A Primer on Pharmaceutical Pricing, Costs and Reimbursement

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Abstract

The high prices of therapeutic drugs represent one of the most frequent sources of questions, confusion, and frustration among outsiders to the healthcare industry. Even industry veterans are hard-pressed to explain why prices continue to rise year after year in the United States. The typical explanations concerning the return on R&D, innovation, and manufacturing pricing power, while valid in their own right, fall short of offering a complete explanation.

This white paper attempts to explain the economic forces behind drug pricing and presents a primer on the key players in the industry, and how they impact the market. We also discuss current efforts to curb price increases and offer our predictions on what the future holds.

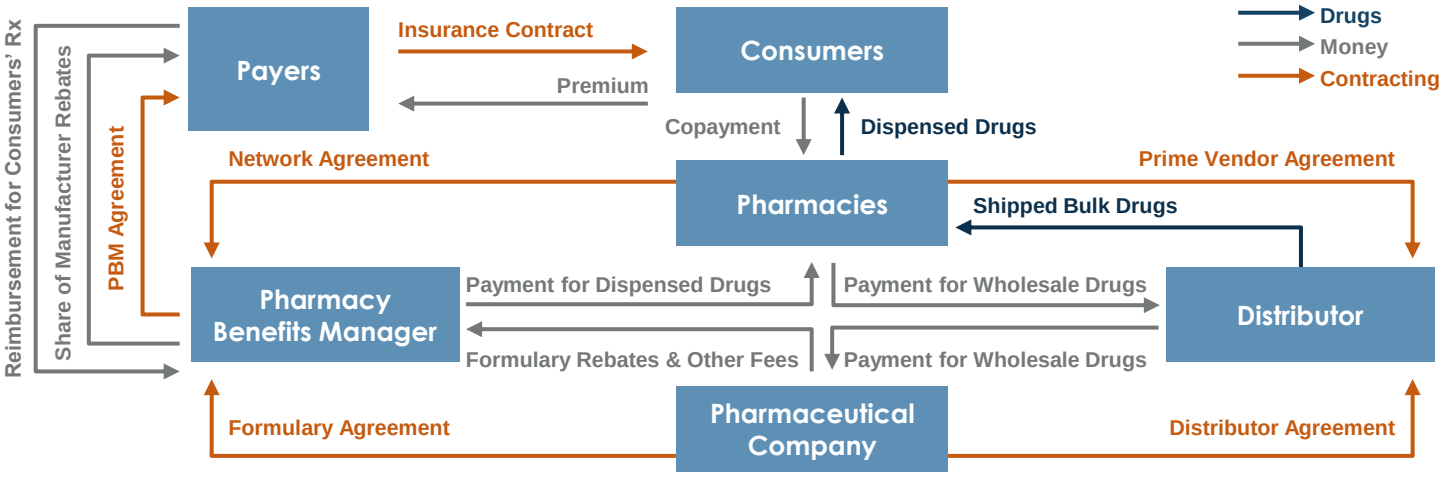
The best way to understand the relationships between industry players is to examine them in the context of basic economic principles and the distortions that make the market for therapeutic drugs unique. Among the most significant of these distortions are:

- Lack of price transparency, particularly with respect to the role of the PBM
- The splitting of the roles of the consumer (the patient), the decision-maker on the most appropriate therapeutic option (usually the physician), and the payer (most often private insurance or Medicare)

This second distortion highlights more than anything else the strange world of drug pricing. Consider a world in which the market for beverages were run this way. Rather than going to the corner store to buy a drink and deciding between a soda or kombucha, for example, one would need to find a provider – a hypothetical hydration expert in this case – to prescribe a specific beverage. Perhaps after stating a preference for a traditional soda, our consumer is prescribed a Coke®. At the corner store, the consumer would receive the drink but pay only a fraction of its price in the form of a hydration copay. A third party, to whom our consumer's employer pays monthly hydration benefit dues, pays for the Coke® after negotiating a group Coke® price. Neither the provider nor the consumer has any idea what the Coke® "costs." The entity that pays for the Coke® (the insurer) doesn't do so directly but owns or contracts with yet another third-party (a PBM or GPO) to negotiate large contracts with Coca-Cola®, Pepsi®, and other suppliers, with secret rebates attached that are kept from others in this network of transactions. There are different price points at different parts of the chain. In such a scenario, it would not be much of a surprise that the price of Coke® would keep going up, given the enormous information asymmetry between market participants. This is the US pharmaceutical industry in a simplified nutshell.

This paper will first explain the roles of the therapeutic drug market participants and the distortions introduced by these role definitions, then discuss the current and future trends in the industry.

The chart below lays out the complexity of the flow of product, money, and orders, and we will start the explanation with a brief summary of price transparency.



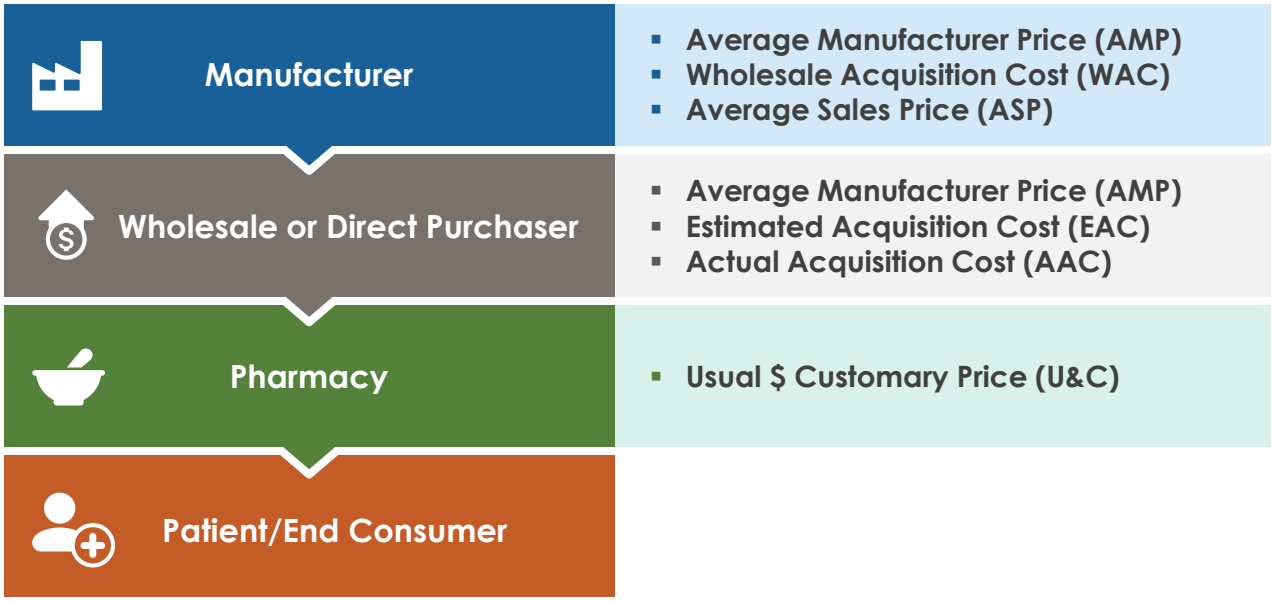
Lack of Pricing Transparency

Pricing Key Points

1. **Multiple Pricing Methods and definitions all have a necessary function, but cause tremendous confusion.**
2. **Price, Charge, and Cost are different concepts, depending on point of view, and may be completely unrelated to each other.**
3. **AWP is the mostly commonly used, although controversial.**
4. **Patients are often shielded from the true cost of their therapy.**
5. **Contracts affect pricing, reimbursement, and formulary, and leverage determines favorability to pricing.**

