MassBio®

Value of Health Series

PART II

Public Payers in the U.S. & Key International Markets

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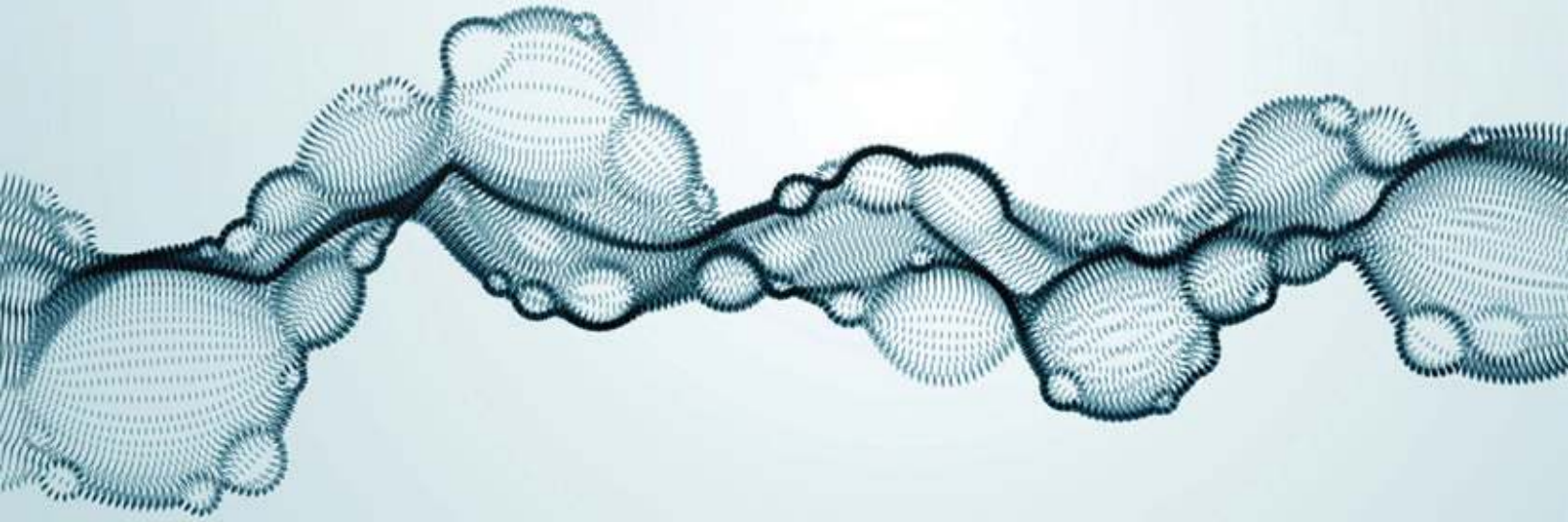

Public Payers in the U.S. & Key International Markets

Introduction

Part I of MassBio's Value of Health series—a major, new initiative to explore the future of the biotech industry through the prism of drug pricing—examines the value equation from the perspectives of the various healthcare stakeholders, the increased use of health technology assessments (HTAs) in the U.S. in determining value, the current state of innovative payment methods with private payers, and the importance of real-world evidence in demonstrating the long-term value of therapies. The goal of the series 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.

While Part I focuses almost exclusively on how to best demonstrate value to private payers, the public insurance market in the U.S. is a critical piece to understand as it covers more than one-third of insured Americans. Just as important, manufacturers must consider the unique process for approval, access, and reimbursement in international markets, with many operating as single-payer systems. This paper will explore Medicare and Medicaid in the U.S., existing access and reimbursement issues for innovative therapies and cures, proposed changes to those programs that could impact access and reimbursement, and barriers that exist to innovative payment models. The paper will also consider those key international models of assessing value and determining access, what the U.S. may be able to learn from them, how the global landscape is shifting, and highlight emerging markets like China that are moving toward the realm of "must consider" when developing an international strategy.

U.S. Public Payers

Combined, Medicare and Medicaid provide insurance to more than 36% of Americans – totaling more than 100 million lives. Each of these programs covers a well-defined population: Medicare for those older than 65; and Medicaid for low income individuals, families, and children, and those with disabilities. Both programs were created under federal law and are overseen by the Centers for Medicare & Medicaid Services (CMS). However, while Medicare is administered federally through CMS, Medicaid is a joint federal/state program that is run on a state-by-state basis. This distinction is important to understand how Medicare/CMS and Medicaid/state governments think about value, access, and reimbursement of prescription drugs, especially each program's ability to consider and implement innovative payment models, such as value-based arrangements (VBAs) and outcomes-based payments over time.

