranded, price-competitive generics model of the US, it seems likely that the US unbranded, price-competitive generic model will eventually become the norm in most countries.

The relatively high concentration on the purchaser side of the US generic market probably contributes to low generics prices. As discussed earlier, the US retail pharmacy market has become concentrated into large chains and large national wholesalers purchase on behalf of independent pharmacies. These concentrated buyers purchase a sufficient absolute volume and market share to have significant leverage in price negotiations with generic suppliers. Because these large purchasers are the decisionmakers for (intramolecule) generic substitution, generic suppliers target their discounts to them in the first instance, whereas originator companies target discounts on onpatent drugs to payers or PBMs who are the decisionmakers with respect to formulary design and (intermolecule) therapeutic substitution. The system relies on competition at the retail pharmacy and PBM levels to pass on these discounts on generics and onpatent brands to ultimate payers and consumers.

Competitive pressure on generic prices also depends on number of generic competitors. Price competition is weaker when there are few generic competitors, which occurs in at least two instances. First, the Hatch-Waxman Act intentionally grants a 180-day exclusivity to the first ANDA generic to successfully challenge all relevant patents. During those 180 days, the originator typically maintains or raises its price, but may also launch an authorized (licensed) generic to capture some of the more price sensitive market. During this period of at most two generics, their pricing is typically approximately 60–80% of the originator price. By contrast, once the exclusivity period expires, if multiple competing generics enter, generic prices fall rapidly to 10–20% of the preexpiry originator prices. Thus, the much higher price and margin during the exclusivity period creates an incentive for generic firms to incur the significant litigation costs and risks in challenging patents. Second, more complex formulations and specialty drugs with small markets typically attract fewer generic competitors than oral formulations with large markets. With fewer competitors, generic prices and margins can remain relatively high.

## Brand Pricing after Patent Expiry

The evidence indicates that originator firms typically raise prices before and after patent expiry, rather than reduce price to compete with generics. One theory that accounts for such pricing is that the originator pursues a segmentation strategy (Frank and Salkever, 1992). In this model, before patent expiry, the originator selects the profit-maximizing price based on the weighted average of price elasticities of all customers in the market. After patent expiry, the more price elastic customers switch to generics, and the originator targets only the most brand-loyal, price-inelastic customers, which results in a higher, profit-maximizing price. This model was appropriate in the early 1990s, when many consumers in the US paid out-of-pocket for drugs and pharmacy substitution was less the norm. It is also useful in understanding price competition in self-pay, branded generic markets in emerging markets. However, in the current US context where most consumers have tiered insurance coverage and most states have pharmacy substitution, the price-inelastic market segment is very small. Moreover, during the 180-day exclusivity period, some originator firms have given

some payers sufficiently high discounts to get the originator drug placed on the generics tier, such that consumers have no reason to prefer generics. This strategy rarely continues beyond the 180-day exclusivity period, presumably because the discount required to compete on price with generics becomes too large.

A second rationale for originators to raise price before and after patent expiry is to encourage patients and payers to switch to a new formulation or a follow-on version of the drug that still enjoys patent protection or data exclusivity and therefore is not subject to generic competition. For example, before the patent-expiry on the standard twice-a-day tablet formulation, the firm may launch a once-a-day, timed release version of the drug that receives some market exclusivity for doing new clinical trials. By raising the per-day price of the old tablet such that it exceeds the price of the new delayed release formulation, the firm encourages payers and patients to prefer the new formulation. If the script is written for the exclusivity-protected formulation, pharmacies cannot substitute a generic because substitution is permitted only within the identical formulation. Such launch of a new formulation or product, together with price increase on the older formulation, is the most effective defense against generic erosion on a patent-expired drug in the US.

## Biosimilars

In contrast to the price-competitiveness of generics for small molecule (chemical) drugs, biosimilar versions of biologics are unlikely to compete aggressively on price in the US, for several reasons. First, the higher clinical trial and manufacturing costs of biosimilars are expected to result in fewer competitors. Second, the greater complexity of biologics molecules means that the FDA is unlikely to declare them to be substitutable with the originator or with each other, except possibly for the simplest biologics. If pharmacies cannot substitute, physician-prescribers will be the decisionmakers. Thus biosimilars in the US will likely be branded products, detailed to physicians and marketed on brand rather than price, more like branded originator drugs than unbranded, price-competitive chemical generics. It is possible that payers may use tiered formularies, tiered cost-sharing, step edits, and prior authorizations to attempt to drive utilization toward preferred biosimilars, in which case they may extract significant discounts. However, this would be a departure from their current passive role with regard to use of biologics and other specialty drugs.