Obfuscated by design

Despite recent calls for increased transparency from President Trump, the American Medical Association, and the Center for Medicare and Medicaid Services (CMS), drug pricing remains complicated.[1,2,3] There are many different pricing methods, illustrated below, which were created to serve a variety of different purposes.[4] These methods serve as indicators between the manufacturer and wholesaler, wholesaler and pharmacy (or clinic), and pharmacy to the patient.[5] Even within these channels, there are often multiple pricing indicators, for example, between the manufacturer and the wholesaler are the Average Manufacturer Price (AMP), the Wholesale Acquisition Cost (WAC), and the Average Sales Price (ASP). Obviously, the actual value attached to each of these methods differ as well, as does the reason for their existence.



[1] https://www.forbes.com/sites/joshuacohen/2018/10/17/improving-drug-price-transparency-from-removing-pharmacy-gag-clauses-to-reforming-the-rebate-system/#74b4fd98303b
[2] https://healthpayerintelligence.com/news/cms-proposes-drug-price-transparency-in-television-ads
[3] https://wire.ama-assn.org/ama-news/drug-pricing-needs-transparency-physicians-say
[4] https://www.uspharmacist.com/article/understanding-drug-pricing
[5] https://www.uspharmacist.com/article/understanding-drug-pricing

The pricing methods found most “upstream” in the supply chain, thus closest to the manufacturer, often serve to signal the value a manufacturer would like to associate with their product. Although Average Wholesale Price (AWP) and Suggested Wholesale Price (SWP), are more often an indicator between the wholesaler and a pharmacy, these methods along with WAC have become common benchmarks for use in commonly describing “price,” particularly among payers, PBMs, and pharmacies. They may be thought of as the MSRP or “sticker price” used in other industries.

One very general rule of thumb puts AWP at 20% above WAC.[6] WAC covers research, production, and profit. AWP is a multiple of WAC.

It is likely that the proposed Trump legislation mandating the inclusion of price in Direct-to-Consumer (DTC) advertisements will use the WAC price, although this remains to be finalized.[7] The convention that “no one pays sticker price” holds only somewhat true here, with that truth and subsequent price determined by amount of buyer leverage. Given that these “list price” methods (AWP, SWP, and WAC) become something of a baseline, they are most often the pricing methods used for determining discounts, such as from manufacturer to wholesaler or beyond, or for creating chargemasters (data tables that a hospital or clinic uses to determine charges that it intends to pass on to a third-party payer via the bill). Likewise, these can be the methods used for creating media press release estimates of pricing when a new therapy is launched.

Common Terms and Acronyms Used in Drug Pricing	
Federal upper limit (FUL)	A price ceiling used by the Centers for Medicare and Medicaid Services (CMS) to control prices for certain medications paid to pharmacies
Maximum allowable cost (MAC)	A price ceiling, similar to the FUL, established at the state level
Usual and customary price (U&C)	The average cash price paid at a retail pharmacy
Average wholesale price (AWP)	An estimate of the price retail pharmacies pay for drugs from their wholesale distributor. This price is calculated and published by companies such as Medi-Span and First Databank.
Wholesale acquisition cost (WAC)	An estimate of the manufacturer’s list price for a drug to wholesalers or other direct purchasers, not including discounts or rebates. The price is defined by federal law
Average manufacturer price (WP)	The price a manufacturer charges wholesalers or pharmacies that purchase directly from the manufacturer after discounts. This price is defined by federal law.
Average sales price (ASP)	A calculation of the weighted average of manufacturer’s sales price for a drug for all purchasers, net of price adjustments. This price is defined by federal law.
Estimated acquisition cost (EAC)	An estimate of the price generally paid by providers for a drug. Formula specific for each state as defined by the state Medicaid agency
Average acquisition cost (AAC)	An estimate of retail pharmacy acquisition costs for drugs through a review of actual pharmacy invoices
Dispensing fee	The amount reimbursed to the pharmacy to cover the charge for professional services and overhead costs
National Drug Code (NDC)	An 11-digit code used by Medicaid to identify a drug based on its manufacturer, strength, and package size

[6] https://www.drugs.com/article/average-wholesale-price-awp.html
[7] https://www.cms.gov/newsroom/press-releases/cms-proposes-require-manufacturers-disclose-drug-prices-television-ads
[8] https://uspharmacist.com/article/understanding-drug-pricing

AWP: The undisputed champion indicator of a price nobody pays

The Average Wholesale Price (AWP) is an especially common and somewhat controversial benchmark.[8] Some key points to note about AWP are as follows.

AWP is:

- Used for pricing and reimbursement
- Compared to "list price" or "sticker price"
- An elevated drug price
- Rarely what is actually paid, by any purchaser at any point
- "Ain't what's paid!"

However, AWP is not:

- A true representation of market prices
- A government-regulated figure
- Inclusive of discounts or rebates

AWP remains an extremely popular pricing method despite the problems reviewed, largely because of historical convention. While not an ideal reference, it is well-accepted throughout the industry for a variety of uses. WAC, however, is most frequently used as a starting point for pharmacy purchases from wholesalers. While WAC reflects some degree of reality, AWP has long been the undisputed champion of listed price, such as in the press, as well as trade and academic articles.

Actual price paid is determined by leverage and contract

What price do the various players pay? It may, in fact, be none of the prices referenced above. The wholesaler, pharmacy, or Pharmacy Benefits Manager (PBM) pay based upon negotiated costs from contracts and net of rebates. The manufacturer or drug marketer may get what they can negotiate back from these buyers.

Likewise, hospitals and clinics also frequently purchase their medications on contract. This contract price may be a direct contract with the manufacturer, or through an intermediary such as a Group Purchasing Organization (GPO).[9] Contract prices, like the contracts themselves, are almost never made public, but typically fall within a reasonably narrow band with occasional glaring exceptions. It should be noted that the contract often stipulates pricing confidentiality. Predictably, this relationship is ruled by microeconomics, where the best contracts are negotiated by the players with the best leverage, whether that be via volume, exclusivity, degree of differentiation / commoditization, or other similar factors. Some products have much deeper discounts than others, but a wide rule of thumb is that contracted prices are usually 50-85% of wholesale, with occasional "deals" for more. A large integrated delivery network, comprising multiple hospitals and clinics, has more leverage than a single clinic. A manufacturer with a first-in-class or orphan product has more leverage than a product with multiple agents in the class. A major retail pharmacy chain has tremendous buying power as well, whereas a small, independent drug store may have little leverage or buying power.

