



PHARMACEUTICAL MANAGED ENTRY AGREEMENTS

Lessons Learned from Europe, the United States,
Canada and Australia

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EXECUTIVE SUMMARY

BACKGROUND

Healthcare systems are struggling with balancing uncertainty and providing access to innovative health technologies.

It can prove difficult to align the disparate objectives of payers and drug manufacturers, but a solution—in at least some cases—may be found in the use of managed entry agreements (MEAs). These deals, negotiated between payers and manufacturers, make reimbursement conditional on a drug meeting specified targets—financial, performance-based, or a combination of the two approaches.

A performance or outcomes-based agreement (OBA) tracks the effectiveness of a drug in a defined patient population over a specified period of time and directly links the price or reimbursement of the product to the clinical or economic outcomes achieved. OBAs typically:

- involve data collection post regulatory approval;
- distribute risk between the payer and the manufacturer;
- address uncertainty in cost or effectiveness outcomes; and
- directly link pricing or reimbursement to outcomes.

OBJECTIVE

A comprehensive literature review of the trends, challenges, and opportunities in key international markets was conducted by the authors to provide clarity on the feasibility of such innovative OBAs.

Specifically, the payer reimbursement environment in Europe, Australia, Canada, and the United States was explored for this

analysis.

Based on the results of this analysis a series of key questions was developed for payers and manufacturers to consider when laying the groundwork for an OBA.

INTERNATIONAL EXPERIENCE

EUROPE

Italy is by far the most active practitioner of managed entry in Europe. The country's managed entry strategy is underpinned by an extensive national system of online registries. Registry-based MEAs saved the Italian healthcare system €531.8 million in 2017.

Historically, England's National Institute for Health and Care Excellence (NICE) focused on negotiating simple discounts in preference to OBAs. However, the National Health Service (NHS) has recently expressed interest in exploring a wider range of MEAs, including price-volume agreements, conditional reimbursement, deferred payments or annuity-based pricing, outcomes-based payments, product-service bundling and deferred payments.

Spain is a relative latecomer to managed entry, and most of the activity to date has been at the regional or local level. Catalonia has been the autonomous community most active in managed entry. The majority of deals are risk-sharing agreements, but expenditure ceilings are also common.

The French healthcare system makes use of price-volume agreements, reductions to list prices to prevent parallel exportation, clawbacks if orphan drugs exceed specified

thresholds, limits on the daily cost of therapy, dosing or number of units prescribed for a given medicine, and outcomes-based agreements. In 2017, MEAs saved the French healthcare system €1.365 billion, an increase of 197% in just five years.

Unlike most other markets, MEAs in Germany typically relate to drugs that have been on the market for several years, rather than new medicines. There have been few, if any, new publicly disclosed MEAs in the last decade, but a number of key stakeholders in the German healthcare system have commented on the possibility of making greater use of managed entry strategies for high-priced new drugs, such as advanced therapy medicinal products.

The Dutch government turned to managed entry in 2006 in an attempt to control pharmaceutical expenditure and reduce regional variations in access to medicines. In 2012, however, the government decided to move away from outcomes-based MEAs to financial arrangements. The number of such deals increased from 16 in 2015 to 25 in 2017. Savings from these arrangements grew from €66.7 million in 2015 to €132 million in 2017.

The first national MEA in Sweden was signed in November 2014. There are currently 22 financially-based schemes covering drugs that have combined sales equivalent to 15% of total pharmaceutical sales in Sweden. The deals relate primarily to TNF- α inhibitors, hepatitis C therapies, and oncology drugs. Savings from these MEAs increased from SEK259 million in 2015 to a projected SEK940 million in 2017.

AUSTRALIA

In Australia, OBA proposals are considered by the Pharmaceutical Benefits Advisory Committee (PBAC) based on unmet need, the importance of additional clinical data, and an agreement by manufacturers to

ensure confidentiality and partake in an eventual review of the evidence.

A study from January 2012 to May 2016 found that 5% of MEAs were outcomes-based.

OBAs are primarily implemented to address uncertainty surrounding overall survival benefit and for antineoplastic agents.

The most common form of implementation involved a review of the evidence and revision of reimbursement if applicable.

