Dissecting drug pricing: Supply chain, market, and nonmarket trends impacting clinical dermatology

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In the United States, drug costs account for approximately 10% of health care expenditures and are expected to grow over the next decade.[1] Because of a combination of rising drug prices, increased out-of-pocket costs, and increased use of specialty drugs, a growing number of Americans cannot afford their medications. This issue is particularly relevant for the treatment of skin diseases, where retail prices of select brand name dermatologic medications increased an average of 363% in real terms between 2009 and 2015, while the general and average pharmaceutical inflation rose only 11% and 23%, respectively.[2,3] In this article—part of a health policy series reviewing a wide-range of policy topics impacting clinical dermatology[4]—we provide an overview of how drug prices are set, with an emphasis on microeconomic factors that drive their complexity in the United States, and discuss trends in drug pricing that are relevant to both the present and future delivery of dermatologic care.

ENTITIES IN DRUG PRICING AND THE FLOW OF REBATES

Multiple entities and factors influence the price of a drug (Fig 1). Patients and employers hire insurance companies, which pay pharmacy-benefit managers (PBMs). In turn, PBMs pay pharmacies, which buy drugs from wholesalers, which buy drugs from manufacturers. Drug manufacturers, in effect, must pay PBMs in order to obtain access to formularies and tiering. These payments are delivered in the form of rebates, and some of this money may be passed on to insurance companies and patients.

Rebates are postsale reimbursements paid to PBMs and insurers by drug manufacturers that can be used to incentivize the use of certain drugs. In some cases, rebates have been used to determine which drugs are included in a formulary and on which "tier" a drug is prioritized. The average rebate is estimated to be 20% off the list price, but may reach upwards of 60%.[5] In competitive drug markets, where there are many drug options to choose from, rebates can be sizable because PBMs and insurers can elect to cover some products and not others; as such, the presence of multiple

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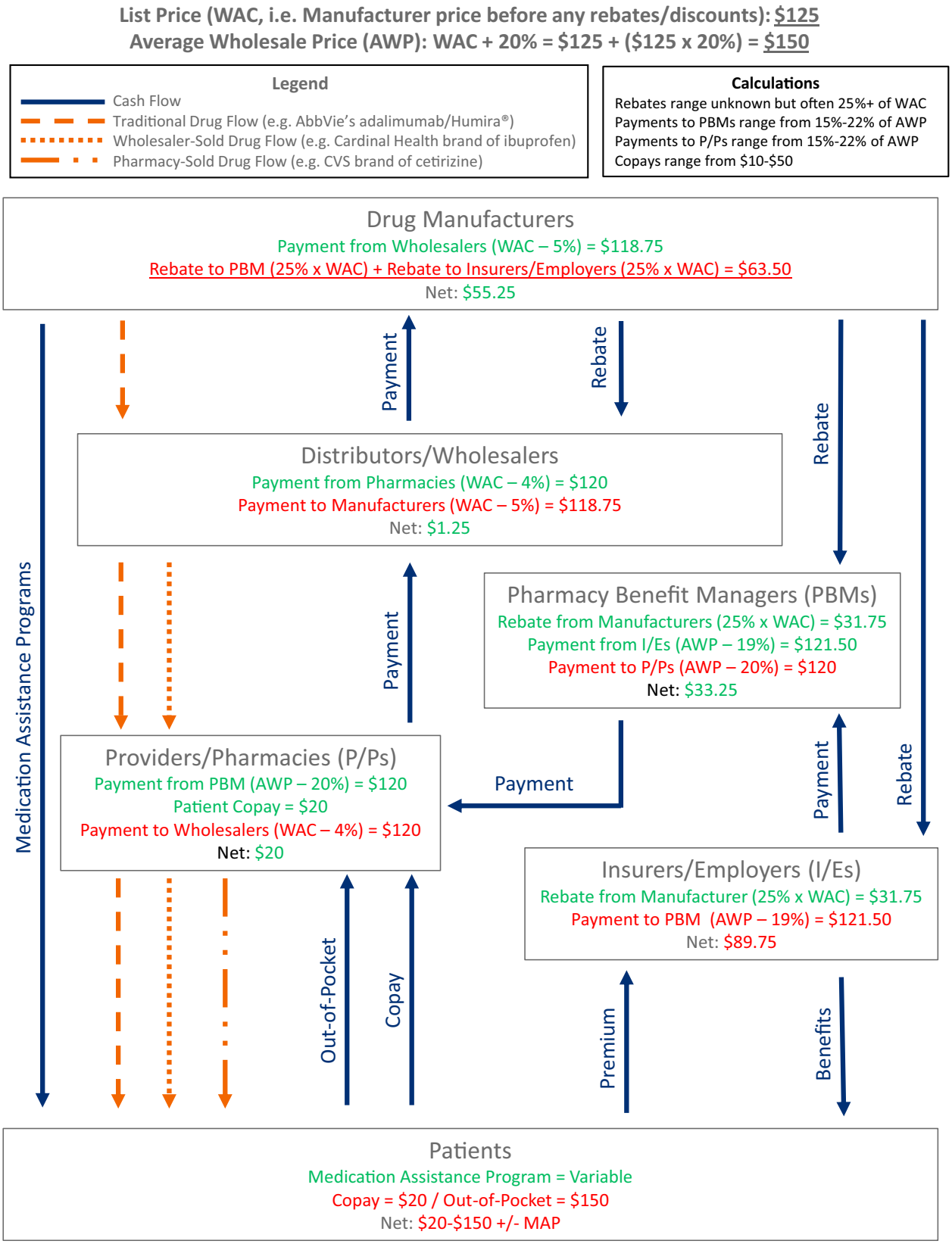