Medicare and Medicaid can be attractive markets for manufacturers but that depends almost wholly on two factors: does the therapy's patient profile align with the patient populations in Medicare or Medicaid? And, does the drug already have competition in the class?

Medicare Part D

Whether through Medicare Part D or a Medicare Advantage (MA) plan, prescription drug coverage is offered to Medicare enrollees by private insurers in a manner similar to the commercial insurance market whereby those insurers and their PBMs create their own formularies, and negotiate their own reimbursement rates, rebates, and discounts for prescription drugs. For consumers, Part D or MA plans are different from a commercial market plan in many ways (e.g. there is no cap on out-of-pocket Rx costs in Part D/MA). However, from a drug manufacturer's perspective, the primary difference between Part D/MA plans and the commercial market is that Medicare plans must adhere to federal statute, which dictates minimum coverage standards for prescription drugs. Therefore, for biopharma companies, negotiating reimbursement rates with Medicare will be similar to the commercial market even if the dynamics (covered population, benefit design, out-of-pocket costs, etc.) are not exactly similar.

Medicare Part B

Therapies that are administered by a healthcare professional in an outpatient setting are covered under Medicare Part B. In Part B, coverage and payments for these therapies are handled directly by CMS instead of through private insurers as in Part D. The percentage of drugs covered under Part B is growing alongside the increased approval and usage of specialty drugs, which are largely infused therapies.

For drug manufacturers bringing a new therapy to market that will be covered under Part B, the system is completely unlike the commercial insurance market and in many ways is more straightforward. Once CMS provides a therapy with coverage and coding for reimbursement, therapies in Part B are purchased directly by the provider and are reimbursed at a rate of the Average Sales Price of the drug (ASP) plus 6%. Under this system, Medicare is not making value determinations, but using the average sales price (net of rebates and discounts) of the drug nationally across payers.

However, novel drugs covered by Part B can present a challenge. CMS coverage, coding, and payment decisions may be non-existent for first-in-class therapies. If those do not exist, Medicare will not reimburse providers for those medicines. If therapies are added by CMS to an existing CMS reimbursement code that covers similar therapies, that reimbursement rate may not cover the provider's cost for the drug. This is already creating patient access challenges and has the potential to get worse as more innovative, first-of-a-kind medicines come to the market that require CMS to make new coverage and coding decisions.


The recent commercialization of CAR-T therapies is an example of how CMS is responding to such therapies and the implications it has for patient access. Although the first CAR-T therapy has been approved by the Food and Drug Administration (FDA) for almost two years now, CMS is still in the process of finalizing CAR-T's coverage, coding, and payment models. Post-FDA approval, CMS did act quickly to create new reimbursement codes for CAR-T that reimbursed at a fair, reasonable level. However, CMS's coding covered outpatient administration of the drug only. As hospitals soon learned, CAR-T patients are better served in an inpatient setting due to potential complications and side-effects of the drug. In an attempt to remedy this, CMS has twice assigned CAR-T therapies to an existing inpatient billing code (DRG) that, in both cases, only paid for a small fraction of the drug's cost let alone any hospital expense. As of this writing, CMS has only just issued a national coverage determination ensuring reimbursement to any healthcare facilities administering CAR-T. However, it is still unclear how CMS will proceed to ensure that hospitals are getting adequately reimbursed for CAR-T administration so that in turn, patients will have providers that are willing to administer the treatment. As it currently stands, CMS is only reimbursing at approximately 65% of the drug's cost. Many observers do not expect a suitable outcome for all parties for years to come.

As more innovative medicines are approved, especially those that will be covered under Part B, such as cell and gene therapies, CMS's limitations toward ensuring adequate reimbursement has the potential to significantly impact the marketplace and patients' ability to access breakthrough drugs through Medicare.

Policy Spotlight
International Pricing Index in Medicare Part B

The Trump Administration has proposed a pilot program in Medicare designed to reduce prescription drugs costs by tying reimbursement rates for certain Part B drugs to the average of the drug's price in Canada, Japan, and 12 other European countries. In advocating for this approach, the Administration argues that other countries are paying much less for the same prescription drugs and that isn't fair to U.S. citizens. According to HHS Secretary Alex Azar, this program seeks to reduce the cost of the "most expensive drugs in Medicare Part B" by 30% as well as reduce patient out-of-pocket expenses. In reality, this proposal has the potential to restrict or delay access to breakthrough therapies for Medicare patients as it moves Medicare toward a government price setting model similar to the reference countries, the majority of those which have socialized health care systems that more often restrict, delay, or deny coverage for treatments based solely on budget impact.

