



Fee-for-value in the pharmaceutical industry: a policy framework applying data science to negotiate drug prices

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INTRODUCTION

In 2013, Valeant Pharmaceuticals, a specialty pharmaceutical company, received the intellectual property rights to a lead poisoning treatment known as Calcium EDTA as part of a \$2.6 billion deal to acquire Medicis Pharmaceuticals. Prior to the acquisition, the price for Calcium EDTA was stable at \$950. However, by the end of 2014, Valeant had increased the price of the drug in the USA to \$26,927, a 2700 per cent increase in 1 year.¹ Meanwhile, 500 miles away, over 8000 children in Flint, Michigan, were suffering from one of the worst lead poisoning crises in history, caused by the city's decision to opt out of receiving water from Detroit and instead draw it directly from the Flint River in April 2014 in an effort to save money.² At the same time, Mylan, a global pharmaceutical company, increased the price of the EpiPen, an emergency epinephrine autoinjector to treat anaphylaxis, from \$100 for a two-pack in 2007 to over \$600, or six times the original price, by 2016.³ The EpiPen isn't subject to price sensitivity; like insulin for patients with diabetes, it's a life or death drug. Patients simply don't have the choice to go without it.

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¹ Ed Silverman, *Huge Valeant Price Hike on Lead Poisoning Drug Sparks Anger*, STAT NEWS, Oct. 11, 2016, <https://www.statnews.com/pharmalot/2016/10/11/valeant-drug-prices-lead-poisoning/> (accessed Dec. 14, 2016).

² THE NEW YORK TIMES, *Events That Led to Flint's Water Crisis*, Jan. 21, 2016, <http://www.nytimes.com/interactive/2016/01/21/us/flint-lead-water-timeline.html> (accessed Dec. 14, 2016).

³ Aaron Carroll, *The EpiPen, a Case Study in Health System Dysfunction*, THE NEW YORK TIMES, Aug. 24, 2016, <http://www.nytimes.com/2016/08/24/upshot/the-epipen-a-case-study-in-health-care-system-dysfunction.html> (accessed Dec. 14, 2016).

Pharmaceutical price gouging isn't limited to a few drugs or corporations. From 2009 to 2015, 30 medicines with sales of \$1 billion or more per year underwent price increases of over double the rate of inflation as measured by the consumer price index, even when estimated discounts negotiated by health insurers and pharmacy benefit managers were taken into account.⁴ The average annual increase in retail prices for prescription drugs was 9.4 per cent, six times the general inflation rate of 1.5 per cent. For brand name drugs, it was 12.9 per cent, over eight times the rate of inflation.⁵ The United States pays more for drugs than any other country, leaving economists and ethicists worried that 300 million Americans are subsidizing drugs for the rest of the world.⁶

Under current regulatory policy, because of the lack of price transparency and the inability for many payers to negotiate, pharmaceutical manufacturers can charge whatever they please, setting exorbitant prices that defy normal market forces. As a result, there is often little correlation between how much a drug costs and its efficacy or safety profile. Drug companies justify high prices by pointing to high costs for research and development, patent protection, and the small market size for rare diseases.⁷ The Food and Drug Administration (FDA) has even, in certain cases, encouraged this, by providing extended market exclusivity for drugs meant to treat orphan diseases in an effort to increase research and development.⁸ Policymakers have proposed regulations to mandate that a certain percent of pharmaceutical revenue be allocated to research and development;⁹ however, that alone would be unlikely to lower market prices and instead might incentivize pharmaceutical companies to command higher prices to reach R&D expenditure benchmarks.

Part of the problem is that the multi-payer healthcare system in the USA has led to a fragmented market for purchasing drugs, which reduces the ability of payers to negotiate prices. Unlike European government-run healthcare systems, Medicare, the single largest US payer for prescription drugs, by law cannot directly negotiate prices with drug manufacturers.¹⁰ This is largely due to the influence of the pharmaceutical lobby, who argued that allowing Medicare to negotiate drug prices would undermine the revenue needed to sustain pharmaceutical innovation.¹¹ Medicare Part B is required

⁴ Robert Langreth, Michael Keller & Christopher Cannon., *Decoding Big Pharma's Secret Drug Pricing Practices*, BLOOMBERG, June 29, 2016, <https://www.bloomberg.com/graphics/2016-drug-prices/> (accessed Dec. 14, 2016).