Fig 1. Simplified figure originally published by Kaiser Health News[75] showing the complex cash flow of prescription drugs from manufacturing to patient acquisition. For each entity in the supply chain, green font denotes its cash inflow, while red font denotes its cash outflow.

manufacturers with head-to-head competitors are associated with higher class-level rebates.[6]

PBMs leverage their demand aggregation and control of market access to negotiate rebates based on drug list prices. Rebate details are usually only partially disclosed to insurers and patients.[7] Therefore, rebates, which are often instrumental drivers in drug tiering, drug pricing, and preferred formularies selection, carry a substantial lack of transparency,[8] and these drug rebates drive PBM revenue. The retrospective nature of rebates prevents final drug prices from being accessible at the time of distribution[7] or even when a drug is added to a formulary. Formulary design is therefore not necessarily based on clinical data or cost effectiveness. Rather, PBMs and insurers may design their tiered formularies based on the rebates a drug manufacturer awards, which may lead to "auctioning" of formulary access.[9] In extreme cases, a costly drug may be in a preferential tier when cheaper, safer, or more effective generic alternatives are available.[9] Rebate reliance may also reduce the value proposition for cheaper drugs manufactured by small companies, which are less attractive to both PBMs, who would receive reduced rebates, and wholesalers, who would receive proportionally smaller fees because of lower volumes.

Rebates from drug manufacturers to PBMs grew approximately 5 times faster than pharmaceutical firm net revenues between 2011 and 2016[10] and represent a major key to understanding drug price increases.[11] Consequently, rebates have become a focus across multiple US government levels, resulting in US Food and Drug Administration[12] and state legislative initiatives.[13] The complexity of this system, with money flowing in both directions, obscures true costs and real prices.

Drug manufacturers

Drug manufacturers (ie, pharmaceutical companies) set an initial drug price, known as the wholesale acquisition cost or list price. (Common drug pricing terms and definitions are shown in Table I.) Brand name drugs account for 72% of drug spending but only 10% of all dispensed prescriptions in the United States.[14] For brand name medications, patents confer pharmaceutical companies a time-limited market exclusivity (ie, a monopoly) during which time they can set a price that cannot be undercut by competitors with the same drug. (Competitors with other drugs in the same therapeutic class, also known as "brand–brand competition," could still technically undercut price, but brand–brand competition has not been shown to be effective in lowering list prices.[15]) One justification for the high prices of brand name drugs is the need to recuperate the costs and risk of research and development (R&D). However, high R&D costs are not solely responsible for rising drug prices,[16,17] and 1 aggregate study found no evidence of an association between R&D costs and prices.[18] Nevertheless, developing a drug is expensive, and a manufacturer must bear the liability costs, which are substantial in the United States. Sectors driven by intellectual property and protection, such as the pharmaceutical industry, may require higher profitability because of increased financial risk.