Contracts have a sizable influence on pricing and reimbursement as well as influence on formulary decisions. If a therapeutic class has multiple similar agents with similar indications and efficacy, then the one that can be had least expensively (either via direct cost or rebate mechanism) will inevitably be the preferred formulary agent. This rule holds true at the hospital / clinic level as well as for the payer / PBM. However, each may designate a different preferred agent within a class, which can lead to issues in authorization.

[9] https://www.drugs.com/article/average-wholesale-price-awp.html
[10] https://www.beckershospitalreview.com/finance/4-of-the-largest-gpos-2017.html

End user is often shielded from true cost burden

Co-pay or co-insurance may serve to insulate the patient from the full cost of therapy. However, the total cost burden between the patient and payer may be either an acquisition cost, a benchmark cost, or a pre-determined contracted rate plus (or minus) a percentage split between the insurer and the patient. Even in a "high deductible" plan, it is rare the patient pays the full burden of care, especially after an out-of-pocket maximum is reached. As predicted by economic principle, when price is artificially held low, by co-pay, co-insurance, and perhaps premiums paid by an employer, demand can be higher than otherwise expected.

In some cases, however, the relationship reverses. Because of contracted rebates that are not passed on to the consumer, *the patient may actually pay more than the payer*.[10] In fact, in some cases the payer may make money on these prescriptions, which is theoretically used to offset premiums.[11]

Price is in the eye of the beholder: Price, Cost, and Charge are heavily dependent upon point of view

It is worth nothing that price, charge, and cost are three different concepts. If price is what is listed in an online ordering portal or catalog, then the charge is what shows up on a patient bill. The charge is almost never equal to the price paid; often, the charge and the price are completely unrelated. For example, a hospital or clinic may acquire a medication using one of a variety of available prices (most commonly their contracted price), but subsequently charge a patient based upon a percentage / multiple of AWP or SWP, or some other pricing method based on minimums or averages.

What is "cost"? Cost is beyond the scope of this discussion, but ultimately it is the amount paid by the entity whose point of view you wish to evaluate, after all overhead and allocations have been factored. The Healthcare Financial Management Association (HFMA) uses the following definitions[12]:

- To the patient, cost is the amount payable out of pocket for healthcare services, which may include deductibles, copayments, coinsurance, amounts payable by the patient for services that are not included in the patient's benefit design, and amounts balance billed by out-of-network providers. Health insurance premiums constitute a separate category of healthcare costs for patients, independent of healthcare service utilization.
- To the provider, cost is the expense (direct and indirect) incurred to deliver healthcare services to patients.
- To the insurer, cost is the amount payable to the provider (or reimbursable to the patient) for services rendered.
- To the employer, cost is the expense related to providing health benefits (premiums or claims paid).

HFMA also notes that while the charge is what is asked of uninsured and underinsured patients, ultimately, most end up paying much less. This often becomes something of a negotiation as well.

[11] https://www.drugchannels.net/2019/02/how-health-plans-profitand-patients.html
[12] https://www.drugchannels.net/2019/02/my-wall-street-journal-op-ed-dont-blame.html
[13] https://www.hfma.org/content.aspx?id=28786

Reimbursement: The Disconnect Between End User, Prescriber, and Payer, and the Confusing Role of the PBM

Reimbursement Key Points

1. **Reimbursement depends on whether a drug is administered in a clinic or dispensed in a pharmacy.**
2. **PBMs play an increasingly important role in the reimbursement of pharmacies such that they are likely to have a role in medication infusion clinics in the future as well.**
3. **Strategic and sophisticated coding techniques make a material difference in reimbursement for the clinic, and pharmaceutical companies can help design and educate on this strategy.**

Reimbursement is determined by administration vs dispensation

Reimbursement can take several different forms, particularly depending on whether a drug is administered or dispensed. Simply put, hospitals and clinics administer drugs to patients, and pharmacies dispense drugs, although there are exceptions where the opposite happens in both scenarios. If a medication is taken (or more likely, given) immediately, it is usually considered “administered,” and if instead it is sent home, then it is “dispensed.” This distinction matters, as it determines reimbursement methods.

Medications that are administered are typically reimbursed through the medical, as opposed to pharmacy, benefit. In the case of a Medicare-eligible patient, this is the Medicare Part B (“doctor’s office”) benefit. There is a time lag for the actual cash transfer in this case, due to the claims process: The encounter with the patient must be completely documented and closed prior to claim submission. This claim is then processed for payment, which can take anywhere from weeks to months.

Most high cost medications, such as newer oncology therapies, require a prior authorization process to be completed before administration. This process can take anywhere from hours to days, and customarily requires a physician and staff to complete payer paperwork that documents the necessity of the chosen therapy. Rules for turnaround time exist, especially for Medicare patients, but prior authorization is almost never an instantaneous process. And depending on the medication and payer, this process might be quite cumbersome. Lastly, if a drug manufacturer offers a discounting program for the indigent or un(der)-insured, this is the opportunity for the clinic to try to take advantage of the program on behalf of the patient.

For administered medications, providers code the procedure with a HCPCS (or CPT) code, most commonly through facility coders or, increasingly, automatically via electronic health record software. The Healthcare Common Procedure Coding System (HCPCS, pronounced "hick picks") is a set of procedure codes based on the American Medical Association's Current Procedural Terminology (CPT). The CPT code describes physician procedures and the HCPCS code often describes the equipment, including drugs, used. This is compiled onto a bill with an ICD-10 (International Clarification of Diseases) diagnosis code and submitted to the payer, where utilization management (UM) software looks for a diagnosis/ procedure code match and reimburses accordingly via their loaded (i.e., existing) contracts. Such UM software is pre-loaded with tables created with evidence-based matches for diseases and therapies. For example, if a specific drug is FDA-approved for use as first-line therapy in a disease, this bill is likely reimbursed with no further steps.

Currently, CMS reimburses clinics for outpatient infusions at Average Sales Price (ASP) plus 6%. ASP, once again, is a weighted average of manufacturers sales prices, and defined by federal law. However, the Trump administration is currently proposing basing payment on international sales prices, which are lower. They project that this change would save $17.2 billion for Medicare over five years.[13] The wide-ranging implications of this proposal, while important, exceed the scope of this paper.

[14] https://www.modernhealthcare.com/article/20181025/NEWS/181029944/new-cms-pay-model-targets-soaring-drug-prices

Advanced therapies and "off-label" use may require more steps

If a bill is submitted requesting payment for a medication that is not FDA-approved for a certain disease state or commonly in use and supported by published evidence, a denial of payment may result. Documentation of progression to the current disease state may also be required. For example, even if a medication is accepted as salvage therapy, the bill may be denied if no record exists for the use and failure of first- and second-line agents. Once a bill is denied, it is forced into an appeal process where the treating physician and medical director at the payer negotiate in a peer-to-peer discussion about the appropriateness of the therapy. If deemed appropriate, the bill is often paid, but all of this must take place outside of software algorithms. Of course, best practices around the prior-authorization processes may avoid these denials.

Coding sophistication can significantly impact reimbursement, particularly for new drugs and biological products.[14] When a new product is approved, the Center of Medicare and Medicaid Services (CMS) does not assign a HCPCS code immediately and billing requires use of a generic code. Using J3490 ("unclassified biologics") may result in minimal reimbursement ($35) for an expensive new biotech agent.