⁵ AARP Press Center, *AARP Report: Retail Prescription Prices Increasing Six Times Faster Than Inflation*, AARP, Feb. 29, 2016, <http://www.aarp.org/about-aarp/press-center/info-02-2016/report-retail-prescription-prices-increasing.html> (accessed Dec. 14, 2016).

⁶ Robert Langreth, Blacki Migliozi & Ketaki Gokhale., *The U.S. Pays a Lot More for Top Drugs Than Other Countries*, BLOOMBERG, Dec. 18, 2015, <https://www.bloomberg.com/graphics/2015-drug-prices/> (accessed Dec. 14, 2016).

⁷ Sydney Kuplin, *5 Reasons Prescription Drug Prices Are So High in the U.S.*, TIME, Aug. 23, 2016, <http://time.com/money/4462919/prescription-drug-prices-too-high/> (accessed Dec. 14, 2016).

⁸ Enrique Seoane-Vazquez et al., *Incentives for Orphan Drug Research and Development in the United States*, 3 ORPHANET J RARE DIS. 33 (2008).

⁹ Carolyn Johnson, *Clinton Unveils Plan to Stop Price-Gouging on Old Drugs*, THE WASHINGTON POST, Sept. 2, 2016, https://www.washingtonpost.com/news/wonk/wp/2016/09/02/clinton-unveils-plan-to-stop-price-gouging-on-old-drugs/?utm_term=.b8ef4d97b03a (accessed Dec. 14, 2016).

¹⁰ Theodore T. Lee, Abbe R. Gluck, & Gregory Curfman, *The Politics Of Medicare And Drug-Price Negotiation (Updated)*, HEALTH AFFAIRS BLOG, Oct. 20, 2016, <http://healthaffairs.org/blog/2016/09/19/the-politics-of-medicare-and-drug-price-negotiation/> (accessed Dec. 14, 2016).

¹¹ *Id.*

to cover drugs and medical services deemed to be ‘reasonable and necessary’, leaving open a wide interpretation for what constitutes a ‘reasonable’ service.¹² This contrasts with most European systems, in which the decision to include a drug within a formulary is at the government’s discretion. In most instances, Medicare cannot refuse to provide coverage for a particular drug, no matter the cost, to patients.

VALUE-BASED REIMBURSEMENT IN HEALTHCARE

Healthcare as a service industry has been transitioning from a fee-for-service enterprise to fee-for-value, in which reimbursements are directly tied to standardized quality metrics and patient outcomes. This began with the 2012 Pioneer Accountable Care Organization (ACO) program¹³ and continued with the final rules for the Medicare Access and CHIP Reauthorization Act of 2015¹⁴ (MACRA), the latter providing the foundation for value-based physician payments beginning in 2019.

As a result of the unsustainability of the pharmaceutical market under the tension of high prices,¹⁵ public backlash, and broader reimbursement trends in healthcare, payers and drug manufacturers have begun experimenting with proposals to bring value-based reimbursements to pharmaceuticals. Some payers and benefits managers, including the United Kingdom’s National Health Service and Express Scripts in the United States, respectively, have negotiated variations of value-based contracts with pharmaceutical companies, coupling payments for a particular drug to corresponding indications and surrogate patient outcomes such as readmission rates and changes in blood count. The price of the drug varies depending on how well it performs within either a single patient or a given patient population. Payers and patients pay the premium price to manufacturers when the medication achieves desired outcomes. If the drug does not work as advertised, then manufacturers receive a lower price, or do not get paid at all.¹⁶ This may pressure pharmaceutical companies to align their incentives with those of the payers.

Value-based pricing contracts allow patients to receive drugs that are otherwise expensive with uncertain outcomes. Pressure from insurers is a large driver of the shift toward value-based drug pricing.¹⁷ Private insurers might decline to include new, expensive drugs in their health plans, but may be more open to include drugs for which their manufacturer has negotiated value-based contracts. This strategy allows the US healthcare system to contain costs without restricting the ability for patients to access new, but expensive, breakthrough therapeutics. For example, in October 2016, Anthem, which provides health insurance for nearly 38 million people in the USA, refused

¹² CGS Administrators, *Medically Necessary and Reasonable*, Jul. 30, 2012, http://www.cgsmedicare.com/hhh/coverage/hh_coverage_guidelines/1e.html (accessed Dec. 14, 2016).

