MassBio®

Value of Health Series

PART I

How to Define the Value of Prescription Drugs to Ensure Patient Access

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Introduction

For a growing number of therapies, especially specialty drugs, manufacturers can no longer assume payer coverage and patient access based on regulatory approval alone. Increasingly, manufacturers are being asked to first demonstrate the "value" of the drug—to patients and to the healthcare system—and thus, justify its price, before being added to a payer's formulary, which is comprised of those prescription drugs they'll cover in part or full.

This demonstration of value will ultimately determine who has access to new therapies, but it also determines how patients gain that access. Value determinations can influence whether payers add additional barriers to certain drugs such as requiring prior authorization from physicians or implementing step therapy, which forces patients to fail first on less expensive drugs before trying others. The challenge? There is no objective or shared measure of value.

This whitepaper explores the value equation from the perspectives of the various healthcare stakeholders, drawing from insights from a MassBio advisory group [see Appendix]. Its goal is to educate biopharma companies, especially those in early and mid-stages, about the current and expected environment they're operating in, and considerations these companies must make to ensure patient access when their drug comes to market. It is our belief that the sooner companies start thinking about value and how they will demonstrate it, the fewer hurdles to patient access will exist.

For MassBio and our membership, this issue is especially timely. We're at an inflection point, with science that's been tested for decades finally becoming a reality for patients and a payer system that has not caught up with this level of innovation. Myriad factors are combining to alter the status quo—with policymakers demanding action, and healthcare stakeholders agreeing that we must come up with real solutions. If we don't come together and address the value equation as an industry and ensure patient access to all new therapies, government or other stakeholders will—and they will likely get it wrong.

"Value" Means Something Different to Everyone

Key constituencies measure value differently, and it's critical to understand where each are coming from as the industry tries to agree on a common value equation.

Patients

Patients want to be healthy and productive. They want to trust that their doctors and payers act in their best interest and will do everything they can to restore their health. They want new, safe, and effective treatments to come to market quickly, and do not want hurdles to access them. They seek drugs with limited side effects, that are convenient to administer, and allow them to go about their normal daily routine. Patients tend not to think about healthcare costs until they're faced with the bill or until someone they love gets sick. It's *personal*.

Policymakers

When state and federal policymakers consider the value of prescription drugs, they are largely driven by two considerations: 1) what their constituents are saying about their experiences accessing their prescriptions, especially their out-of-pocket costs; and, 2) the impact of drug prices on state Medicaid and federal Medicare budgets. Considerations about patient access and policy's impact on the innovation of new therapies tend to be tertiary.

Payers

Payers think first and foremost about the budget impact of prescription drugs. Their value equation carefully considers many different factors including comparative effectiveness and patient population size so they can best gauge whether covering a drug improves outcomes for their covered lives at a reasonable cost. Payers also budget annually and have to contend with patients' ability to change insurers annually, thus, limiting their consideration of long-term costs avoided in their value equation.

Providers

Providers have a multifaceted view of prescription drugs' value. Depending on the provider, they can administer drugs in-patient, out-patient, or through doctor's office visits. Increasingly, new, specialty therapies are administered only in hospital settings. This can create a value-add for the provider through hospital markups on drugs, but can also present providers with significant reimbursement challenges depending on the type of drug, especially with public payers.

Investors

Investors understand that biotech is a risky business and has a high percentage of failure. But they also expect to receive big returns for the associated risks—especially since these returns can take upwards of 10 years to come to fruition. Investors must think about new paradigms in healthcare, how new therapies can positively impact the practice of medicine, and who will have access to them at the time of approval. In a way, investors have to understand the current and future perspectives of all the other stakeholders, or they cannot be successful.

Society

We're always making tradeoffs in the U.S. on what we spend on education, the military, healthcare, and other important areas, but what sets healthcare apart is denying access to care is "un-American" to some and those that put this care out of reach are subject to major public scrutiny. In this environment, there is an expectation that sick people will be taken care of, and value is not often a consideration. If there is any discussion or debate over value to society, it's increasingly only based around price.