For biosimilars that require infusion in a physician office, the nonsubstitutable biosimilar would receive a different reimbursement code from the originator and have a separate ASP. Under current Part B reimbursement, this could discourage price competition by biosimilars, because reducing the price would reduce the physician's margin. The PPACA therefore provides that the 6% margin would be calculated on the originator's ASP, regardless of whether the originator or the biosimilar is dispensed. This eliminates any financial incentive for physicians to prefer the originator versus the biosimilar, but still provides at best weak incentives for biosimilars to compete on price.

As availability of clinically similar biologics increases, including both biosimilars and 'bio-betters,' payers may attempt to change reimbursement rules for specialty drugs in order to stimulate some price competition and value-based purchasing. Some US payers are requesting comparative effectiveness data and evidence of outcomes as a condition of favorable formulary placement. Some payers are also starting to adopt bundled payments for episodes of care that includes drugs. If providers are at risk for the cost of drugs as part of a care episode, they have strong incentives for cost-conscious choices with respect to volume and type of drugs. In addition to DRGs for inpatient care, Medicare has adopted bundled payment for dialysis, and at least one private payer uses bundled payment for certain episodes of cancer care. Therapeutic reference pricing, as used in Germany for certain classes of drugs, has also been mentioned in the US, but so far seems unlikely.

## Discussion and Conclusions

The US reimbursement system for pharmaceuticals, which permits manufacturers to set prices freely and relies on patient cost-sharing and health plan bargaining to drive discounts off these prices, has been reasonably effective at constraining prices for drugs in crowded classes with clinically close substitutes. Once generic entry occurs, pharmacy substitution and reimbursement incentives assure low generic prices and rapid generic erosion. However, for specialty drugs – which typically have few close therapeutic substitutes and include many biologics – current insurance reimbursement and cost-sharing arrangements create incentives for manufacturers to set high prices with few constraints, especially for physician-dispensed drugs. Although patients nominally face very significant cost-sharing, such cost-sharing is ineffective at constraining manufacturer prices due to supplementary insurance, stop-loss limits, manufacturer coupons, and patient assistance programs. The ACA stop-loss limits will further reduce the elasticity of demand facing manufacturers for high-priced drugs. Stop-loss limits provide appropriate financial protection for patients but imply that other payer constraints on prices may be appropriate.

After double-digit growth rates in the late 1990s, the rate of growth of drug expenditures has moderated since the early 2000s in the US. This is due largely to savings from patent expirations and consequent generic erosion on many high-volume drugs, combined with a modest flow of new drugs that have generated insufficient new sales to replace sales lost to patent expiries. The resulting savings to payers and consumers have created budget headroom for higher prices on newly-launched drugs and substantial postlaunch price increases. However, this will change as the wave of patent expiries tapers off around 2015 and if the recent uptick in number of new drug approvals continues.

Thus, the combination of an increasing share of new drugs (biologics, orphan drugs, and other specialty drugs) for which traditional PBM/PDP-tiered formulary mechanisms work poorly, with more (and appropriate) stop-loss limits on patient cost-sharing under the ACA, make some change in reimbursement mechanisms increasingly likely. Although none of the ACA provisions relate directly to pharmaceutical

reimbursement, the inducements for bundled payments and outcomes-based reimbursement for hospital and physician providers may eventually spill over to pharmaceuticals. If payers require evidence of comparative and cost-effectiveness, as an input for making coverage and reimbursement decisions, this would incentivize manufacturers to set prices commensurate with incremental health benefit delivered. This form of flexible and indirect price constraint, that aligns prices with incremental health benefit, provides more appropriate incentives for R&D and for efficient use of drugs than either the status quo or alternative price control mechanisms that have been proposed.

*See also*: Biosimilars. Markets with Physician Dispensing. Patents and Regulatory Exclusivity in the USA. Pharmaceutical Marketing and Promotion. Pharmaceutical Pricing and Reimbursement Regulation in Europe. Regulation of Safety, Efficacy, and Quality

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