Existing Challenges in Navigating CMS & Medicare Uncertainty Around Value-Based Arrangements

Currently, there are no VBAs between a manufacturer and Medicare. Structurally, it is challenging for Medicare to make "one-off" deals with individual companies. Instead, Medicare as a federal, nationwide program seeks to make changes that work generally. Additionally, it is unclear whether federal law gives CMS the authority to negotiate directly with a manufacturer over price, or if there is a mechanism available for Medicare to receive money back from a manufacturer if the VBA specifies a refund/rebate based on a patient not meeting certain clinical outcomes. That is not to say that manufacturers are not interested in the potential for VBAs in Medicare, but the current path forward is uncertain including questions about whether Congress would need to act to proactively authorize or remove barriers that include the federal anti-kickback statute, Medicare Average Sales Price, and Medicaid Best price implications.

Navigating CMS Can Be Tricky, But A Solution May Exist

A new office within CMS, the Medicare Pharmaceutical and Technology Ombudsman, was created as part of the 21st Century Cures Act in 2016. According to CMS, "This role is to help support customer service and innovation in the Medicare program by receiving and looking into concerns and questions from pharmaceutical, biotechnology, medical device, diagnostic product manufacturers, and other stakeholders regarding Medicare coverage, coding, and payment for products already covered or for which coverage is being sought." As more emerging biotech companies commercialize their products and have no prior experience with CMS and Medicare, this office could serve as an entry point to seek guidance on coverage, coding, and payments. In cases of novel therapies that do not have existing Medicare codes, this office may be especially helpful in finding the right people and departments within CMS that can help ease the path toward patient access before a product reaches the market.

Recommendations

- **If you expect your therapy to be covered in Medicare as outpatient or inpatient, seek early, pre-approval discussions with CMS about coverage and coding. A mutual understanding of whether CMS can and will cover the therapy under existing codes, or if new codes and coverage determinations are needed, will help limit patient access challenges post-approval.**

- **If your commercialization strategy includes the possibility of VBAs in other insured populations, have direct discussions with CMS about the viability in Medicare depending on the therapy, patient population, and scope of the expected VBA model.**

Medicaid

Medicaid is a federal program but is administered on a state level. Thus, while structurally similar, each state Medicaid program is different and should be considered as 50 individual payers. State Medicaid programs make decisions on everything including eligibility requirements, drug formularies (via preferred drug lists), drug prior authorization requirements, supplemental rebate agreements, and whether to utilize new tools such as VBAs. In addition, state Medicaid programs have fixed, annual state appropriations, that in conjunction with federal dollars, fund the program. Each state has their own budget reality, and this will inform how they administer Medicaid. This is an important distinction from the commercial insurance market which also operates on annual budgets but has various tools and levers to deal with costs, such as raising rates or increasing patient cost-sharing in future years.

Prescription Drug Coverage in Medicaid

Prescription drugs are an optional Medicaid benefit, but currently all states provide outpatient prescription drug coverage. Manufacturers voluntarily participate in the Medicaid Drug Rebate Program. Federal statute dictates that every state Medicaid program that offers an outpatient drug benefit must cover all prescription drugs as long as the drug's manufacturer agrees to pay the federal minimum rebate (23.1% for most drugs), or offer states the drug's "best price"—the lowest price paid by any other payer (with limited exceptions—Veterans Affairs, Department of Defense, Medicaid Part D).

Medicaid's "best price" provision was passed into law in 1990 to help lower drug costs in Medicaid, and is working as intended. By combining the best price provision with state Medicaid programs' ability to negotiate further supplemental rebates, states, in most cases, receive significantly higher average rebates and discounts on drugs than commercial or Medicare plans. For example, in Massachusetts, data from the Center for Health Information and Analysis (CHIA) shows that Massachusetts' Medicaid program, MassHealth, reported receiving average rebates equal

to 52% of total pharmacy spending compared to commercial plans in Massachusetts that reported only 12%.

Part of that negotiating power stems from the various multi-state purchasing pools, created by states where one PBM uses group purchasing power to negotiate supplemental rebates for that pool of states. There are three major purchasing pools: National Medicaid Pooling Initiative (10 states + DC) and Top Dollar Program (six states), both run by Magellan Rx, and the Sovereign States Drug Consortium, (run and owned by 12 states).