> *"The payer for a therapy will not always reap the full value from that therapy (e.g. commercial payer does not get benefit of improved work productivity, the employer does). There is no one stakeholder that is incentivized to pay for full value, which complicates the equation."*
>
> *—Clark Paramore, Head of Value Demonstration, bluebird bio*

It's no surprise that it's near impossible to satisfy each constituent, since each views the value of drugs in such different ways. It's up to us, as an industry, to develop a clear and consistent case for value that incorporates these various viewpoints and more importantly, speaks to them.

How the Industry Makes the Case for Value

Traditionally, biopharma companies overwhelmingly consider four factors when setting price and making their case for value:

- Costs of R&D
- Cost of production / commercialization
- Financial returns to fuel future innovation
- Value of the therapy to patients, the healthcare system and society in terms of improved outcomes & cost avoidance


However, as the pricing debate grows and becomes more top of mind to the average American, the first three factors above are becoming less relevant in terms of proving value of a therapy. Healthcare stakeholders must understand the need to cover costs of R&D, production, and future innovations, **but, the more effective and contemporary methodology when it comes to price and value is around improved outcomes and cost avoidance.**

Improved outcomes

Does your therapy improve patient health? Does it solve an unmet medical need? Is it incrementally or substantially better than the current standard of care? Does it improve ease of use or compliance? Are there fewer side effects for the patient? Does it improve their quality of life and possible longevity? Do you have data to back this up? These are critical questions to ask when making the case for value.

"Costs avoided can be harder to convince payers since it can clash with their year-by-year view of the world. It can also be hard to convince even public payers when the cost equation has to do with non-healthcare expenses and therefore relate to other agencies, e.g. increased tax revenue or decreased home caregiver costs, rather than, say, hospital bills."

—Anna Turetsky, Vice President, Lightstone Ventures

Cost avoidance

Can you show that your drug prevented chronic care, a costly hospitalization, or an organ transplant? Can you prove that your drug allowed a patient to go back to work and contribute to society? Can you demonstrate the impact to the caregiver? Cost avoidance is likely the hardest to measure, but the most important. It requires the ability to track real-world evidence from patients—often over many years—and relies on our capacity to track non-healthcare expenses, like increased worker productivity.

Third-parties have attempted to create their own methodologies when it comes to assessing value, which are important to consider.

Recommendations

- When making your case for value, prioritize methodology around improved outcomes and cost avoidance.
- Create the necessary mechanisms to track these outcomes and costs avoided early on—even before clinical trials.
- Start making the case for value to payers, providers, and patients during clinical trials or earlier (even during discovery/preclinical development) and prior to regulatory approvals.

Third-Party Value Assessments — The Increased Use of Health Technology Assessments

U.S. regulatory approvals, and thus payer coverage, have historically been decided based on a drug's clinical safety and effectiveness data. Increasingly, payers employ comparative effectiveness measurements to determine reimbursement and patient access for new therapies—but there is no uniform method across payers. Health technology assessments (HTAs) seek to create a standardized, data-driven, and evidence-based approach to measuring the value of a drug. Supporters of HTAs argue they are the best tool available to make rational decisions about limited healthcare resources.

Regulators and payers in the EU regularly utilize HTAs and have for decades. In fact, it's part of the formal reimbursement process in many EU countries. HTAs are used more sparingly in the U.S. and have historically focused more on certain areas such as oncology or cardiology, until the creation of the Institute for Clinical and Economic Review (ICER) in 2006.

ICER, which models itself after the UK's National Institute for Health and Care Excellence (NICE), seeks to influence drug pricing and reimbursement decisions by private and public payers. Funded by various interested stakeholders, ICER performs value assessments of drugs and releases reports that determine if the drug is priced appropriately. The fact that a large source of ICER's funding is from payers and non-profits that are antagonistic to the biopharma industry has raised questions about whether its value determinations are truly objective.

In practice, ICER serves as a resource for private and public payers seeking to determine appropriate reimbursement levels for drugs—what ICER believes is the drug's real value. Payers can use this information as a starting point for manufacturer negotiations for determining whether certain drugs should require prior authorization or step therapy, or to remove the drug from their formulary altogether. Recently, state Medicaid programs are considering if and how to use ICER data to help set prices for certain drugs.