¹³ Centers for Medicare and Medicaid Services, *Pioneer ACO Model*, Dec. 1, 2016, <https://innovation.cms.gov/initiatives/Pioneer-aco-model/> (accessed Dec. 14, 2016).

¹⁴ Centers for Medicare and Medicaid Services, *Quality Payment Program*, <https://qpp.cms.gov> (accessed Dec. 14, 2016).

¹⁵ Alison Kodjak, *Fight to Lower Drug Prices Forces Some to Switch Medication*, NATIONAL PUBLIC RADIO, Jan. 25, 2016, <http://www.npr.org/sections/health-shots/2016/01/25/463809474/fight-to-lower-drug-prices-forces-some-to-switch-medication> (accessed Dec. 14, 2016).

¹⁶ Stephen Barlas, *Health Plans and Drug Companies Dip Their Toes Into Value-Based Pricing*, 41 P T. 39, 53 (2016).

¹⁷ Tracy Staton, *Most U.S. Payers Are Eyeing Outcomes-Based Drug Pricing: Report*, FIERCEPHARMA, Jun. 20, 2016, <http://www.fiercepharma.com/pharma/most-u-s-payers-are-eyeing-outcomes-based-drug-pricing-report> (accessed Dec. 14, 2016).

to cover Exondys 51, a drug for duchenne muscular dystrophy (DMD) sold by Sarepta Therapeutics, due to doubts about the safety and efficacy of the medication despite FDA approval.¹⁸ The cost of Exondys 51, \$300,000 per patient per year, has neurologists worried that, unless Sarepta negotiates a value-based deal that makes it cost-effective for insurers to offer Exondys 51 to all DMD patients, insurers will restrict access to the drug to only patients who are similar to those that met the inclusion criteria for Exondys 51's clinical trials.¹⁹

This scenario is likely to occur more often following passage of the 21st Century Cures Act, signed into law in December 2016. The Cures Act relaxed FDA approval standards and made it easier for certain drug classes to obtain market approval. For example, Cures permits certain regenerative therapies to receive approval based on clinical anecdotes and surrogate marker endpoints, such as tumor shrinkage, instead of clinically validated outcomes such as increased life expectancy from robust clinical trials.²⁰ This places a greater burden on insurance companies, along with clinicians and patients, to gather and evaluate information on a drug's safety and efficacy. As a result, if insurers believe that clinical trial data isn't robust enough to merit a new drug's inclusion within their formularies, they may push for value-based contracts to avoid potentially paying a premium for an ineffective, or even dangerous, treatment; ideally, this will help deter manufacturers from conducting weak clinical trials simply to speed up a drug's market release date.

The following two sections explore variations of value-based negotiating tactics of two international, government-run health systems, the United Kingdom and Norway, and how their strategies have influenced the development of value-based reimbursement models among both public and private actors in the United States.

Public sector value-based drug pricing

Most government-run healthcare plans, such as in the United Kingdom, Norway, and Canada, already evaluate drugs to some extent under an outcomes-based framework. England's National Institute for Health and Care Excellence, NICE, puts pressure on pharmaceutical companies by analyzing and recommending which drugs are worth covering based on their relative value to patients.²¹ In cases when a drug is rejected by a government health agency for failing to meet standards for clinical or cost-effectiveness, manufacturers will often reduce its price to increase its relative value. Because the National Health Service covers all UK citizens, manufacturers have no choice but to negotiate prices or lose out on the entire market.

In Norway, the Norwegian Medicines Agency (NMA) reviews patient data to determine the cost-effectiveness of a new drug and whether or not they should include

¹⁸ Ed Silverman, *Anthem Declines to Cover Sarepta Drug for Duchenne, Citing Doubts Over Data*, STAT NEWS, Oct. 7, 2016, <https://www.statnews.com/pharmalot/2016/10/07/anthem-duchenne-sarepta-fda/> (accessed Dec. 14, 2016).

¹⁹ Ed Silverman, *Doctors Expect to Prescribe Sarepta's DMD Drug Despite Insurance Concerns*, STAT NEWS, Sept. 27, 2016, <https://www.statnews.com/pharmalot/2016/09/27/doctors-sarepta-insurance-coverage-worries/> (accessed Dec. 14, 2016).

²⁰ 21st Century Cures Act, H.R. 34, 114th Cong. (2016).