Making the Case for Value of Prescription Drugs in Medicaid

In many ways, making the case for value to state Medicaid programs is similar to the process with commercial payers. This is especially true for products new to market and first-in-class. State Medicaid programs, in the same way as commercial payers, want to know what is in the pipeline and their potential new costs, and which manufacturers may be interested in pursuing alternative payment mechanisms. Early conversations do happen between manufacturers and Medicaid programs and their PBMs to address these questions. Those conversations can be beneficial so that both parties are prepared when a new therapy comes to market.

States Making New Efforts to Measure Value and Constrain Costs

Despite their significant savings compared to other payers, states are increasingly seeking ways to constrain their total drug spending with a focus on "high cost" drugs that have no competition. Because they cannot exclude drugs from the formulary to control costs, these states are exploring alternative methods to restrict the use of medicines they believe are either high-cost or low-value. According to these states, existing tools such as preferred drug lists (their formulary), prior authorization, quantity limits, or step therapy are not enough to lower their total drug spend.

> *"Medicaid tends to be a very siloed market. You go in and talk to a state Medicaid agency and they're typically given a budget and are expected to stay within that. There has historically been little discussion about overall value across entire healthcare dollar, although this may be changing."*
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> *—Health Economics & Outcomes Research Director, Large Biopharma Company.*

Policy-wise, certain states have been considering legislation that instructs a state entity to assess the value of a prescription drug, and if the price the state is paying for the drug is deemed too expensive the state will institute a variety of measures designed to pressure the manufacturer to lower the price through supplemental rebates. In some cases, states are seriously considering whether to formally or informally utilize a third-party HTA, such as the Institute for Clinical and Economic Review (ICER), and their clinical effectiveness research, to assess a drug's value.

Policy Spotlight: New York State's Medicaid Drug Growth Spending Cap

In 2017, New York State passed a law creating a Medicaid drug growth spending cap designed to evaluate which drugs are cost-drivers in Medicaid, examine those drugs' value, and set a proposed supplemental rebate level the manufacturer should pay the state. The state encourages manufacturers to agree to a supplemental rebate of at least 75% of that target level by threatening the imposition of utilization management on all of the manufacturer's drugs, such as requiring prior authorization, promoting other drugs, and even directing managed care plans to stop covering the drugs if negotiations ultimately fail.

This law is impacting a wide swath of drug companies in a real and measurable way while the program's scope is growing. In the two years since the law has been in place, the number of companies targeted for supplemental rebates has grown from 12 to 25. Although it is not public how much New York Medicaid has received in additional supplemental rebates on the targeted drugs since the law was implemented, the consensus is that drug companies are being pressured to pay additional supplemental rebates (rebates that are voluntary by federal law) based on an arbitrary valuation process. And because these proposals impose penalties for declining to offer supplemental rebates, companies feel pressured to comply in the face of additional access restriction on their products.

Challenges to Medicaid Coverage, Reimbursement, and Access

Bundled Payments

Currently, in 48 states, therapies that are administered in an inpatient setting are paid for under "bundled payments" where the state Medicaid program reimburses the provider for the cost of the drug and the hospital costs through a single, pre-set payment. In many cases with innovative, first-in-class therapies, these bundled payments may not cover a provider's cost for the drug, or their own costs, as the bundled payment rates are determined based on outdated or inapplicable assumptions about drug costs and associated hospital costs. With specialty drugs representing a growing share of Medicaid drugs, and many requiring administration in an inpatient setting, this creates a situation where hospitals may choose not to administer certain drugs because they are losing money on each patient. Presently, this is not happening at any magnitude, but it is easy to envision a near-future where it does cause patient access issues. Two states so far – Massachusetts and New York – have unbundled drug and hospital payments in Medicaid on a limited basis in connection with the reimbursement of certain gene and cell therapies. These policies are generally intended to reimburse hospitals for the actual cost of the therapies to better ensure adequate hospital reimbursement levels and, as a result, greater patient access. Because there is not yet a national pathway for unbundling these costs in Medicaid, other states may begin considering actions like MA and NY.

Value-Based Arrangements/Outcomes-Based Payments Over Time

Five states have received state plan amendments (SPAs) from CMS allowing them to link payment for prescription drugs to outcomes—Colorado, Massachusetts, Michigan, Oklahoma, and Washington. According to CMS, these specific SPAs provide a: "value-based supplemental rebate agreement template [that] includes an approved framework for states to negotiate and enter into manufacturer-specific agreements and includes such parameters as the utilization period, outcome-based benchmarks, intervention population for which benchmarks will be measured, and evaluation methodology." Under this template, states and manufacturers have a clearer path to enter into VBAs where risk is shared between the two parties and states have the potential to reduce pharmacy costs by paying less or not at all for drugs that are not producing patient outcomes as expected. Yet, despite the SPAs, challenges such as data collection and agreed upon financials will likely continue to constrain the widespread use of VBAs in Medicaid.