In contrast, use of C9399 (also "unclassified drugs and biologicals") will result in a payment of 95% of AWP until ASP is set, or until a final status code or permanent HCPCS code is established.[11] However, this code must be accompanied by the product NDC and presents an opportunity for a manufacturer or marketer to provide some value helping a provider obtain reimbursement for using their product. Astute manufacturers and marketers help end-users (such as clinics) code strategically, via hotlines and detailed instructions on medication websites.

Reimbursement with dispensing is faster but occasionally involves more restrictive guardrails

Medications that are dispensed are reimbursed much more quickly. This routinely occurs with immediate adjudication at point of sale, and with the cash transfer within days to weeks. The dispensation process can also require prior authorization, depending upon the medication in question. There may be some delay if a plan requires a prior authorization, with rules depending on plan type, and speed depending on physician paperwork turnaround. This process takes place through the pharmacy benefit: for Medicare patients it is the Part D ("prescription drug") benefit. It is seen at the point-of-sale dispensation in the retail environment, but can also occur via mail order, and through other mechanisms as well.

The additional player in the dispensation world is the Pharmacy Benefit Manager (PBM), as mentioned above.[15] In short, the PBM is the financial and clinical guardrail intermediary between the payer and the pharmacy, and a clearinghouse of sorts for medication-based claims. PBMs are contracted by payers to handle the utilization management function of the prescription world, and increasingly are being involved in claims and support for administration (medical benefit) claims as well. At no point do PBMs physically handle drug or biologic products, although many own specialty pharmacy subsidiaries, but they serve as the "switch" for the movement of financial transactions for such claims. Though they do not act as an insurer, they move large money amounts and are subsequently reimbursed by payers. PBMs contract and partner with third-party payers, although many larger third-party payers have acquired or developed PBMs, such as UnitedHealthcare's relationship with OptumRx.

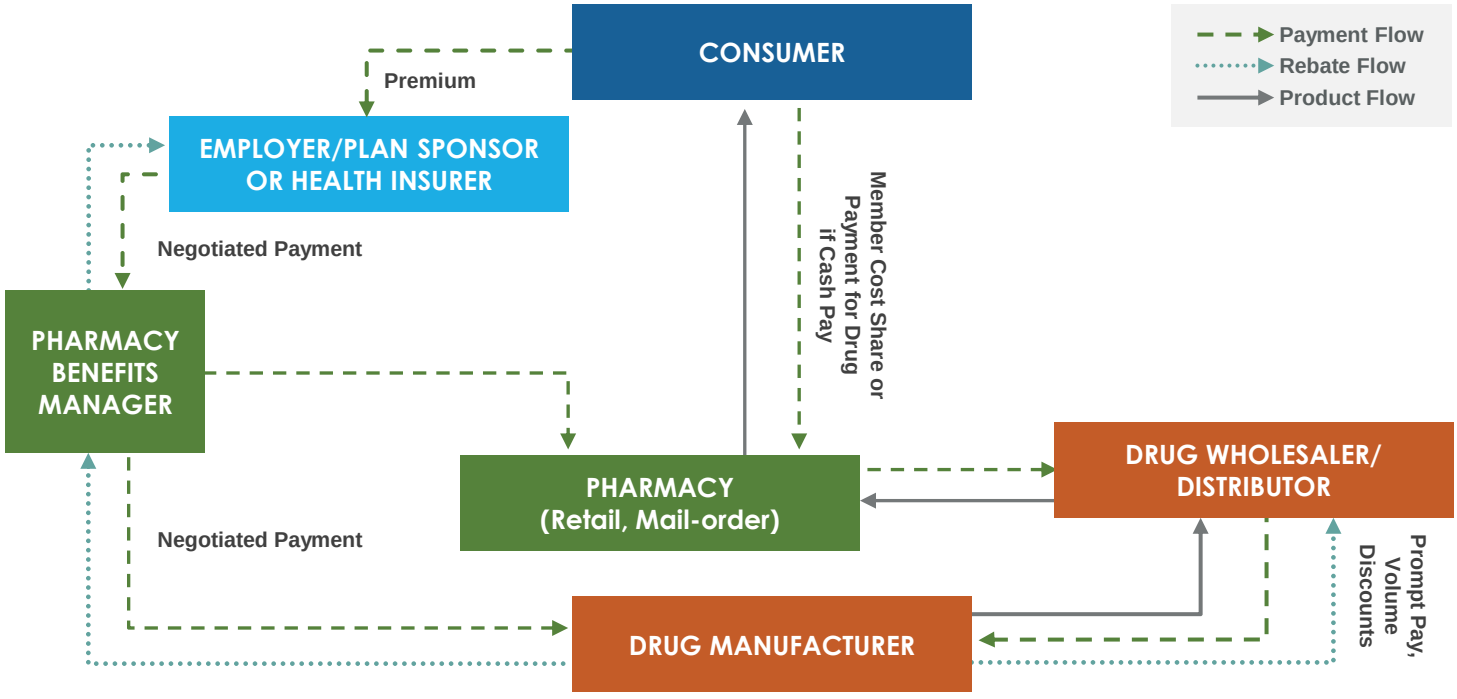
[15] Kirschenbaum B. Results Depend on Essential Basics: Navigating the Revenue Cycle, February 2018.
[16] https://www.investopedia.com/articles/markets/070215/what-pharmacy-benefit-management-industry.