On its face, there is a reasonable argument for an independent organization that can use a standardized value assessment for all drugs, but the biopharma industry must advocate for a fair methodology that satisfies as many healthcare constituents as possible—and offer solutions for those that fall short. Although the biopharma industry and patients share common frustrations with ICER, especially how its methodology places a price on a patient's life, it's important to understand how ICER evaluates drugs.

ICER utilizes cost per quality-adjusted life year (QALY) estimates as a benchmark for comparing the value of different treatments, as they measure both quantity and quality of life. QALYs, however, are controversial because many, patient groups especially, believe they are not patient focused, may be used as rationing tools by payers, and are often perceived as dehumanizing. Despite these criticisms, HTAs increasingly rely on QALYs as the basis for cost-effective analyses. When assessing the long-term value of a therapy, ICER takes into account:

Comparative clinical effectiveness

ICER assigns a grade from "A" to "I" based on the net benefits vs a comparator therapy. A grade "A" offers "substantial" benefit, and "D" offers "negative" benefit with "I" representing "insufficient evidence."

Cost-effectiveness

To determine the cost per QALY, ICER uses an equation that boils down to [$New - $Old / (QALYs New — QALYs OLD)]. If the cost-effectiveness benchmark is above $100,000 to $175,000 per QALY, ICER determines the therapy as low value.

Qualitative considerations

This is where ICER considers factors like reduced health disparities, reduced caregiver burden, and improved worker productivity. However, despite collecting this information directly from patients and caregivers, it's unclear how ICER ultimately uses that information in its final analysis, if at all. This is the least understood component of their methodology—and the one most in need of transparency.


ICER then reviews the short-term affordability of a therapy, or the budget impact. For this, they look at the utilization (driven by clinical need) multiplied by the net cost to determine the appropriate level of spending.

ICER is becoming more embedded across the health-care system and is already having an outsized impact on reimbursement and coverage decisions. In fact, just last year the New York State Drug Utilization Review Board used cost-effectiveness estimates from ICER to set negotiating parameters for supplemental rebates in the state's Medicaid program. Companies with drugs in the pipeline must seriously contend with how a potential ICER review of that drug will impact its future success and its ability to reach patients who need it.

Case Study

In August 2018, CVS Health, which operates one of the country's largest pharmacy benefit managers, announced a new effort to allow its Caremark clients (health plans and self-funded employer groups) to exclude drugs from their formularies that don't meet a benchmark of $100,000 per QALY in analyses by ICER. While this excludes those drugs deemed "breakthrough" therapies by the FDA, it still has the ability to impact access for countless drugs that patients want or need access to, or to put in place more restrictions like step therapy.

"By identifying cost-effectiveness benchmarks and budget thresholds to which a technology can be compared, ICER weighs in on what level of spending is appropriate. However, judgments about proper spending are better rendered by actual decision makers (payers and their enrollees) in consideration of specific budget constraints, preferences, and tradeoffs. To be sure, payers can and do ultimately make their own decisions; the question is what influence ICER assessments have on payers, and on what basis ICER imposes its own sensibilities about whether drugs are "over-priced" and the appropriate amount of spending."

—Peter Neumann, Director, Center for the Evaluation of Value and Risk in Health, Tufts Medical Center

Recommendations

- Determine the cost-effectiveness of your therapy against ICER's current methodology (what's public).
- Find ways to engage with ICER to help improve their methodology; offer solutions for better accounting of and transparency around qualitative considerations.
- Advocate, as an industry, for a fair methodology that satisfies as many healthcare constituents as possible.
- Create a mechanism to engage with patients on an ongoing basis to measure and prove the long-term benefits of a therapy.

Innovative Payment Methods — Spotlight on Value-Based Arrangements

Even in cases where ICER may determine that a drug's price is consistent with its long-term value, there are still considerations companies must make around budget impact of a drug to private and public payers. As a result, more payers and manufactures are agreeing to new innovative payment models that reward specifically for value over a period of time. These are more often seen with new breakthrough innovations where the long-term benefit may not be as clear. One popular format is a voluntary value-based arrangement (VBA).