Patents and exclusivity drive legal pharmaceutical protection in the United States. Patents protect specific components of a drug, such as formulas, delivery systems, or packaging. They are granted by the Patent and Trademark Office for 20 years from the date of filing and can be bestowed before, during, or after drug approval. Exclusivity grants rights for a drug itself. It is conferred by the FDA upon the drug approval and its duration varies based on its categorization.[19] Standard, brand name drugs receive 3 or 5 years of exclusivity depending on the novelty of their active ingredients,[20] and biologic drugs, synthesized from living organisms, receive 12 years of exclusivity.[21] "Orphan drugs," which target rare diseases, receive exclusivity of ≥7 years.[22] Rare diseases are statutorily defined as those diseases or conditions that affect <200,000 individuals in the United States or those diseases that affect >200,000 individuals but for which the cost of making and marketing a drug cannot be reasonable recaptured from sale of the drug.[23] Dermatologic examples have included rituximab for the treatment of pemphigus vulgaris and adalimumab for the treatment of moderate to severe hidradenitis suppurativa.[24]

Exclusivity most often implies market exclusivity, which protects marketing rights for a drug. However, another form of exclusivity, data exclusivity, prevents prospective generic manufacturers from using the same clinical data submitted by the original owner,[25] thereby impeding the establishment of generic equivalence and hindering competition.

After legal protections expire, the introduction of generics can increase competition, lowering overall prices for a medication. Nevertheless, multiple studies have found that generic price increases can still occur in the setting of reduced competition, where only a limited number of generic manufacturers produce a drug.[26-28] True market competition must exist to support a functioning generic market.

To prevent the introduction of generics, manufacturers may engage in various strategies to extend the effective patent life. This can be done by

Table I. Summary of terminology and definitions used by the pharmaceutical industry

Terminology	Definition
Prices	
Wholesale acquisition cost	The estimated drug price paid to a drug manufacturer by a wholesaler; it does not include discounts or rebates
Average manufacturer price	The estimated drug price paid to a drug manufacturer by a wholesaler, pharmacy/provider, or other direct purchase; it includes discounts and rebates
Average sales price	The weighted average of all drug prices paid to a drug manufacturer by all purchasers (wholesalers, pharmacies/providers, insurers/employers, patients)
Average wholesale price	The estimated drug price paid to a wholesaler by a pharmacy/provider
Average actual cost	The average price paid by a pharmacy for a drug issued from inventory
Usual and customary price	The average of all drug prices paid to a pharmacy by all purchasers (insurers, employers, and patients)
Dispensing fee	The fee paid to a pharmacy to cover overhead costs
Estimated acquisition cost	The estimate of the drug price paid by a provider
Federal upper limit	The price celling for a drug, set by the CMS
Maximum allowable cost	The price celling for a drug, set by state law
Best price	The lowest drug price offered to any purchaser in the United States
Discount	A lowered drug price negotiated with a drug manufacturer
Rebate	A payment paid by a drug manufacturer to purchasers based on the volume purchased
Coupon	A lowered drug price provided to a purchaser at the point of service, such as at a pharmacy
Formulary	A list of drugs approved to be prescribed by a specific provider
Copay	The price that an insurance holder pays for a specific drug, which is typically lower than the normal drug price
Premium	A baseline fee paid by an insurance holder to an insurer
340B price	A discounted drug price available for specific drugs for specific clinics that meet specific, federal low-income patient criteria
Practices	
Patent	Exclusive selling rights for a specific drug for a specific amount of time
Evergreening or life cycle management	A strategy to extending drug patent protection or delay drug selling competition
Submarine patent	A patent application that is intentionally delayed to activate at a later date, extending the overall patent protection time
Risk Evaluation and Mitigation Strategies	An FDA regulation to ensure safe drug distribution that can be used to hinder drug selling competition
Clawback	A profit incurred by an insurer when a copay exceeds the normal sale price
Medication Assistance Program	A discounted drug price provided directly to drug consumers by the original drug manufacturer
Previous authorization	A regulation designed to reduce spending by requiring Insurance approval before a nonformulary drug can be prescribed
Step therapy	A regulation designed to reduce spending by requiring a trial of a specific drug or drug class before alternative drugs will be reimbursed