The Distortion of Incentives

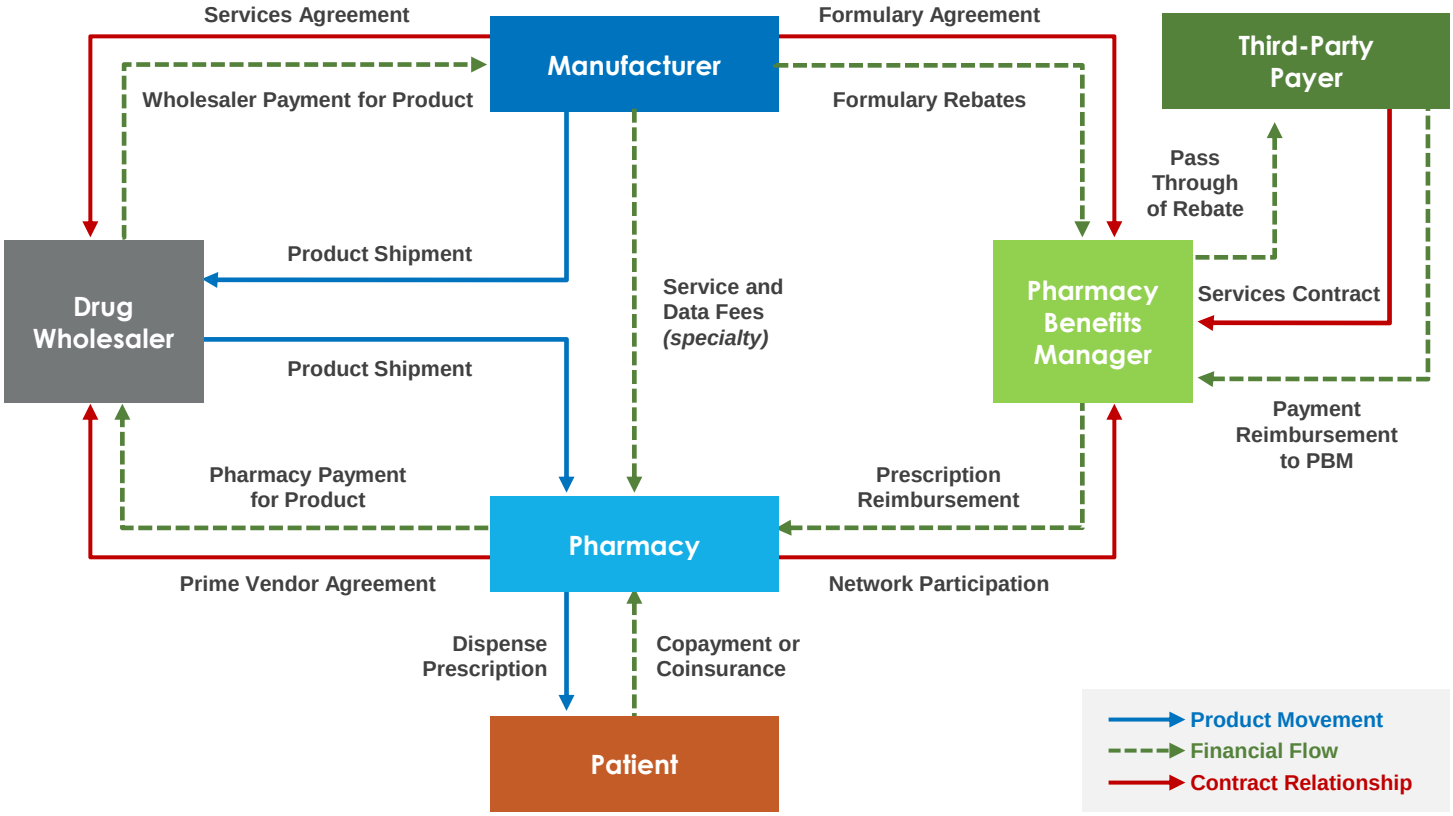
Incentives Key Points
1. Inertia of providers
2. The "conspiracy" between manufacturers and PBMs to create opacity
3. Integration of specialty distribution and manufacturers
Other Drivers to Higher Prices:
1. Manufacturer power in the US
2. The protective power of IP

Follow the money

The incentives in this whole process generally follow the principles of microeconomics. Following the money reveals many of the motivations of all of the players, who seek to minimize their own financial liability.



Source: http://www.shmula.com/pharmaceutical-supply-chain-things-you-didnt-know/8503/



Source: https://drugchannelsinstitute.com/products/industry_report/pharmacy/

It is beyond the scope of this paper to discuss the various types of insurance plans that cover individual patients. We've already discussed how a hospital / clinic / provider design a formulary around efficacy, safety, and cost; payers and PBMs attempt to do the same.

Inertia and Familiarity

We previously noted how the split of the prescriber and payer roles de-emphasizes price. Another result is that habit tends to drive behavior. At the hospital / clinic / provider level, there is an inertia to the formulary: When a physician and allied health care team become familiar with one particular product, the barrier to change increases. Significant cost saving, safety, or efficacy gains are necessary to overcome this inertia.

Formularies are influenced by contracts, but it is the innovator product's contract to lose at the site level or at the group purchasing level, all things considered. Drugs considered "me too" products must also overcome this inertia and provide some benefit.

We acknowledge the studies by McKinsey and Duke's Fuqua School of Business which found a modest "first mover" advantage in market share. While agreeing with the overall observation, we note that exceptions exist, the causes of which must be saved for a future discussion.

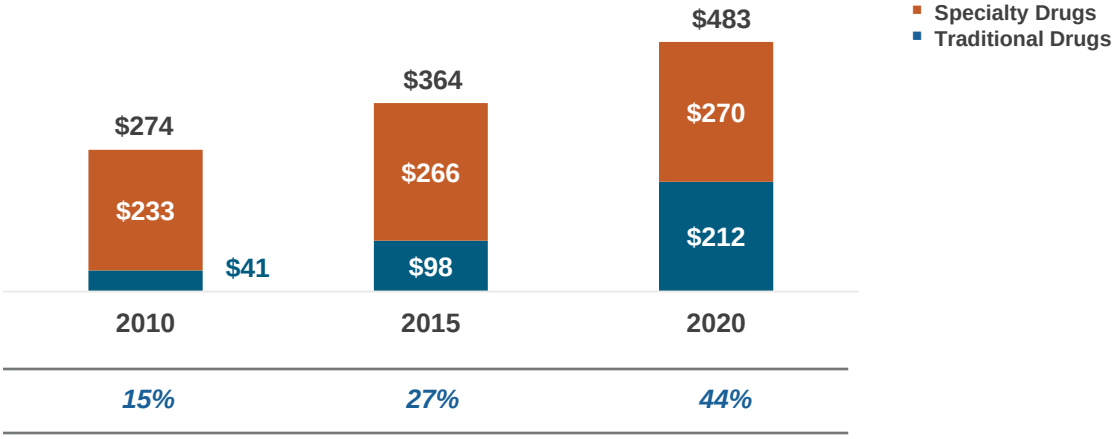
Opacity and Transparency

There are many incentives for manufacturers and PBMs to keep pricing structures opaque. Contracted clients, particularly government payers, may have a choice between "spread pricing" or a fee-based structure.[16] Many choose the spread pricing, whereby the retail pharmacy price is based on one fee schedule and the government payer is charged on a higher one. The argument for "spread pricing" is that it provides for some measure of consistency, allowing for a smoother budget process that is not impacted by the acquisition prices at pharmacies, which are negotiated based on scale / leverage. In a recently publicized break from this method, the state of Ohio passed a "transparency" law, ending their CVS Caremark PBM contracts for state Medicaid programs.[17] This trend does seem congruent with some of the goals of President Trump's goal of lower drug prices. Also reflective of pricing opacity is the trend of increasing "Gross-to-Net" bubble, which topped $150 billion dollars in 2017.[18] What this number reports is the difference between gross revenues (sales at a drug's WAC price) and net revenues (actual revenues received by the manufacturer). The obvious drivers for this are protection of contracts between manufacturers, wholesalers, and PBMs, without alteration of the "value signal" in list pricing.

Increased Supplier Power: Specialty Designation and Controlled Distribution

Manufacturers have tremendous incentives to develop therapeutics that can be considered specialty products. When a manufacturer classifies their agent as "specialty" they can control the distribution channels, even to sole source distributors, and exert greater influence over pricing. These distribution channels can in turn limit product access to certain "specialty pharmacies." What constitutes "specialty" as a designation is a bit nebulous, although it is often an injectable product and, as a rule, an expensive one. Notably, this is an industry-developed distinction and there is no government or regulatory definition for a specialty product. Uptake may face the challenges previously described, but the pricing is lucrative and the barriers to manufactures of generic or biosimilar products are high.