In the simplest terms, value-based arrangements, also referred to as outcomes-based contracts or value-based contracts, describe agreements between drug companies and payers setting the level of reimbursement for the manufacturer's drug based on a patient's health outcomes over time. In practice, this means payers will pay the full mutually negotiated price if the drug meets agreed-upon health milestones, and if it does not, the payer is only responsible for part or none of the drug's cost.

More than 100 VBAs were negotiated between 2014 and 2017 with manufacturers, payers, and patients all deriving real benefit. For patients, they are promised access to new, breakthrough therapies despite any potential value concerns by payers. Some VBAs even offer to reduce or eliminate patients' out-of-pocket costs. For manufacturers, a VBA can ensure their new therapy gains market access. For payers, VBAs help reduce risk by limiting or eliminating payments for drugs that don't work for specific patients.

VBAs also create opportunities to implement additional alternative payment methodologies between payers and manufacturers, such as payment over time for therapies presented as one-time cures. Instead of a one-time payment upfront, a cure's cost would be reimbursed from the payer to the manufacturer based on patient outcomes over one, three, and five years, for example.

Manufacturers of drugs approved under orphan, fast-track, or breakthrough designations may have additional interest in VBAs. To payers, these drugs, many of which offer breakthrough or significant improvements over the existing standard of care, create an array of challenges unlike drugs approved through traditional pathways. Many of these therapies will receive regulatory approval based on small or single-arm trials, and/or the use of surrogate endpoints. This has the potential to create additional complexity as payers try to accurately evaluate the therapy's benefit over time, including introducing a greater level of uncertainty about long-term costs, risks, and benefits. In the end, payers may decide the risk is not worth the effort and end up not covering the drug. A VBA may alleviate those concerns.

We recognize that VBAs are not appropriate for every drug and circumstance. Still, more should be done by industry, public and private payers, and other stakeholders to allow for easier use and scaling of VBAs. Just as important, our industry must start investing in better tools to track outcomes to support VBAs, much of which relies on real-world data and real-world evidence, which we'll explore next.

> *"Now, earlier in development, manufacturers and even investors are considering payer expectations around data collected during trials, which will lead to more robust access, reimbursement and utilization of the product once on the market."*
>
> *—Erin Mistry, Senior Managing Director, Head of Value, Access & HEOR, Syneos Health*

Case Study

In August 2018, Alnylam received FDA approval for ONPATTRO® (patisiran), the first for a new class of drugs called RNA therapeutics, with an indication to address a hereditary rare, fatal genetic disease. Alnylam wanted to ensure broad access for their therapy, so engaged several payers in the U.S. prior to approval, including Harvard Pilgrim Health Care (HPHC), to adopt value-based agreements (VBA). The drug manufacturer approached HPHC with the initial structure for a VBA, one that had clear endpoints with defined clinical benefits, but also flexibility necessary for HPHC to reasonably implement. Since then, Alnylam has completed 10 VBAs with commercial payers in the U.S., guaranteeing access for more than 90% of covered lives. With their proactive approach to engaging payers early on, they've helped ensure the appropriate patient receives the therapy and that it's reimbursed based on the value it provides.

Recommendations

- Consider during clinical trials, based on a drug's regulatory pathway, whether pursuing VBAs may be appropriate to ensure patient access.
- If VBAs seem like a potential option post-approval, start to think about what kind of outcomes-based evidence you would like to include in a VBA, and the best ways to measure that over time.
- The biopharma industry should work together and with other healthcare stake-holders to pursue a standardized VBA template to simplify future VBA negotiations between payers and providers — if only as a starting point, as we know each VBA will look very different.

Engaging Patients to Assess Long-Term Value — The Importance of Real-World Data & Real-World Evidence

Assessing the true value of prescription drugs is dependent on our ability to extract and measure patient reported outcomes and/or costs avoided in the long-term. To do so, our industry must invest in new tools to engage patients beyond clinical trials.