CMS, Centers for Medicare and Medicaid Services; *FDA*, US Food and Drug Administration.

complex patents, legal maneuvers—and sometimes direct payouts—to delay competition even after generic competition approval or patent expiration.[29] Euphemisms for these strategies are "life-cycle management" or "evergreening."[30] One strategy involves filing new patents for the coating, method of administration, or formulation of the drug before general patents expire.[31] These minimal modifications renew patent protection after a biochemical formula has expired, delaying the entry of generics.[32] Furthermore, submarine patents[33]—patents whose issuance and publication are intentionally delayed by the applicant—are used to ensure that official approval is not granted until years after the original filing and thus to extend the effective date of exclusivity. For instance, etanercept (Enbrel) has been marketed since 1990, but its manufacturer, Amgen, was granted a patent in 2012 that guarantees protection until 2029.[34] Firms may even initiate patent litigation cases and appeals that they are projected to lose in order to stall for more

revenue-generating time for their brand name drugs.[35]

In some cases, firms may also leverage governmental regulations to stifle competition. Roche was cited by the FDA for delaying generic competition for isotretinoin (Accutane) through "gaming" tactics.[36] As a further example, Celgene used the US government's Risk Evaluation and Mitigation Strategies (REMS) program to create 14 new distribution-related patents and prolong exclusivity for thalidomide,[30,37] even though thalidomide was developed in the 1950s and, with its original patent issued in 1954 long expired, is technically available as open access.[37] REMS was designed to ensure safe usage of potentially harmful drugs[30]; however, REMS can also be deployed to block drug sample access for generic competitor equivalence tests, reducing competition and leading to high prices. The unnecessary costs and lost price reduction opportunities created by REMS and similar programs have been projected to cost the US health care system $5.4 billion annually,[38] and it is unclear if the benefits of patented REMS programs outweigh their costs. In response, multiple pieces of legislation from both major political parties relating to REMS reform have been introduced in Congress.[39,40]

Two categories of generic medications exist: small molecule drugs and biosimilar drugs. Small molecule generic medications, such as steroids, are simple chemical compounds, while biosimilar drugs are complex, biological formulations that are equally therapeutic but not identical to their analog. Though cheaper than their branded counterparts, biosimilar drugs have faced slow adoption in the US market because of higher costs, stricter legal and regulatory barriers, and greater provider concern for efficacy and safety.[41] Within dermatology, biosimilars for 2 blockbuster drugs, adalimumab (Humira) and etanercept (Enbrel), have been approved in the United States but are not currently being sold because of litigation and patent protection barriers.[42]

Distributors/wholesalers

Distributors, or wholesalers, buy drugs from a manufacturer and then sell smaller volumes to pharmacies and providers. Some of the largest US distributors include McKesson, AmerisourceBergen, and Cardinal Health. Distributors usually supply inventory, physically deliver the products to locations around the country, and share the risks, costs, and logistical responsibilities of product delivery with the manufacturer, including the return of unused medications. Wholesalers are compensated primarily based on the list price of the drug.

PBMs, insurers, employers, and patients

PBMs have become a major part of the pharmaceutical supply chain and are highly profitable.[43] PBMs aggregate demand from drug consumers, including patients, providers, employers, and insurers, to leverage economies of scale and theoretically lower medication prices and rebates. They negotiate with drug manufacturers to design formulary tiers, administer outpatient prescription drug benefits (including previous authorizations) for insurers and large employers, organize Medicare Part D benefits for the Centers for Medicare and Medicaid Services, manage pharmacy networks and distribution, and distribute drugs to patients through mail order programs.[8] The 3 main PBMs in the United States represent 80% of the market[44] and include Express Scripts (recently acquired by Cigna[45]), CVS Health (recently acquired Aetna[46]), and OptumRx (a branch of UnitedHealth Group). A consolidated PBM market with just 3 major players has resulted in further shifts in market power. First, dominant PBMs can negotiate higher rebates and have the market power to pass fewer savings on to insurers. Second, consolidated PBMs can increase spread pricing (ie, the difference between the amount that PBMs make from a rebate and the amount that PBMs pay to the pharmacy) by reducing the amount that is paid to pharmacies.[44,49] Finally, consolidated PBM markets have allowed PBMs to replace distributors with their own mail-order units.