Provisions established for MEAs in the 2010 Memorandum of Understanding (MOU), signed by the Minister of Health and Ageing and Medicines Australia, have opened the door for OBAs and while uptake was initially slow, their experience is steadily increasing.

CANADA

In 2010 the Canadian federal, provincial, and territorial bodies began negotiating MEAs as a collective through the pan-Canadian Pharmaceutical Alliance (pCPA).

Canada is not yet very active in terms of negotiating OBAs.

According to a 2016 report, Canada has engaged in six OBAs.

Of the few mentioned within the literature, the (A) payment for performance and (B) conditional treatment continuation types are most noted.

Canada has limited experience to date, but payers are attempting to optimize the use of outcomes and real-world evidence, with the province of Alberta having established itself as a leader (Alberta RWE Consortium).

On a national level, a proposed supplemental process for expensive drugs for rare diseases (DRDs) is under consultation,

incorporating the use of RWE requirements (when applicable) and MEAs. Continued reimbursement would be contingent on the evaluation of RWE considering pre-determined targets. This proposed change in policy may facilitate the use of more OBAs in Canada to support access to specialized high-cost drugs.

THE UNITED STATES

Between 2009 and the first half of 2018, 43 OBAs negotiated in the United States were mentioned in public statements (many more undisclosed).

A 2017 survey of health plan executives found that 70% of respondents had a favorable attitude toward OBAs. Another survey found that 80% of pharmaceutical companies that had undertaken such deals judged them to be somewhat or very successful.

Concerns about best-pricing regulations and anti-kickback legislation have sometimes been a deterrent to negotiating OBAs in the United States. However, a recent US government policy document seeks to remove “government impediments to value-based purchasing by private payers.” The FDA Commissioner has said that “selling models should be able to tie the price of drugs more closely to the usefulness of the clinical setting in which they are prescribed.”

The US government is also “considering further use of value-based purchasing in federal programs.” Although the Centers for Medicare and Medicaid Services has recently abandoned a pioneering value-based contract for Novartis’s Kymriah® (tisagenlecleucel), the agency remains committed to “moving to value-based payment for high-cost drugs and therapies.”

KEY CHALLENGES

The negotiation of OBAs poses considerable challenges and these barriers prove largely universal to the jurisdictions analyzed:

- **Cost** - Resources and time required to establish and execute are administratively burdensome. Rebates may not offset costs of establishing the agreement itself.
- **Data infrastructure** - Different data systems add difficulty in negotiation. Limited or inappropriate infrastructure limits the capacity to capture patient level data.
- **Performance metrics selection** - Linked to infrastructure, which can create limitations in what data can be captured. Forced to rely on surrogate markers, which may not reflect the outcome of interest.

KEY QUESTIONS

In laying the groundwork for an OBA, payers and manufacturers need to address the following questions:

- (1) **Outcomes** - Are the chosen outcomes appropriate and measurable?
- (2) **Timelines** - Are the timelines realistic and understood by all parties?
- (3) **Impacts** - How will research findings impact pricing and reimbursement?
- (4) **Funding** - Is it clear who will fund the research?
- (5) **Data Management** - Who will collect and analyze the data?
- (6) **Costs** - Are the costs acceptable?
- (7) **Uncertainty** - Will further research address uncertainty regarding a drug’s clinical or economic benefits?

OUTLOOK AND IMPLICATIONS

Official data from France, Italy, the Netherlands, and Sweden show that financially-based MEAs can deliver significant—and growing—savings for healthcare systems. These results will encourage governments to continue, and expand, such initiatives.

Savings from OBAs may be much more modest. Nevertheless, payers around the world—including NHS England, German health insurance funds, the national government and some regional administrations in Spain, the Swedish government and the US administration—have recently expressed interest in exploring a range of approaches to managed entry.

For managed entry strategies to be successful for all stakeholders, payers and pharmaceutical companies need to understand—and agree—which type of deals are suitable for which drugs.

Coverage with evidence development (CED) is likely to become much more important in the future as growing numbers of drugs qualify for accelerated regulatory approval.

The continued growth of outcomes-based MEAs could be hampered by insufficient capacity to keep up with demand.

Pharmaceutical companies need to prepare for the increasing role that digital health technology will play in their businesses, including MEAs.