Pharmacy Industry Revenues, Traditional vs. Specialty Drugs, 2010-2020



Lastly, there are also some incentives at play regarding where treatment is given. The payer has a degree of control over the place of care. In a fee-for-service scenario, potentially any and all medication options are open for use, again subject to the payer's prior authorization process. However, an integrated delivery network, or IDN, is a closed system of multiple hospitals and clinics (such as the Veteran's Administration system, Ascension Health, Catholic Health Initiatives, or HCA), which again may preclude the use of certain agents through the formulary system. Although complexity of therapy typically determines whether an agent can be simply dispensed for at-home use by a patient or requires supervision in a clinic, the payer and PBM may become involved. The prior authorization process creates incentives avoid the most expensive agent as front-line therapy in some cases. "Step Therapy" programs serve a similar purpose. Patient or provider biases can also preclude a fair trial of the first-line agents.

[17] https://www.bloomberg.com/graphics/2018-drug-spread-pricing/
[18] https://www.ajmc.com/newsroom/ohio-tells-medicaid-pbms-that-2019-will-be-a-time-for-transparent-contracts
[19] https://www.drugchannels.net/2018/04/the-gross-to-net-rebate-bubble-topped.html

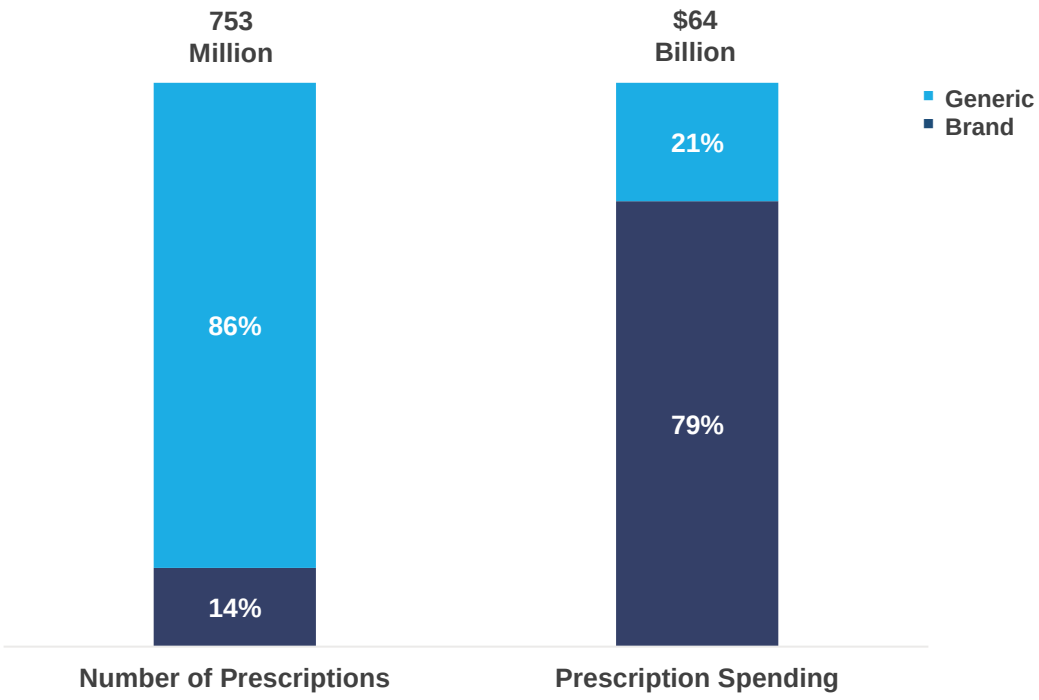
Other Non-Distortive Factors Driving up Prices

Manufacturer Power in the US

Often people question why drug prices are so much higher in the US than in other countries. Microeconomic principles provide an explanation. In many countries, a single payer wields massive buying power, whereas the US has much more competition. Institutions like NICE act as gatekeepers to domestic markets, playing manufacturers against each other. CMS is positioned to play a similar role, but its mandate forbids doing so. We note that the idea of expanding the role of CMS to include price negotiation is gathering political bipartisan political momentum, though nothing is concrete yet.

The Power of Intellectual Property

In 2008, the ACA was based and with it a 12 year protection of data exclusivity for biological products, in addition to the patent protection of 20 years of application date. The limited monopoly granted by intellectual property law is often credited for spurring innovation, but it also does lead to higher overall prices. Drugs that enjoy continuing patent protection represented only 14% of total consumption but 79% of total market in dollars in 2017.[19] The combination of these government-granted monopolies with strong manufacturer power can impact the balance between payer and supplier.



Source: Kaiser Family Foundation

[20] https://www.kff.org/medicaid/fact-sheet/medicaids-prescription-drug-benefit-key-facts/

Current Efforts in Containing Prices

What the government and the industry is doing about rising prices

1. **Drug prices continue to rise with the current champion at just about two million US dollars, but perhaps not by as much as the headlines imply.**
2. **Calls for controls on drug prices continue, with the government making several attempts at the margins.**
3. **Pay-for-performance is trendy, but efficacy and cost-containment remain questionable.**
4. **Trump's Blueprint for Americans First may have a long-term impact.**

Why do drug prices continue to rise?

Any effort to address this question fairly should include recognition of the complexities involved. While drug prices do rise year after year, the rate of change has slowed.[20] The patient may not share this as a perception when Humalog® has gone from $20 in 1996 to $275 today, far outpacing CPI, which has fluctuated between 0 and ~3.8% for the past 20 years.[21] Premier, a major GPO, has projected a 3.8% increase in contracted drug costs for 2020[22] and rival GPO Vizient anticipates 4.3%.[23] These values have varied over the years. What has also risen is the "Gross-to-Net" bubble, which highlights the difference between list (gross) price and actual revenues received after all rebates as discussed previously.[24] This means that net price is in fact rising at a slower rate than list, though we acknowledge this is of little comfort to the consumer.

Blockbuster prices

So-called "Blockbuster" drugs continue to proliferate with headline-grabbing prices. As recently as 5 years ago, the launch of direct-acting antiviral therapy for curing Hepatitis C was controversial at around $100,000 . Costs have only risen since that time. Luxturna, a gene therapy that can cure an inherited form of blindness, costs $850,000 for a one-time treatment.[25] Spinraza, for Spinal Muscular Atrophy (SMA) costs $750,000 the first year and about $375,000 annually thereafter.[26] The chimeric antigen receptor T-cell therapy (CAR-T) class, which treats certain leukemias and lymphomas, currently comprises two agents: Kymriah at $475,000 and the somewhat less expensive Yescarta at $373,000.[27,28] Andexxa, which is a reversal agent for modern anticoagulants in emergent situations, will cost anywhere from $27,500 to almost $50,000 per reversal needed.[29,30] Given the complexities in manufacturing and preparing many of the advanced therapies, costs are only expected to rise. Providers, clinics, and hospitals wrestle with these costs. On the one hand, the therapies are truly revolutionary and life-saving; on the other hand, there is legitimate worry about acquisition cost, reimbursement, and sustainability.