²¹ Andrew Ward, *Drug Prices: Tweaking the Formula. UK Regulators Are Under Pressure From Big Pharma As Well As Patients*, FINANCIAL TIMES, Apr. 25, 2016, <https://www.ft.com/content/b034a38e-0abf-11e6-9456-444ab5211a2f> (accessed Dec. 14, 2016).

it within their drug formulary.²² Evaluations are based on a requested manufacturer reimbursement price, fixed at or under a preset government cap, along with a comparison of the drug's performance against existing therapies, usually measured in terms of quality-adjusted life years (QALYs). Similar to negotiations with the UK, manufacturers who have drugs rejected for coverage in Norway will counter by either providing additional performance data or offering a lower price. For example, the NMA deemed the osteoporosis injection Prolia to be cost-ineffective when compared to Aclasta, an existing osteoporosis drug. Aclasta, which belongs to a different drug class than Prolia, was deemed to protect against fractures for a longer duration following treatment than Prolia. As a result, Amgen and GlaxoSmithKline PLC, the manufacturers of Prolia, reduced their reimbursement price in order to smooth the way into the market. Norway then agreed to cover Prolia at a cost of \$260 for women over 75 years old, a demographic for whom patient data illustrated improved outcomes. Medicare, on the other hand, paid \$893 per syringe of Prolia with no age threshold, and no objective evaluation of efficiency.²³

The Centers for Medicare and Medicaid Services has recently declared its aim to experiment with indication-specific pricing within the Medicare Part B program, which includes medications prescribed in outpatient clinics and physician offices. Two of the proposed strategies include (1) outcomes-based pricing, altering prices based on clinical effectiveness through risk-sharing agreements with manufacturers,²⁴ and (2) reference pricing, setting a benchmark price for therapeutically similar drugs and reimbursing drugs that produce outcomes comparable to cheaper drugs at the price of the cheaper treatment.²⁵

Private sector value-based drug pricing

Pharmaceutical companies have also taken the initiative to experiment with value-based reimbursement models. Novartis, a multinational pharmaceutical company, launched a heart failure drug, Entresto, which was found to reduce the risk of hospital readmission for heart failure patients by 21 per cent in a trial published in the *New England Journal of Medicine*.²⁶ Novartis has negotiated a contract with insurance companies in which Novartis will be paid a premium if patients taking Ernesto stay out of the hospital more often than patients taking other, less expensive medications for heart failure.²⁷ Insurers covering patients who benefit from Ernesto will pay the premium

²² International Society for Pharmacoeconomics and Outcomes, *Norwegian Guidelines for Pharmacoeconomic Analysis in Connection With Applications for Reimbursement*, 2, http://www.ispor.org/peguidelines/source/Norwegian_guidelines.pdf (accessed Dec. 14, 2016).

²³ Jeanne Whalen, *Why the U.S. Pays More Than Other Countries for Drugs*, THE WALL STREET JOURNAL, Dec. 1, 2015, <http://www.wsj.com/articles/why-the-u-s-pays-more-than-other-countries-for-drugs-1448939481> (accessed Dec. 14, 2016).

²⁴ Peter Bach, *Indication-Specific Pricing for Cancer Drugs*, 312 JAMA 1629, 1630 (2014).

²⁵ Sham Mailankody & Vinay Prasad, *Implications of Proposed Medicare Reforms to Counteract High Drug Prices*, 316 JAMA 271, 272 (2016).

²⁶ John McMurray et al., *Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure*, 371 NEW ENG. J. MED. 993, 1004 (2014).

²⁷ Tess Stynes, *Novartis Reaches Entresto Pay-for-Performance Deals With Cigna, Aetna*, THE WALL STREET JOURNAL, Feb. 9, <http://www.wsj.com/articles/novartis-reaches-entresto-pay-for-performance-deals-with-cigna-aetna-1455038859> (accessed Dec. 14, 2016).

price for the drug, but theoretically their clinical improvement as a result may reduce their overall, long-term medical costs.