Insurers and employers, who fund a large portion of insurance in the United States, assume the risk for health care costs in exchange for premiums and copays. For insurers and, secondarily, employers, opaque and retroactive rebates can confer financial advantages compared with directly reducing prices for patients. PBMs negotiate a rebate from the drug manufacturer that is typically a percentage of the full list price of a drug and pass a part of that rebate to the insurer in the form of a "discount," which in turn may theoretically result in a reduction of premium costs. In reality, much of the rebate is retained by PBMs as profit ("retained rebate"). Maximization of the retained rebate reduces neither insurance premiums nor copays. Therefore, rebates may only indirectly benefit patients.[44,47,49] In some situations, patients with high-deductible plans may pay the full list price for a drug, allowing the PBM and, secondarily, the insurer to keep any prenegotiated rebates, and in some cases, the PBM and insurer may pocket >50% of the price paid by the patient.[48] The percentage-based rebate system incentivizes PBMs to favor a higher list price, and therefore PBMs often grant formulary status to higher-priced drugs where

the percentage rebate (and thus PBM profit) is greater.[49]

At the pharmacy counter, insured patients are charged drug prices based on either a permutation of the wholesale acquisition cost or the net purchasing price billed to their insurance, which is set by the PBM and insurance as part of benefit design. In some cases, this baseline drug price is cheaper than the drug price with insurance and patient copays, and it would be cheaper to buy the drug outright with cash instead of using insurance. However, if the patient still uses insurance in this scenario, the insurer may retain the difference, known as a "clawback."[50] Before October 2018, insurance companies could use "gag clauses" to prevent pharmacists from informing customers if a drug would be cheaper to buy without insurance[51]; these gag clauses are now being outlawed. Furthermore, the complexity of the current system makes copay prediction nearly impossible.

Many manufacturers fund medication-assistance programs that provide free medications to qualifying patients, often limited by patient immigration status. Many firms also offer copay assistance programs to reduce patient out-of-pocket expenses.[52] Of note, pharmaceutical companies cannot reduce Medicare and Medicaid copays because of statutory requirements. However, drug manufacturer–financed charities that offer medication-assistance programs are often exempt from this restriction.[53] These programs have undoubtedly eased access to necessary brand name drugs; however, in the long term they may distort markets and drive patients to higher-cost options by removing any tiering or copay differentials that would otherwise incentivize doctors to prescribe and patients to take generic or lower-cost drugs when they are available.[54]

TRENDS IN DRUG PRICING

Higher drug prices benefit several stakeholders. Drug manufacturers such as Valeant—now Bausch Health—and Turing Pharmaceuticals have been scrutinized for raising prices on drugs for rare diseases.[55] However, clinicians have also been implicated in raising prices. For instance, in Medicare Part B, which uses a "buy and bill" model of reimbursement (ie, the clinician purchases the intravenous infusion first and then bills for it after it is administered in the clinic), clinicians profit from the "spread" between their purchase costs, which are generally much less than the list price, and Medicare reimbursement.[56]

Another trend across the drug supply chain has been consolidation. Many distributors have begun vertical integration to include direct sales of their own private-label drug lines, such as McKesson's Sunmark division.[57] Some PBMs and insurers have merged, such as Cigna and Express Scripts,[45] as well as CVS and Aetna.[46] Vertical mergers between PBM and insurers can result in the PBM differentially increasing drug costs of rival insurers and also create a barrier to entry for new PBMs and insurers. Likewise, vertical mergers between PBMs and pharmacies (eg, CVS–Caremark) may harm competition from other pharmacies by having the PBM preferentially steer service towards its own pharmacy[44,49] and facilitate an increase in differential spread pricing. It is not clear whether consolidation will create cost synergies and reduce prices as advertised, or whether these "megamergers" will create conflicts of interest that reduce competition, hinder smaller firms from entering the market, and ultimately increase prices.[58]

Health systems have also consolidated to increase bargaining power. In 2018, Intermountain Healthcare launched a joint venture of health care providers to form a nonprofit, generic drug company to combat rising generic drug prices.[59] However, it is unclear whether this partnership will be able to enter provider formularies without being blocked by PBMs.