In addition, with the recent, and expected, future approvals of one-time cures, there is increasing interest among manufacturers and payers around implementing a payment-over-time model instead of requiring a one-time, lump sum when the therapy is administered. Such payment-over-time models would likely also be outcomes-based like VBAs where the installment payments are linked to expected clinical benefit. From a payer perspective, this model eliminates large one-time payments and shares the risk with the manufacturer. From a manufacturer's standpoint, this model could help ensure patient access as payers would be more likely to cover and reimburse for the therapy if they do not have to pay a large, upfront cost and if the risk is shared.

However, no state Medicaid program has yet offered a pathway to manufacturers for outcomes-based payments over time. Federal law may present certain barriers, including how such arrangements would impact Medicaid best price in cases where a manufacturer is ultimately paid less than the full price for a therapy. Another challenge is patient portability. For example, if one state program agrees to a payment-over-time model with a manufacturer relative to the treatment of a particular patient, and the patient moves to another state, or even changes to Medicare or a commercial plan during the term of the contract, which payer is responsible for making the remaining payments? While CMS has created a pathway for states to utilize certain VBAs in Medicaid, it's currently unclear if they have the mechanisms necessary to allow states to use payment-over-time models.

Case Study: Treating Hepatitis C in Louisiana: An Innovative Payment Model

Years after the first hepatitis C (HCV) cures were approved by the FDA, the state of Louisiana continued to restrict access to its Medicaid beneficiaries and incarcerated population due to budgetary concerns. In 2017, only 1% of these nearly 40,000 patients had received HCV treatment, yet Louisiana was not able to increase its healthcare budget to treat more patients despite prices of HCV therapies significantly decreasing. After much consultation, Louisiana became one of the first states to explore a subscription model for HCV – a scheme that enables a payer, for a fixed, upfront fee to a pharmaceutical company to treat as many patients as possible over a fixed time period. This model would help Louisiana reach its goal of eliminating HCV among Medicaid beneficiaries and prisoners in the state, while staying within existing budget constraints. Ultimately, a true subscription model was not feasible under guidance the state received from the Centers for Medicare and Medicaid Services (CMS). Nonetheless, in July 2019, Louisiana reached a different agreement with Asegua Therapeutics, a wholly-owned subsidiary of Gilead Sciences, in which Asegua will provide unlimited access to treatment for five years to Medicaid and corrections patients in Louisiana. Unlike a subscription model, the state will pay for Asegua's HCV therapies on a per unit basis up to an agreed upon amount—or an annual expenditure cap. Once the state reaches this expenditure cap, the state will be reimbursed by Asegua for subsequent treatments without any utilization limits. These types of innovative payment models have potential for curing large populations of HCV while helping to address short-term affordability concerns.

Recommendations

- Understand the epidemiology of your therapy and its target population to best determine your therapy's market potential in Medicaid and Medicare.
- Know the existing and expected competition in your therapy's class to assess the potential Medicaid marketplace for your therapy. When drugs have competition, Medicaid is a strong negotiator.
- Have early conversations with state Medicaid programs, PBMs, and multi-state purchasing pools before your drug comes to market. This is especially important if your therapy expects to serve a large patient population, has high yearly or one-time cost, or if you seek alternative payment methodology such as a VBA.
- Expect that, in a similar manner to the commercial market, your therapy will be subject to value assessments from state Medicaid programs with or without an entity like ICER.

Key International Markets

Disease knows no borders, and neither do biopharma companies when they're bringing new drugs to market. Global spending on medicines reached $1.2 trillion in 2018 and is set to exceed $1.5 trillion by 2023, according to a new report by IQVIA. It's not always easy to navigate a highly disparate, complex global market, however it is critical manufacturers have a thoughtful global pricing, access, and reimbursement strategy to ensure patients around the world have similar opportunities for a healthier future as those in the U.S.

What countries to prioritize and the specific strategy to use when seeking approval and reimbursement is dependent on a number of factors, especially the target patient population. However, there are some key countries and common characteristics that offer insights into how to navigate this increasingly complex landscape. The main differentiator between almost all of the key global markets and the U.S. is that most foreign countries are single-payer systems, meaning the government is the sole payer. Some countries are more innovative in terms of thinking about value, testing new ways to reward for value with alternative payment models. While others are more restrictive, prioritizing budget impact over patient access. Despite some commonalities among certain countries, especially those in the European Union (EU), companies must still approach reimbursement on a country-by-country basis.