New drugs cannot be approved by the FDA without clinical trials that measure their safety and efficacy, but real-world data (RWD) and real-world evidence (RWE) are becoming increasingly important in monitoring patient outcomes post-approval and supporting regulatory and coverage decisions. In December 2018, the FDA launched a **Real-World Evidence Program**, providing a framework for evaluating the potential use of RWE to "help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy drug post-approval study requirements." The FDA defines RWD and RWE as:

- RWD are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources, such as electronic health records (EHR), claims data, patient registries, and patient-generated data
- RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

"As an organization, we do not believe there is some magic set of questions that will lead to the perfect formula which is why RWE and direct input from patients (through a variety of means) is so important."

—Terry Wilcox, Co-Founder & Executive Director, Patients Rising NOW

While the increased use of RWE has many benefits, the focus of RWE for the biopharma industry should be around proving the long-term effectiveness of therapies, and therefore the value to patients, the healthcare system, and society.

To facilitate the collection of RWD, the FDA recently launched the **MyStudies app**, a digital platform that developers can use to collect RWD directly from patients. The app is built on open source code so companies can adapt it for their specific RWE needs, while ensuring compliance with FDA's regulations and guidance for data authenticity, integrity, and confidentiality. While this is still in its infancy, it's an exciting development for biopharma companies to take advantage of—especially those that don't have the resources to invest in their own tools for RWD collection.

The FDA has an ongoing partnership with Flatiron Health to pool cancer patient data from electronic health records to improve regulatory and treatment decisions. Flatiron is also working with several biopharma companies to do the same and is considered a leader in trying to solve the greatest challenge around using real-world evidence: the ability to combine and provide access to real-world clinical data stored across thousands of disconnected clinics, medical centers, and hospitals.

Other organizations, including patient advocacy groups like LUNGevity, Global Healthy Living Foundation, and Cancer Support Community, have registries for measuring patient experiences in varying degrees. There are also new digital technologies that rely on more passive engagement from patients, such as wearables that can continuously monitor patient physiological, behavioral, and environmental data in real-time.

> *"Both uses of RWE (for clinical trials and post-approval) need to be planned well in advance, and the methodology tested during clinical trials to show that the data gathering process works. The shortcomings for both patient-reported outcomes (PROs) and RWE today are the lack of planning—which needs to bedone much earlier in clinical development—not as an after-thought."*
>
> *—Colin Wight, CEO, GalbraithWight*

Case Study

In partnership with Robert Goldberg, Ph.D. and the Center for Medicine in the Public Interest (CMPI), Patients Rising has launched the Patients Rising Access Research Institute where they are in the early stages of developing and implementing a machine-learning platform called ProsPER! Through support from biopharma industry and others, this platform is an attempt to counter ICER claims that they're unable to use RWE to inform value assessments. Using ProsPER!, Patients Rising proved that it is possible to collect and evaluate real world patient data from social media and electronic health records to inform treatment decisions and value assessments. The next phase of development is to design a mobile responsive website where they encourage patients to share insights, answer polls, and other questions to determine value.

Recommendations

- Think about clinical trial participants as *the* customer — the individuals that really matter — and build relationships that can carry over to the commercial stage.
- Invest in new digital tools to engage patients, either privately or by taking advantage of open source frameworks (ex. FDA MyStudies App, Flatiron, wearable devices, social media sites).
- Support efforts for biopharma companies and digital health companies to collaborate and converge.

Conclusion

At a time of unprecedented medical innovation and a promise of more remarkable cures and treatments to come, the biopharma industry is facing mounting pressure about the costs of these therapies. It's our responsibility as an industry and individual companies to clearly demonstrate the value and therefore justify the price of these new innovations to patients, the healthcare system, and society.

It's no longer acceptable for the various healthcare stakeholders to point fingers at one another. We must embrace collaboration between manufacturers, payers, and providers to come up with innovative payment models and solutions for ensuring access. And we must invest in and engage with digital technologies that will allow new therapies to better work within the growing value-based healthcare system that relies on data and measurable outcomes.

At the end of the day, it's incumbent upon us to think about value earlier than we ever thought necessary—and to lay the groundwork for making the case for the long-term value of new, breakthrough innovations. ■

Stay Tuned

for Part II and III of our Value of Health Series:

- ***Public Payers in the US and Abroad***
- ***Potential Disruptors' Impact on the System***

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Appendix

MassBio Value of Health Advisory Group

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