Express Scripts and CVS have taken a nuanced approach to value-based reimbursements, arguing for variable prices on drugs depending on outcomes related to specific indications, ie certain illnesses or symptoms, rather than entire therapeutic categories.²⁸ The oncology drug Herceptin provides an example of the CVS approach to drug pricing. Herceptin is indicated for breast cancer and gastric cancer and evaluated on the basis of decrease in tumor size. It has performed well against the former but has only a marginal benefit against the latter. Herceptin would thus command a premium price only for patients with breast cancer and be offered at a discount when used for patients with gastric cancer.²⁹ The controversy surrounding this method of pricing, however, is that prior to Herceptin, patients with gastric cancer had no other option for treatment. Even the modest increase in survival rates among gastric cancer patients with tumor variations indicated for Herceptin was meaningful for that population, and led to an increase in initiatives to study immunomodulatory responses to variations of gastric cancer.³⁰

Benefits and challenges of value-based drug pricing

Value-based reimbursement provides a financial incentive to pharmaceutical companies to develop truly innovative drugs, instead of making small modifications to existing products in order to extend patent protection. It also helps promote generation of clinical trial data that clearly outlines risks and benefits of the drug relative to status quo options. Additionally, medications in the same drug class that currently command premium prices would be subject to comparisons against each other, providing downward pressure to both decrease costs and improve clinical outcomes.³¹ As a result, only one drug in each class will be able to win the ‘best in class’ label and demand a premium price relative to the others.

However, treatment variation, adjuvant therapies administered concomitantly with the drug in question, difficult-to-measure long-term healthcare costs, and subjective metrics to gauge value, such as ‘quality of life’ and multipliers for ‘novelty of treatment’, have made it difficult to scale value-based pricing.³² Additionally, drug companies worry that pharmacy benefit managers and insurers may pocket savings rather than allow them to trickle down to patients and that payers may purchase medications at the cheapest indication and use them off-label.³³

²⁸ Peter Loftus & Anna Mathews, *Health Insurers Push to Tie Drug Prices to Outcomes*, THE WALL STREET JOURNAL, May 11, 2016, <http://www.wsj.com/articles/health-insurers-push-to-tie-drug-prices-to-outcomes-1462939262> (accessed Dec. 14, 2016).

²⁹ Tracey Walker, *CVS, Express Scripts Plan Value-Based Drug Pricing*, MANAGED HEALTHCARE EXECUTIVE, Apr. 3, 2016, <http://managedhealthcareexecutive.modernmedicine.com/managed-healthcare-executive/news/cvs-express-scripts-plan-value-based-drug-pricing?page=0%2C1&trendmd-shared=1> (accessed Dec. 14, 2016).

³⁰ Krishna Gunturu et al., *Gastric Cancer and Trastuzumab: First Biologic Therapy in Gastric Cancer*, S THER. ADV. MED. ONCOL. 143, 151 (2013).

³¹ Barlas, *supra* note 16, at 39–41.

³² Peter Bach, *A New Way to Define Value in Drug Pricing*, HARVARD BUSINESS REVIEW, Oct. 6, 2016, <https://hbr.org/2015/10/a-new-way-to-define-value-in-drug-pricing> (accessed Dec. 14, 2016).

³³ Ed Silverman, *How Much Should That Drug Cost? Depends What Disease It Treats*, STAT NEWS Mar. 22, 2016, <https://www.statnews.com/pharmalot/2016/03/22/drug-pricing-indication-specific/> (accessed Dec. 14, 2016).

Applications of data science for value-based pricing

Utilizing clinical data analytics to monitor health outcomes after a product is approved for marketing may alleviate some of these concerns from manufacturers and even improve patient response to treatment. Value-based pharmaceutical pricing offers the opportunity to use data from electronic health records, population health software, patient-reported information, and insurance claims to both expand the market for current drugs and regulate drug prices to reflect their relative value to patients. This would require precise tracking of when drugs are prescribed and for what indication along with the collecting of outcomes measures information. However, short of an infusion of government funds and resources, the capacity to fund, build, and maintain this level of data infrastructure and analysis will likely fall on private payers.

Designing effective value-based contracts for drug reimbursement is only possible with high-quality longitudinal outcomes data that is easy to both share and access. Digital health platforms and experimental delivery models have become promising in high-cost therapeutic areas, such as oncology.³⁴ Electronic medical records (EMR) systems, including those prevalent in large hospital systems such as Epic³⁵ and oncology-specific data analysis platforms such as Flatiron Health,³⁶ provide an early foundation for clinicians and scientists to collect and measure discrete, concrete patient outcomes and match them to novel cancer treatments. Additionally, the legislative push for interoperability and open access to medical records would allow technology companies and data scientists to build machine learning algorithms to mine EMR data and detect patterns in response to treatment and provide clinical decision support to care teams.³⁷