[21] https://www.drugchannels.net/2019/01/drug-prices-are-not-skyrocketingtheyre.html
[22] https://www.nytimes.com/2019/03/04/health/insulin-price-humalog-generic.html
[23] https://healthpayerintelligence.com/news/prescription-drug-prices-set-for-3.8-increase-in-2020
[24] https://newsroom.vizientinc.com/newsletter/supply-chain-management-news/vizient-drug-price-forecast-projects-increase-prices-2019-20
[25] https://www.drugchannels.net/2019/01/drug-prices-are-not-skyrocketingtheyre.html
[26] https://www.cnbc.com/2018/01/03/spark-therapeutics-luxturna-gene-therapy-will-cost-about-850000.html
[27] https://www.nytimes.com/2016/12/30/business/spinraza-price.html
[28] https://www.onclive.com/web-exclusives/novartis-sets-a-price-of-475000-for-car-tcell-therapy
[29] https://www.reuters.com/article/us-gilead-sciences-fda/fda-approves-gilead-cancer-gene-therapy-price-set-at-373000-idUSKBN1CN35H
[30] https://www.fiercepharma.com/manufacturing/portola-s-andexxa-bleeding-antidote-wins-fda-nod-but-will-get-limited-release
[31] https://secure.medicalletter.org/w1549a

Although these prices look like nose bleeds, it's worth noting that some of these compare to lifetime treatments. A one-time $850,000 gene treatment is much less expensive than 20 years of chronic treatment at over $100,000/year. Taking into account the lesser burden on patients to receive treatment over time, the argument that expensive therapies can in fact save the healthcare system money is all the more compelling. Indeed, while Zolgensma's recent launch at over $2M received media headlines, ICER's cost effectiveness modeling largely validated the price point (as always, assuming key assumptions are met), even as it highlighted the effort by AveXis/Novartis to price to the very edge of value.

The same case can be made for a curative $375,000 dollar cancer treatment that can be much less expensive than the current standard of care alternatives.

Government and advocacy for affordability

Rising drug costs and corresponding affordability issues have long been a favorite problem for patients, press, and politicians to bemoan in America. It has been politically problematic. Medicare Part D was a signature piece of legislation for the George W. Bush administration, and yet it has required revisions in the years since, in attempts to improve affordability and cost consistency for the patient, such as the effort to "smooth the 'donut-hole.'" Candidate Trump ran on a pro-business platform, while simultaneously calling for increased affordability of drugs – a proposition President Trump has had some difficulty reconciling. Recently, he signed "Right to Try" legislation, which gives terminally ill patients access to experimental medications that have cleared Phase 1 clinical studies, outside of the typical research protocol. This legislation has been mildly controversial politically, but is pertinent to our topic here, as it impacts expense.[31,32] Economically speaking, it does not benefit pharmaceutical manufacturers to provide pre-approval drugs, at cost or for free, to patients outside the typical approval process, and they are not required to do so. Providing an experimental agent, by law, cannot be profitable for the company developing it, but federal law does allow companies to recover the costs associated with the care.[33] In other words, they can require payment up to and including full cost, but not beyond their cost (which would yield profit.) Additionally, other costs associated with the experimental therapy can be charged, and insurance companies are not required to pay for any of these ancillary costs. Critics note that it may cause terminally ill patients to make poor financial decisions based upon very incomplete and preliminary data. There are no FDA safety mechanisms, by design. Ultimately, "Right to Try" doesn't dramatically change the landscape as a majority of states already allow it, and the FDA previously had an IND process in place with somewhat more patient oversight.

The Pros and Cons of Pay for Performance

"Pay for Performance" has been a trendy topic in health care reimbursement circles, particularly in industry opinion/editorial pages. The concept has found fans among providers, policy-makers, patients, and the media. Escalating costs have given rise to some novel attempts. Janssen-Cilag, the makers of Velcade® (bortezomib), a novel agent for multiple myeloma costing $50-100,000 annually (US), suggested a refund scheme for the United Kingdom's National Health Service (NHS) plan.[34] NHS's National Institute for Health and Care Excellence, or NICE, typically makes clinical and formulary recommendations based on a threshold value of British pounds (£) per Quality-Adjusted Life Years (QALYs), a threshold Velcade failed to meet. Per the UK's National Institute for Health and Care Excellence (NICE) summary, "Velcade (Bortezomib) is slightly above NICE's usual £30k per QALY threshold. When used as monotherapy, Velcade has a cost per QALY of £33.5k". For better or worse, NHS and NICE have set a price threshold on life-years saved. If a drug simply costs more than the "value" of life-years saved, it is deemed cost ineffective. By refunding NHS for non-responders as defined by objective blood values, Velcade became more cost effective by ultimately lowering the cost to the whole, and therefore more palatable to the UK health system.[35]

[32] https://icer-review.org/announcements/icer_comment_on_zolgensma_approval/ and https://icer-review.org/ announcements/sma_evidence_report
[33] https://www.cnn.com/2018/03/22/health/federal-right-to-try-explainer/index.html
[34] https://www.cbsnews.com/news/right-to-try-bill-trump-signing-will-it-help-terminally-ill-patients-today-2018-05-30/
[35] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351264.pdf
[36] https://www.nice.org.uk/guidance/ta129/documents/department-of-health-summary-of-responder-scheme2
[37] https://www.pharmaceutical-journal.com/news-and-analysis/nice-gives-response-rebate-scheme-for-bortezomib-the-go-ahead/10005252.article?firstPass=false

A similar example is the arrangement that Novartis has made with Cigna and Aetna for Entresto, a novel heart failure therapy.[36] A marker of heart failure complication is 30 day readmission, which becomes a target for hospitals and payers both. In this new model, if the therapy reduces (or fails to reduce) re-admissions, Novartis's revenue changes through a bonus and refund structure. In this case, the primary target is reduction in the proportion of customers with heart failure hospitalizations.[37] This aims to replicate results from Entresto's clinical trials, a bar not often met under "real world" conditions. This specific arrangement involves a base drug rate, along with fluctuating rebates based upon performance. ICER, the independent Institute for Clinical and Economic Review watchdog group, has determined Entresto to be slightly overpriced for the economic value it provides; this pricing program theoretically realigns the mismatch. In 2009, Procter & Gamble reached a similar arrangement with Health Plan Alliance for Actonel®, an osteoporosis drug, in effect providing a rebate when a covered patient suffered a bone fracture.[38]

Novartis has also been exploring value-based reimbursements for their $475,000 CAR-T therapy Kymriah.[39] This collaboration is remarkable in that instead of negotiating with a private payer, Novartis' counterpart is the Centers for Medicare and Medicaid Services (CMS). Novartis have also announced that they would not charge for the therapy if it does not work within a month.[40] Initial data for the medication showed an 83% response rate for certain types of leukemia.

As a concept, Pay for Performance certainly does have serious shortcomings, however. Physicians note that the above-mentioned Entresto and Actonel ideas do nothing to incent physicians prescribing for the drug, may increase paperwork burden, and offer no motivation for patient compliance with the medication. If failure occurs, the payer may recoup some benefit, but not the physician or patient. A Harvard study showed no improvement in quality or cost savings, and illustrated disincentives for the sickest patients.[41] Results like these have CMS seeking to roll back their Merit-based Incentive Payment System (MIPS), in order to avoid penalties under MACRA (The Medicare Access and CHIP Reauthorization Act of 2015).[42] Critics charge that there is no real evidence suggesting any pay for performance programs have improved quality, cost, and outcome measures. The concept remains popular, however, because simple fee-for-service medicine is widely accepted as unsustainable in its current form. An answer to the affordability question remains uncertain.