In addition, government intervention has targeted rising drug prices at a federal level through programs such as the federal 340B drug pricing program, created in 1992 after the 1990 Medicaid Drug Rebate Program increased drug prices for public hospitals.[60] More recently, drug price negotiation by the federal government on behalf of Medicare beneficiaries has drawn considerable media and political attention, with many arguments for and against the policy.[61] The Trump Administration has introduced various proposals, such as indexing Medicare drug prices to the drug prices in comparable countries, increasing direct-to-consumer pharmaceutical advertising regulations by requiring drug price disclosure in television commercials, and banning rebates to PBMs and insurers.[62] To this end, in April 2019, US Department of Health and Human Services Secretary Alex Azar proposed Medicare and Medicaid regulations requiring PBMs to apply their rebates toward direct price reductions for patients, in an effort to increase transparency and prevent rebates from returning to insurers or PBMs. Another proposal introduced in early 2019 called for replacing PBM rebate payments that are based on a percentage of list prices with flat administrative fees, which would thereby diminish the present incentive for PBMs to support higher list prices from manufacturers.[63] The American Academy of

Dermatology Association is cautiously supportive of proposed regulatory changes to rebates, provided that the cost reduction for patients outweighs premium increases.[64] However, these initiatives have faced significant resistance from both the private and public sector, yielding minimal impact on pricing thus far.[65]

Independent, nonprofit efforts to moderate drug prices have also been launched, including the DrugAbacus[66] and the Institute for Clinical and Economic Review,[67] which advocate for drug pricing based on consumer value rather than costs or market competition. While these initiatives have faced scrutiny over their methodology and conflicts of interest,[68] their influence has been salient, mostly recently with the launch of Regeneron and Sanofi's eczema drug Dupixent (dupilumab), which was priced below analyst forecasts based in part on months of negotiations with PBMs and, notably, personal meetings between the CEO of Regeneron and the Institute for Clinical and Economic Review.[69]

CONSIDERATIONS FOR CLINICAL DERMATOLOGY

Dermatologists can reduce some medication costs by increasing their use of generic and biosimilar drugs that have proven safety and efficacy.[70] Though careful prescribing is not easy, one analysis projected over $944 million in Medicare savings over 5 years if dermatologists prescribed the cheapest topical corticosteroid within a specific potency class by switching between generics (eg, from clobetasol propionate to betamethasone dipropionate ointment in an optimized vehicle).[71] In addition to previous authorization and step therapy, the automatic substitution of clinically interchangeable but pharmaceutically equivalent drugs can reduce costs. However, these policies are fraught with administrative challenges,[72-74] which may particularly affect small specialties that manage a large number of rare diseases, such as dermatology. Furthermore, generic medications are no longer universally cheaper than their branded equivalents. While it still usually applies to large drug markets with multiple generics (eg, statins, angiotensin-converting enzyme inhibitors, and calcium channel blockers), the dysfunction and price spikes in the smaller generic markets means that on any given day, a branded medicine in these areas may be cheaper than a generic. However, because of the lack of transparency at the point of care, physicians rarely know which is the cheapest option.

In conclusion, high drug prices in the United States are driven by a complex web of interconnected relationships and payments among stakeholders in the drug supply chain. The regulatory landscape has resulted in longer than intended monopolies and conflicts of interest between value and payment. At a system level, the lack of transparency results in increased overall costs, and at the point of care it creates a major barrier to physicians' being effective stewards of resources and considering end cost to the patient in their clinical decision-making. Dermatologists must keep abreast of innovative means of quality improvement and cost reduction, advocate for effective policy, and help patients by minimizing drug costs through careful prescribing.

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