Machine learning allows computers to sift through thousands of example cases; in this case, outcomes data related to medication use from medical records, along with whether the outcome was beneficial. This is known as a training set. Computers then use that experience to solve the same problem in newly obtained medical records. Effectively, the computer is trained to solve by example. Many of the recent breakthroughs applying machine learning to problems in medicine have been via deep learning, a form of machine learning inspired by the structure and function of neurons in the human brain. Deep learning research has already identified a range of clinically relevant information from medical records, ranging from drug–drug interactions from clinical notes³⁸ to diabetic retinopathy from retinal fundus photographs³⁹. Deep learning algorithms are capable of learning what features of a dataset to focus on themselves based on prior examples, allowing them to identify previously unseen connections between inputs and outputs. Applied to value-based drug pricing, this might include identifying novel side effects when evaluating therapeutics and retrospectively identifying drug

³⁴ Mitchell Mom & Ashlee Adams, *Digital Health Funding 2016 Midyear Review*, ROCK HEALTH, <https://rockhealth.com/reports/digital-health-funding-2016-midyear-review/> (accessed Dec. 14, 2016).

³⁵ Epic Systems Home Page, <http://www.epicsystems.com> (accessed Dec. 5, 2016).

³⁶ Flatiron Health Home Page, <https://flatiron.com> (accessed Dec. 5, 2016).

³⁷ Andrew L. Beam & Isaac S. Kohane, *Translating Artificial Intelligence Into Clinical Care*, THE JAMA NETWORK, Dec. 13, 2016, <http://jamanetwork.com/journals/jama/fullarticle/2588761> (accessed Dec. 14, 2016).

³⁸ Srinivasan Iyer et al., *Mining Clinical Text for Signals of Adverse Drug-Drug Interactions*, 21 JAMA 353, 362 (2014).

³⁹ Varun Gulshan et al., *Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs*, THE JAMA NETWORK, Dec. 13, 2016, <http://jamanetwork.com/journals/jama/fullarticle/2588763> (accessed Dec. 14, 2016).

combinations that produce better outcomes.⁴⁰ Because deep learning models can be hosted on cloud software⁴¹ and, in theory, become more accurate as their training set grows, scaling algorithms to collect more outcomes data may not only be relatively inexpensive and cost-effective, but also provide more nuanced evaluations of treatment outcomes over time.

PROPOSALS FOR VALUE-BASED PHARMACEUTICAL REGULATORY POLICY IN THE UNITED STATES

The following is a proposed framework for establishing baseline drug prices based on clinical trial outcomes and utilizing postmarket monitoring to evaluate value relative to competing products over time. The framework is guided by international regulatory policy, innovations in digital health, and feasible additions to the value-based pricing strategies currently being tested in the United States.

Legislative policy

The US government will need to take certain regulatory steps to establish the groundwork to scale value-based pricing in the pharmaceutical industry. Similar to current CMS value-based reimbursement pilots for Medicare Part B mentioned earlier, the government could implement a similar pilot for value-based contracts in Medicare, the program that subsidizes prescription drugs, through a limited waiver of the ban on Medicare drug price negotiation. The pilot project would need to select a specific drug class and then decide whether CMS as a central entity or individual drug plans would lead negotiations with manufacturers. However, because Congress is unlikely to allow Medicare to directly negotiate drug prices, regulatory steps should favor making the posttrial clinical outcomes of drugs and their net costs more transparent, in an effort to exert downward pressure on prices.

Primarily, Congress should (1) authorize and fund the FDA to comparatively evaluate drugs using metrics such as QALYs and disability-adjusted life years from clinical trial data, and (2) establish an independent drug review board within either the FDA or as part of the Patient-Centered Outcomes Research Institute established by the Patient Protection and Affordable Care Act. The Institute is up for reauthorization in 2019, which offers the opportunity to amend its role to include the direct evaluation of pharmaceuticals.⁴² This would allow each medication to be given a recommended base price for each indication based on performance in clinical trials relative to similar drugs in its class and the manufacturer's asking price.

Congress is unlikely to allow CMS or other government agencies to set strict price controls, but it can help make pharmaceutical prices more predictable by offering a price recommendation and transparency to payers and enacting policies to limit the rate of price inflation. Congress could mandate that manufacturers make the net price

⁴⁰ Yen Low et al., *Synergistic Drug Combinations From Electronic Health Records and Gene Expression*, JAMIA, Dec. 9, 2016, <http://jamia.oxfordjournals.org/content/early/2016/12/09/jamia.ocw161.abstract> (accessed Dec. 14, 2016).