Value, Access, & Reimbursement in Developed Nations

After gaining approval in the U.S., most companies will

then look to the developed countries with the largest populations or those with the best financial opportunities in terms of high pricing. Companies almost always prioritize the top five European markets (EU5), which include Italy, France, Germany, Spain, and the United Kingdom (UK). All of these countries are regulated both at the EU level by the European Medicines Agency (EMA) and at the individual country level. Beyond the EU5, companies then explore markets in other key EU states, along with Canada and Japan.

When looking at countries that have been most progressive in terms of adopting innovative pricing methods or rewarding for value, the EU5 offer interesting insights. The EU5 has generally been more receptive to working with manufacturers to engage in innovative pricing agreements like VBAs, especially when there's uncertainty around long-term effectiveness or value outside of a clinical trial. This is due in part because most of these countries have an easier time administering and tracking a VBA within single-payer systems, but also because they have more receptive policy environments to do so compared to markets like Medicaid in the U.S., where states have to get specific waivers to engage in alternative payment models like a VBA. However, despite this reality, they have not taken off in a major way, similar to what we have seen with private payers in the U.S.

International Spotlight

Germany offers an interesting case

study for how a country has attempted to lower drug prices by increasing transparency and encouraging healthy competition among drug manufacturers. Like the U.S., Germany relies on private, nonprofit health insurers, called sickness funds, which Germans are required to enroll in. These funds have strict limits on patients' out-of-pocket costs, limiting co-pays to only 10 euros per prescription, with no deductibles. New drugs seeking approval and reimbursement have to go through a rigorous evaluation by a non-government agency, the Institute for Quality and Efficiency in Health Care (IQWiG), which serves as the basis for decision-making by the Federal Joint Committee (G-BA), the public legal entity made up of physicians and dentists, hospitals, and insurers. The IQWiG undergoes a three-month evaluation and issues a public report that determines if the new therapy offers added benefit compared to existing treatments. Manufacturers and other stakeholders can weigh in and offer comments regarding whether they disagree or agree with the assessment. If a manufacturer cannot show added value, it can only charge as much as the existing therapy. If they can prove otherwise, the manufacturer negotiates with the sickness fund, agreeing on a price that each fund is required to pay for at least a year after the new drug is introduced. This model is not without its faults, as there have been instances of manufacturers pulling out of Germany altogether if they can't agree on a price, but it does offer an interesting mix of U.S. and European models for access and reimbursement.

Consolidation Among Health Technology Assessments in Developed Nations

HTAs have been used around the world for decades and are part of the formal regulatory and reimbursement process for most developed countries, especially in the EU. For those countries, the results of an HTA help determine what the payer, government or private, will reimburse for a given drug. In some cases, if a drug manufacturer does not agree to that price, their therapy will not gain approval in that country. However, more often the government or the paying entity will use the results of an HTA to negotiate drug prices, with some countries being more open in terms of rewarding for value than others.

The U.S. is one of the only developed nations that does not use a formal HTA process to determine cost-effectiveness and reimbursement, although private payers do use the results from assessments completed by ICER, the most influential HTA in the U.S., to negotiate drug prices see Part I for more on ICER. Japan recently completed a successful pilot project to create a formal HTA and is now in the process of implementing that new HTA process. Other countries continue to adapt their own HTA processes.

In Europe especially, there has been a move to consolidate HTAs, recognizing that it's highly inefficient to have each country develop its own way to determine cost-effectiveness. In 2004, the European Commission and Council of Ministers recognized HTAs as a political priority and made a commitment to establish a "sustainable European network on HTA." This led to the creation of the European Network for Health Technology Assessment (EUnetHTA), which has since engaged in several projects to improve collaboration among European HTAs and ultimately establish a permanent HTA working structure for Europe. Although most countries agree that a standardized clinical effectiveness assessment would be helpful, they do not believe Europe will ever be able to agree on an economic / affordability assessment because each country has so many distinct variables that would impact the equation. Some countries also see this as an intrusion of the sovereign rights of each EU country to determine their healthcare priorities and processes. Regardless, there continue to be more collaborations forming both in the EU and around the globe.

In January 2019, ICER announced a project to develop and test new methods for evaluating potential one-time cures in collaboration with the UK's National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH). The following month, NICE and CADTH launched a new collaboration to offer parallel scientific advice to the life sciences industry to streamline the process for biopharma companies, recognizing that it's not easy to satisfy the requirements of disparate HTA's across the globe. We're even seeing emerging markets look to established HTAs in the developed world for partnership opportunities and lessons learned.