In the years ahead, payers and manufacturers will need to tailor MEAs to the growing pipeline of high-priced advanced therapy medicinal products, some of which may be dosed just once, but have effects that potentially last for many years.

Pharmaceutical companies will need to deal with a growing range of partners for MEAs—at local, regional, national, and even supranational levels.



INTRODUCTION

Healthcare payers around the world face growing challenges in providing timely access to innovative medicines. A burgeoning pipeline of biologics, orphan drugs, advanced therapy medicinal products, and other high-priced medicines has the potential to have an enormous impact on healthcare budgets. Increasingly, regulators are seeking to expedite the marketing authorization of the most innovative medicines, and physicians and patients are eager to use these products.

Payers likewise want to ensure that effective new drugs are readily available, but they are also conscious of several difficulties: uncertainty at launch regarding the true value of new therapies that have an immature evidence base, concerns about appropriate use of new therapies (in particular, limiting prescriptions to patients who respond to a treatment), and potential budget impact. For their part, drug manufacturers are keen to secure market access for their new products as soon as possible, yet they do not want to set their list prices too low, not least because

of the threat of a downward spiral of prices as a result of the expansion of international reference pricing.

It can prove difficult to align the disparate objectives of payers and drug manufacturers, but a solution—in at least some cases—may be found in the use of managed entry agreements (MEAs). These deals, negotiated between payers and manufacturers, make reimbursement conditional on a drug meeting specified targets—financial, performance based, or a combination of the two approaches. MEAs are known by a variety of designations, including:

- conditional reimbursement,
- performance-based risk-sharing agreements (PBRsAs),
- outcomes-based agreements (OBAs),
- outcomes-based pricing and reimbursement arrangements (OPRAs),
- patient access schemes (PASs), and
- product listing agreements (PLAs).

This white paper will use MEA as the standard designation for these deals but will use other terms (e.g., OPRA, PAS, PLA) that are employed in referenced sources.

“These deals, negotiated between payers and manufacturers, make reimbursement conditional on a drug meeting specified targets—financial, performance based, or a combination of the two approaches.”

An OBA is an arrangement that tracks the effectiveness of a drug in a defined patient population over a specified period of time and directly links the price or reimbursement of the product to the clinical or economic outcomes achieved (Garrison et al., 2013). While these schemes can vary greatly in their execution, Garrison et al. identified the following five key characteristics of OBAs:

2. Collection of data typically occurs after regulatory approval;
3. Pricing, funding criteria, or continued reimbursement of the product are linked to the outcomes of this data;
4. The data collected address uncertainty in population, size of effect, long-term effect, adverse effects, or patient response, for example; and
5. The agreements distribute risk between the payer and the manufacturer.

This paper explores the reimbursement environment and use of MEAs in Europe, Australia, Canada, and the United States. Based on the results of this analysis, we present a series of questions for payers and manufacturers to consider when laying the groundwork for MEAs. We also assess the outlook and implications for the pharmaceutical industry of the continued growth of MEAs around the world.

1. The manufacturer and the payer agree to utilize data collection to address uncertainty;



INTERNATIONAL EXPERIENCE WITH MEAs

PATTERNS AND PERCEPTIONS OF MEAs

A 2014 study investigated trends in the use of OPRAs in the United States and the five largest European markets (Italy, United Kingdom, Spain, France and Germany). The authors defined an OPRAs as “a scheme between a healthcare payer and a drug manufacturer in which the price, level or nature of reimbursement, or payer coverage of a drug are tied to one or more future clinical or other patient health measures,” which could be clinical or financial and utilization endpoints. From 1994 through 2014, details of 106 OPRAs were published in the five largest European markets. The frequency of OPRAs has increased over time:

- whereas only 46 agreements were signed from 1994 through 2009,

- 60 deals were negotiated between 2010 and 2014, including 25 contracts in 2014 alone.

More than two-thirds of publicly disclosed OPRAs in the five major European markets were in Italy. Oncology drugs accounted for more than 60% of OPRAs (Nazareth et al., 2014).