⁴¹ Google, *Cloud Machine Learning Platform*, <https://cloud.google.com/products/machine-learning/> (accessed Dec. 5, 2016).

⁴² Fred Schulte, *Obamacare Research Institute Plans to Spend \$3.5 Billion, But Critics Question Its Worth*, THE CENTER FOR PUBLIC INTEGRITY, Aug. 4, 2015 <https://www.publicintegrity.org/2015/08/04/17762/obamacare-research-institute-plans-spend-35-billion-critics-question-its-worth> (accessed Dec. 14, 2016).

of a drug, that is, the price negotiated by payers, distributors, pharmacy benefits managers, and other intermediary buyers rather than the list, or sticker, price. The difference between list and net prices has historically been opaque and gave pharmaceutical companies the opportunity to make secretive deals with intermediaries to obscure the true cost of treatment.⁴³ Making net prices transparent may enable more open and efficient market competition among manufacturers and intermediary buyers, which benefits patients by driving down prices, and could possibly improve public trust in the industry. Price inflation regulation may take the form of requiring that manufacturers match each dollar of price inflation to an equal amount of additional R&D spending during the last few years of market exclusivity or increasing tax credits to offset R&D spending that matches price adjustments.⁴⁴

Additionally, multiple private organizations in the United States, including the Institute for Clinical and Economic Review⁴⁵, the Independent Drug Information Service⁴⁶, and Oregon's Drug Effectiveness Review Project⁴⁷, have done comparative effectiveness research regarding the value of different medications. The resulting analysis, from both governmental and non-governmental organizations, could be used not only to help payers respond to manufacturer prices and negotiate discounts, but also determine formularies and educate patients and providers about the relative value of different medications.

Applying data science to negotiate pharmaceutical prices

Following market release, the recommended base price may be recalibrated through a 'value calculator' that collects outcomes data on how well the drug works in practice, including from postmarket phase IV trials, patient-reported information, medical records, and related insurance claims, and standardizes this information in a single database. This encourages collaboration between pharmaceutical manufacturers, insurance carriers, EMR companies, and clinicians to optimize treatment efficacy to maintain reimbursement levels.

Many significant interactions and discoveries about how well a drug works happen after phase III clinical trials end and a drug receives FDA approval. After a drug hits the market, manufacturers sometimes conduct postmarket surveillance (phase IV) trials to oversee possible drug–drug interactions, long-term safety, and rare and long-term side effects, particularly on demographics that may have been excluded from prior studies, such as pregnant women or children.⁴⁸ In some instances, these studies help pharmaceutical companies discover new markets for a drug. In others, they lead to drug

⁴³ Matthew Herper, *Inside The Secret World Of Drug Company Rebates*, FORBES, May 10,, <http://www.forbes.com/sites/matthewherper/2012/05/10/why-astrazeneca-gives-insurers-60-discounts-on-nexiums-list-price/#495270e94fd6> (accessed Dec. 14, 2016).

⁴⁴ David Gilman & Nathan Dowden, *Is Value-Based Drug Pricing Compatible with Pharma Innovation?*, NEJM CATALYST, Jun 14, 2016, <http://catalyst.nejm.org/is-value-based-drug-pricing-compatible-with-pharma-innovation/> (accessed Dec. 14, 2016).

⁴⁵ Peter Bach & Steven Pearson, *Payer and Policy Maker Steps to Support Value-Based Pricing for Drugs*, 314 JAMA 2503, 2504 (2015).

⁴⁶ Alosa Health, *Independent Drug Information Service*, <http://www.alosafoundation.org/independent-drug-information-service/> (accessed Dec. 5, 2016).

⁴⁷ Peter Neumann, *Emerging lessons from the Drug Effectiveness Review Project*, 25 HEALTH AFF. W262, W271 (2006).