> *"The level of cross-border collaboration between HTA agencies is increasing. This includes Early Scientific Advice/Early Dialogue, HTA assessments, and collaborations on regenerative medicines. This could mean a significant reduction in duplication of work & delay—which could be good for Payers, Biopharma, and most importantly for patients. While improvements in methodology by HTA agencies are still needed, what we want to see now is the political will to ensure these collaborative outputs are adopted by each country."*
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> *—Colin Wight, CEO, GalbraithWight*

Early Scientific Advice

HTAs around Europe have been offering early scientific advice to drug manufacturers for decades to guide the evidence requirements for both clinical effectiveness and safety but also regulatory approval and reimbursement. It's a non-binding way to provide insights to companies on the choice of comparators, endpoints, study design, and health economics so they are aligned with what the various regulators and decision-makers want to see. In an effort to consolidate this process, the EMA and EUnetHTA began offering Parallel Consultation in July 2017, which provides a single gateway for requests for early scientific advice for companies seeking approval and reimbursement in Europe.

"Parallel Consultation allows biotechs to de-risk development programs by aligning on an evidence generation approach simultaneously with regulators and HTAs, so that a single development plan can meet the requirements of both licensing and reimbursement. This is particularly helpful with programs raising novel scientific and development questions, such as gene therapies, disease-modifying treatments, or the first medicine for a previously untreatable disease."

—Nicholas Gertler and Matt Diver co-founders at Galen/Atlantica, and part of the core team that developed and piloted Parallel Consultation

Around the same time, the FDA and the EMA launched a program to provide parallel scientific advice to companies seeking approval in both the U.S. and Europe. The goal of the program is to "provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics). Such interactions are expected to increase dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product, provide a deeper understanding of the bases of regulatory decisions, optimize product development, and avoid unnecessary testing replication or unnecessary diverse testing methodologies."

Seeking approval and reimbursement on a global scale is no easy task but taking advantage of early scientific advice programs can help biopharma companies consider how to best demonstrate not only clinical effectiveness and safety, but also value to patients and the healthcare system to ensure broad access.

Case Study

Biogen engaged in a joint assessment of SPINRAZA® (nusinersen) by the Netherlands & Belgium (as part of the BeNeLuxA pilot) in order to:

- **Help patients gain fair, equitable and fast access to SPINRAZA® (nusinersen);**
- **Mitigate difficulties of negotiating with both individual countries; and**
- **Be consistent with Biogen's pricing principles.**

The joint assessment was completed in 11 months, in line with average decision-making timeline for each of the individual countries. The two Ministries of Health finally made different reimbursement decisions—due to their National legal frameworks—to get to a commonly agreed, similar, eligible population for coverage. Almost a year later, the Netherlands approved a registry allowing conditional reimbursement to the broader population.

Such initiatives increase transparency and require all parties to be constructive and solution oriented. Biogen engaged with the Netherlands & Belgium early, and this was critical in driving the process to a timely conclusion. Worldwide, it's the first time a medicine successfully concluded a joint HTA & reimbursement process.

Emerging Markets – Spotlight on China

Emerging markets like China, Brazil, and India are receiving more attention from biopharma companies as these countries' rapid economic growth creates new urgencies around healthcare services and need for innovative medicines. The middle class in these countries is also growing, increasing the pool of patients that can afford more advanced therapies, with local governments expanding healthcare coverage to meet these new demands. Of all the emerging markets, China, now the second largest pharmaceutical market in the world, is one that biopharma companies cannot ignore.

China is home to the world's largest population—a population that is aging more rapidly than almost any other country in recent history, according to the United Nations. The country faces rising medical needs, both from its aging population and a high prevalence of diabetes and lung cancer, which is putting greater strains on the healthcare system and the economy at large. According to IQVIA, China reached $137 billion in medicine spending in 2018, and is expected to reach $140–170 billion by 2023. The IQVIA report credits China's major growth in spending to government reforms to expand health insurance to both rural and urban residents and to modernize the hospital systems and primary care services. According to the World Health Organization, virtually the entire Chinese population is now insured, although what insurance actually covers is extremely limited as China prioritizes cost-containment over cost-effectiveness, so historically only covered the most basic, inexpensive therapies.