President Trump's Blueprint for American Patients First

President Trump and Health and Human Services Secretary Alex Azar have put forward a blueprint entitled "American Patients First" in an attempt to lower drug prices for patients.[43] Full review of this plan is beyond the scope of this paper, but there are some key points relevant to our purposes. The blueprint noted four challenges in the American drug market:

1. High list prices for drugs
2. Seniors and government programs overpaying for drugs due to lack of the latest negotiation tools
3. High and rising out-of-pocket costs for consumers
4. Foreign governments free-riding off of American investment in innovation

The administration has thus proposed the following corresponding strategies for reform:

1. Improved competition
2. Better negotiation
3. Incentives for lower list prices
4. Lowering out-of-pocket costs

[38] http://www.modernhealthcare.com/article/20161210/MAGAZINE/312109949
[39] https://www.cigna.com/newsroom/news-releases/2016/cigna-implements-value-based-contract-with-novartis-for-heart-drug-entrestotm
[40] https://www.ajmc.com/journals/evidence-based-oncology/2013/2013-1-vol19-sp3/value-based-contracting-for-pharmaceuticals-getting-ready-for-prime-time
[41] https://www.pharmaceutical-technology.com/comment/outcome-based-contracts-kymriah/
[42] https://www.xconomy.com/national/2017/08/31/novartis-car-t-results-in-one-month-or-no-charge-why-one-month/
[43] http://annals.org/aim/article-abstract/2664654/value-based-payment-modifier-program-outcomes-implications-disparities
[44] http://www.modernhealthcare.com/article/20180111/NEWS/180119963
[45] https://www.hhs.gov/sites/default/files/AmericanPatientsFirst.pdf

It is our opinion that the participants in the pharmaceutical supply chain will not feel any immediate impact from this plan. We agree with Dr. Adam J. Fein, however, that it holds the potential for long term disruption.[44] This blueprint is not a piece of legislation , but does seem to open the door for legislative proposals. We note with interest the idea of "fiduciary duty for PBMs," although at no point in the plan are Direct and Indirect Remuneration (DIR) fees addressed, a problem that decreases affordability for patients, margin for pharmacy outlets, and potential revenue for manufacturers. One intriguing Part D proposal, however, does require that "a substantial portion of rebates" be applied at the point of sale. This would likely mitigate some of the transparency issues with DIR fees. Trump and Azar also propose that government (such as Medicare plans) be able to negotiate on drug prices and, in a second strategy for reform, be equipped with "better tools." Particularly pertinent to the biotech industry are goals to streamline development of biosimilars and pushing back on limited distribution models.

[46] https://www.drugchannels.net/2018/05/the-trump-drug-plan-short-term-reprieve.html

Future Trends (next 5 years)

First Principles Advisory Group Predictions

- **Full overhaul of insurance system highly unlikely.**
- **Top-down price controls will not happen.**
- **Pharma will continue focus on biotechnology agents up through gene therapy.**
- **PBMs will play an increasing role in clinic-administered medications.**
- **Price transparency will likely increase.**

What won't happen

We anticipate several future trends that are worth examining. The easiest and most obvious predictions are that cash payments won't stop and are unlikely even to slow down, for any type of treatment. Currently, "cash payer" is sometimes used as a type of code for "uninsured," but it can also mean self-insured and health systems may offer discounts and write-offs for prompt cash payments.

A single payer system is unlikely to be politically feasible in the near future in this country. Although we find it somewhat more likely than 20 years ago, we also note the erosion of the PPACA in the US political race to the extremes of the two party system. Any single payer system would necessarily depend upon rationing and triage, a concept unpalatable to Americans.

Price controls seem out of the question for now as well, and there is no hint of it in the Trump blueprint, although it recognizes international price controls as exacerbating the problem domestically. Use of therapy in off-label situations will not be going away at any point soon, either.

If anything, we expect a continued fragmentation of payers, "skinny" plans and high deductible coverages at state level, among payers, and among plans. This will lead to incomplete and uneven access to care, a major criticism of the United States health system, albeit an acknowledged problem in most other systems as well. This is likely to be accompanied by increased bureaucracy in governmental oversight.

What might happen

More interesting are the changes that are more likely to occur. We expect many of the current macro-trends to continue. In the world of drug development, the approval of specialty pharmaceuticals, and their share of all new drug approvals, should continue to increase. The economics of orphan drugs currently favor development and there seem to be no external factors pushing back. We anticipate continued advances in medication therapy as a continued evolution in technology from small molecules to recombinant proteins, to monoclonal antibody therapy, to focused gene therapy. The Trump administration is trying to create a business-friendly environment, and we see no threats to continued innovation at the development level. We anticipate the market for biosimilars to expand, although insufficient margins and sophisticated manufacturing will preclude biosimilar "generics" for some biotech drugs currently on market.

What will happen

We anticipate CMS, and by extension private payers, will continue to pay for therapy winners – those novel agents which do modify and cure diseases. The mechanism for these payments in the next 5 years is unclear; however, a wide variety of mechanisms currently exist. As an example, Steve Miller of Express Scripts, a prominent PBM, is calling for a "new payment model" for CAR-T, while Spinraza goes through at least one state's Medicaid prescription program rather than traditional medical benefit.[45] PBMs will continue to be increasingly involved in breakthrough therapies, even as they move more towards medical benefit drugs. We expect further integration, both by mergers and acquisitions, and operationally between payers and PBMs. Given this, and the fact we expect payers to continue coverage, we envision an increased focus on appropriateness of therapy to indication and disease state. Watch for continued analysis out of groups such as ICER to highlight value vs. benefit. As stated, off-label usage will continue, but coverage for the most expensive items will receive enhanced scrutiny, and non-evidence-based, non-approved therapy / indication matches may not be covered as a benefit.

We anticipate a continued trend towards transparency, particularly in pricing; it enjoys bipartisan political support, if not complete business support. The Trump blueprint does call for increased transparency and potentially immediacy of rebates. We also anticipate more transparency around patient coverage, charges, and costs in the payer arena.

Firms looking to develop novel agents have a friendly regulatory environment although complicated reimbursement pathways to navigate in the next 5 years. However, we anticipate and applaud exciting innovations and advancements.

Conclusion

The current environment of pharmaceutical sourcing, pricing, and reimbursement is complicated, and requires various competencies to navigate. One must understand the network of various players as well as their partnerships and competing motivations. As noted, manufacturers and Pharmacy Benefits Managers (PBMs) both have tremendous incentives to obfuscate costs in order to maximize return. Currently, pharma is enjoying a friendly regulatory atmosphere for development, which we anticipate to continue for the foreseeable future. However, drug companies are also facing increasing pressure for either lower costs or higher value from payers, consumers, watchdog groups, and the government. Therefore, developers must be ready to anticipate pricing pushback and demands for increased transparency. But for now, especially when value can be demonstrated, successful launches will continue to be extremely profitable.

[47] https://www.fiercepharma.com/financials/car-t-and-other-gene-therapies-need-new-payment-model-says-express-scripts

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