⁴⁸ TP Hill, *Conducting Phase IV Clinical Studies: A Moral Imperative?* 6 ECANCERMEDICALSCIENCE 276 (2012).

restrictions or recall, such as the recall of Vioxx in 2004.⁴⁹ While the FDA is supposed to regulate postmarket trial data and adverse drug event reports from MedWatch,⁵⁰ it has lagged in listing possible safety issues found with drugs due to both a backlog of unreviewed postmarket studies and poor standardization of that data for analysis.⁵¹

The value calculator tool would take the shape of an aggregate database composed of factors that payers, clinicians, and patients find make a drug valuable, including cost of treatment, each with the ability to be assigned a relative weight by the payer in question. These factors would vary depending on the therapeutic class of the drug, that is, advantages of an oncology drug, such as life extension and tumor shrinkage, will differ from those of a drug for heart failure, which may include prevention of readmission and pulmonary edema. Drug classes that have discrete, predictive surrogate markers that measure health outcomes, such as those for high cholesterol and cancer, are prime targets for initial trials of value-based pricing. Because data analytics systems to track health outcomes have become increasingly prevalent and continue to spread, particularly as healthcare payment reform begins to scale, there is an opportunity to automate the collection and aggregation of outcomes data across EMR systems for the purpose of determining pharmaceutical value.

The largest challenge facing the development of a universal value calculator is the significant data sharing required between CMS, the FDA, EMR companies, and private payers. Memorial Sloan Kettering Cancer Center has been working on a similar concept, DrugAbacus,⁵² which allows patients and physicians to comparatively weigh oncology drug prices based on personal constitutions of what advantages are ‘valuable’. However, critics of DrugAbacus argue that for diseases driven by significant genetic and cellular variation, such as cancer, an individual patient’s responses to a particular therapy are much more valuable in determining treatment decisions compared to the response of the entire population.⁵³ Additionally, DrugAbacus does not include patient-centered criteria in its calculation, such as patient ‘quality of life’ or ‘feelings of hope’.

Continuous metric monitoring will also shift how therapeutics are delivered to patients. Pharmaceutical companies will have an incentive to package their drugs with ‘digital solutions’, software and/or hardware that aim to support treatment by improving medication adherence, chronic disease management, and overall wellness.⁵⁴

Packaging a therapeutic with a well-designed technology as a bundled solution could improve health outcomes and increase the price that a manufacturer is able to charge for

⁴⁹ The United States Food and Drug Administration, *FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product*, Sept. 30, 2004, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108361.htm> (accessed Dec. 14, 2016).

⁵⁰ The United States Food and Drug Administration, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, <http://www.fda.gov/Safety/MedWatch/> (accessed Dec. 14, 2016).

⁵¹ Sheila Kaplan, *FDA Faulted for Failure to Track Safety Issues With Drugs Already on Market*, STAT NEWS, Jan. 14, 2016, <https://www.statnews.com/2016/01/14/fda-postmarket-study-report/> (accessed Dec. 14, 2016).

⁵² Memorial Sloan Kettering Cancer Center, *Evidence Driven Drug Pricing Project*, <http://www.drugabacus.org> (accessed Dec. 5, 2016).

⁵³ Robert Goldberg, *Jimmy Carter’s Cancer Cure Demeaned By Bach Cancer Abacus*, DRUG WONKS, Mar. 8, 2016, <http://drugwonks.com/blog/jimmy-carter-s-cancer-cure-demeaned-by-bach-cancer-abacus> (accessed Dec. 14, 2016).

⁵⁴ David Champagne, Amy Hung, & Olivier Leclerc, *How Pharma Can Win In a Digital World*, MCKINSEY & COMPANY, Dec. 2015, <http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/how-pharma-can-win-in-a-digital-world> (accessed Dec. 14, 2016).

the drug. This is particularly true in the case of medication adherence, where low numbers can lead to negative health outcomes and make therapies seem much less effective than advertised. Examples of this include mobile applications that remind patients to pick up and refill prescriptions and take their medications on time and electronic pill-boxes that dispense only the correctly prescribed dosage and track adherence. These digital tools, if put into practice, also offer an additional point-of-contact between manufacturers and patients to measure the use and effectiveness of treatments.

CONCLUSION

To negotiate well-designed value-based contracts, manufacturers and payers will need to align their expectations of outcomes measures and define the time period to evaluate those measures. While these value-based proposals are unlikely to serve as a blanket cure-all for all drug classes or indications, the willingness of pharmaceutical companies and payers to experiment with value-based pricing strategies and the challenges they face is indicative of a shift in the industry toward rewarding products that prove their worth and the need for comprehensive data analysis tools to evaluate their outcomes.