Over the last few years, China has worked to modernize its regulatory and reimbursement processes as well, enticing more drug manufacturers to prioritize the country as a key market. For example, China's Center for Drug Evaluation (CDE), China's version of the FDA, has accelerated review timelines for investigational new drug (IND) and new drug approval (NDA) applications, introduced a Priority Review pathway for drugs that meet urgent unmet needs, and removed a requirement to conduct new clinical trials in China for drugs that have already been approved in other countries. China updated the National Reimbursement Drug List (NRDL) in 2017, after an eight-year lapse, and according to a 2018 WSJ article, China's CDE made 48 drugs that are approved in the U.S., Japan, or Europe eligible for fast-track approval in a single week.

While the regulatory environment is certainly more favorable for the U.S. and other foreign innovators, companies are required to signifantly lower their drug prices to gain entrance. According to another WSJ article, manufacturers looking to gain access to China are required to cut their proposed drug prices by 46% on average, with some lowering the costs by more than 90%. For drug manufacters, however, the large patient population in China can help justify the lower price.

Price negotiations are relatively new for China, formally introduced at the national level in 2017. However, China has been taking steps to modernize how they think about value and cost-effectiveness for prescription drugs in the last few years. Although the China National Health Development Research Center (CNHDRC), formerly the China Health Economics Institute, was established in 1991 as a government think-tank, it wasn't until 2008 that they set up a formal division for HTAs to support decision-making for policy makers. In 2010, the UK's NICE partnered with China on a pilot project to support health reform by linking clinical review with cost-effectiveness using an HTA. Since then, China has invested considerable resources developing HTA expertise and networks (see more on the history here), and is now a member of the International Decision Support Initiative (iDSI), which helps low-and-middle-income countries make better decisions about how much public money to spend on healthcare, and HTAsiaLink network, a network of HTA agencies in Asia. The CNHDRC has also gotten the attention of the U.S., receiving a $1.5 million grant from by the Bill and Melinda Gates Foundation in 2017 to establish a formal mechanism for translating HTA evidence into policy. Then, in 2018, China's National Health Commission formally announced the establishment of the National Center for Medicines and Health Technology Assessment. Although there are still barriers to expanding access to new therapies in China, it is evident the country is making major investments in modernizing its reimbursement strategy to make room for some of the more innovative therapies available today.

Beigene Case Study on Partnering in China

In January 2018, San Diego-based Mirati Therapeutics, Inc., a clinical-stage targeted oncology company, partnered with BeiGene, Ltd., a global commercial-stage biopharmaceutical company. The agreement leverages BeiGene's China capabilities, including its clinical team of more than 500 people in China, the largest oncology-focused clinical development team there. It allows Mirati to leverage BeiGene's business in China to expedite and expand their global development program for a new spectrum-selective kinase inhibitor.

The partnership is currently executing on a Phase 1b clinical combination trial with BeiGene's investigational anti-PD1 antibody, tislelizumab, and actively recruiting patients with solid tumors in China and Australia. A key aspect of this partnership is the opportunity to broadly and rapidly evaluate a combination therapy in multiple tumor types and lines—a task that would be difficult and costly in the US/EU alone. These companies have combined their strengths to advance potentially meaningful treatments for cancer patients, with the opportunity to enroll patients in trials faster by also including the large patient populations in China.

Recommendations

- Whenever possible, take advantage of early scientific advice programs before pivotal trial protocols are finalized.
- For smaller- to mid-sized biotechs, consider localized partnership opportunities to break into the global market, especially emerging markets like China.
- Understand each country's HTA processes and what it prioritizes in terms of demonstrating value; consider their results a starting point for negotiation and not the final word on access.

Conclusion

Successfully bringing new therapies and cures to patients, regardless of the market or country, shares a common theme: clearly demonstrating the drug's value to payers is critical to ensuring access and reasonable reimbursement. Public payers are no exception and while the need, methods, and opportunities to show that value differ, together Medicare, Medicaid, and international markets strive to provide the best value to the people they cover and the governments they work for.

In the highly developed healthcare markets within Europe and elsewhere, single-payer or government-directed payers each have their own processes and metrics, but through broad reference pricing across markets, have important influences both within and beyond each country's borders. Emerging markets like China are evolving at an incredible pace, presenting new opportunities for manufacturers to engage, but also posing challenges around how best to do this. In the U.S., Medicare and Medicaid's mandate to cover most every drug puts increased pressure on state and federal budgets and also presents patients with potential access restrictions. Yet, the innovative payment models seen in the commercial market in the U.S., such as the implementation of VBAs, is not being replicated in the public markets here or abroad despite manufacturers' willingness to do so. While it's no doubt that various policy changes among public payers regarding value assessment, pricing, and access are forthcoming, a thoughtful and early approach to demonstrating value should reward companies that can deliver it to all payers. ■

Appendix

MassBio Value of Health Advisory Group

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