Another study analyzed data mined from Health Technology Assessment (HTA) databases in three European markets (Italy, United Kingdom and Spain). In the period 2000 through 2014, there were 80 MEAs in Italy, 45 in the United Kingdom, and 12 in Spain, a relatively late adopter of managed entry. Only 14 drugs or devices were the subject of MEAs in more than one country, and just two—Eli Lilly/Bristol-Myers Squibb/Merck KGaA’s Erbitux® (cetuximab) and AstraZeneca’s Iressa® (gefitinib)—had MEAs

in all three countries. All of the MEAs identified in Italy were OBAs. Similarly, deals negotiated in Spain were all outcomes-based and related to payment by results. In contrast, all but one of the MEAs in the United Kingdom were financially based. MEAs in Italy and the United Kingdom were all national in scope, whereas in Spain agreements were negotiated at the national, regional, and local hospital level. Cancer therapies accounted for 83% of MEAs in Italy and 48% of agreements in the United Kingdom. Ophthalmology drugs and treatments for musculoskeletal disorders ranked second and third in terms of the total number of MEAs in Italy, Spain and the United Kingdom (Tolley et al., 2014).

In primary research, Nazareth et al. (2014) found that healthcare payers and pharmaceutical companies differ significantly in their motives for negotiating outcomes-based MEAs

- **Payers' objectives/interests:** Reduce uncertainty about a drug's outcomes; reduce costs; minimize financial risks; clinical endpoints; medication adherence; resource and financial utilization.
- **Manufacturers' objectives/interests:** Demonstrate value of medicine; secure market access; reinforce partnerships with payers; maintain prices across markets; shift payers' focus from cost to value.

Payers and manufacturers agreed that the success of OPRA depends heavily on effective organization. Data expectations need to be aligned at an early stage, and outcomes data must be unambiguous. It is important for the health economics and outcomes research function to play an active role at all stages of an OPRA. Major obstacles to OPRA include an inadequate data infrastructure, the internal organizational cost and complexity of these agreements, a perceived lack of incremental value and the complexity of negotiating such deals.

Payers and manufacturers generally consider MEAs to be best suited to new therapies that have a potentially high cost per patient and/or a substantial budget impact, as well as drugs that lack real-world evidence (RWE) of their value. However, the focus of managed entry is somewhat different in Germany, where regional health insurance funds prioritize deals on mature drugs that have a substantial budget impact (Nazareth et al., 2014).

A steady increase in the number of national and regional frameworks and guidelines will promote continued growth in the use of MEAs. The growing availability of large, integrated data sources will make it easier to gather the real-world data needed to support MEAs.

EUROPE



ITALY

Italy is by far the most active practitioner of managed entry in Europe. The country's managed entry strategy is underpinned by an extensive national system of online registries, which the *Agenzia Italiana del Farmaco* (AIFA; Italian Medicines Agency) began to develop as long ago as 2005. There are three types of registries:

1. drug product monitoring registries,
2. therapeutic indication monitoring registries, and
3. therapeutic plan registries.

At the end of 2017, 49 pharmaceutical companies had at least one registry on the AIFA platform (Osservatorio Nazionale sull'Impiego dei Medicinali, 2018). As of October 2, 2018, AIFA had 143 active registry-based MEAs:

- 74 appropriate prescribing agreements,
- 42 outcomes agreements,
- 24 financial agreements,
- two outcomes and financial agreements, and
- one appropriate prescribing and financial agreement.

In addition, the agency had negotiated a further 73 registry-based MEAs that had yet to be implemented: 67 appropriate prescribing agreements, five financial agreements and one outcomes agreement. These figures highlight AIFA's clear—and growing—preference for appropriate prescribing agreements over other types of MEAs (AIFA, 2018).

AIFA has two types of outcomes agreements:

1. **Risk sharing** requires pharmaceutical companies to refund part of the treatment cost for non-responders.
2. **Payment by results (PbR)** requires manufacturers to repay in full the treatment cost for non-responders. PbR is used to manage a high degree of uncertainty for drugs that are perceived to have an unfavorable benefit/risk ratio at launch. In 2017, all of the outcomes agreements negotiated by AIFA were PbR schemes (Osservatorio Nazionale sull'Impiego dei Medicinali, 2018).

AIFA also operates two types of financial agreements:

1. **Cost sharing** provides for a discount on the cost of the first cycle of treatment, or the entire course of therapy, for all eligible patients. This type of deal is generally used in cases of uncertainty regarding the potential financial impact of a new medicine (as opposed to uncertainty regarding its effectiveness).
2. **Capping** sets a ceiling on expenditure on a drug per patient, beyond which the manufacturer covers all remaining costs.

Registry-based MEAs saved the *Servizio Sanitario Nazionale* (SSN; National Health Service) €531.8 million in 2017. Capping

accounted for 84.7% of this total, PbR for 6.5% and cost sharing for 5.6%.

In addition to the patient-level MEAs managed through AIFA's registries, Italy makes use of two population-level approaches to managed entry.

1. **Product-Specific Expenditure Ceilings:** AIFA's *Comitato Prezzi e Rimborso* (CPR; Pricing and Reimbursement Committee) negotiates a national limit for spending on a given drug in its first 12 or 24 months on the market. If this limit is exceeded, the manufacturer must refund excess costs to regional administrations.
2. **Price-Volume Agreements** provide for incremental discounts on list prices in response to growing prescription volume. The discounts may be in the form of a price reduction or a refund to the regions.

In 2017, AIFA had 11 expenditure ceilings and three price-volume agreements in place (Osservatorio Nazionale sull'Impiego dei Medicinali, 2018).

“Italy is by far the most active practitioner of managed entry in Europe. The country's managed entry strategy is underpinned by an extensive national system of online registries...”



UNITED KINGDOM

In England, MEAs are generally referred to as Patient Access Schemes (PASs). Since 2009, the PAS Liaison Unit (PASLU), a unit of the National Institute for Health and Care Excellence (NICE), has been responsible for coordinating these deals with manufacturers. PASs may be financially based or one of three types of outcomes-based schemes:

1. **Proven value** – a drug's price may be **increased** in the future based on new evidence of superiority (generally gathered by the manufacturer).
2. **Expected value** – a drug's price may be **reduced** in the future if new evidence (generally gathered by the manufacturer) does not support the price agreed at launch.
3. **Risk sharing** – a drug's price may be **reduced or increased** based on clinical or patient-reported outcomes measures.

As of October 8, 2018, NICE had 184 active PASs with various life sciences companies. In all, 133 (72%) of these deals are simple discounts.

Historically, the significant administrative burden and cost of outcomes-based schemes largely deterred NICE from negotiating outcomes-based deals with manufacturers. In October 2016, however, the government-

“In October 2016, the government-commissioned Accelerated Access Review (AAR) proposed a major overhaul of market access in the UK, including initiatives to promote a broader approach to managed entry.”

commissioned Accelerated Access Review (AAR) proposed a major overhaul of market access in the UK, including initiatives to promote a broader approach to managed entry. For instance, products that are deemed to have transformative status but an immature evidence base could qualify for conditional recommendation by NICE. This arrangement would lead to a period of managed access, provided that the manufacturer and National Health Service (NHS) England had negotiated satisfactory commercial terms.

The AAR also proposed “novel risk-sharing arrangements between the NHS and the innovator that enable both parties to benefit from a product’s success.” In addition, the UK could adopt flexible pricing methods that have been implemented in other countries, such as price-volume agreements, conditional reimbursement, deferred payments or annuity-based pricing, outcomes-based payments, and product-service bundling and deferred payments. The most appropriate pricing method would depend on a product’s value proposition, and the arrangements could change over time, as new evidence was generated or a drug’s patient population expanded. Significantly, the AAR suggested that “payment could be linked to the delivery of value, whereby no payment is made if the expected value has not been delivered” (Accelerated Access Review: Final Report, 2016).

The NHS was receptive to the suggested new pricing methods. In the *Introduction to the AAR final report*, Simon Stevens,

the CEO of NHS England, writes: “Where it makes sense, we’ll increasingly be open to agreeing innovative win/win product-specific reimbursement models, incorporating a mix of outcomes-based, annuity-based and volume-based pricing deals” (Accelerated Access Review: Final Report, 2016).

As of October 8, 2018, PASLU had negotiated 31 commercial access agreements (CAAs), equivalent to 17% of all PASs. To date, almost all CAAs that have been negotiated relate to oncology drugs. CAAs are typically characterized by some form of conditionality—financial, outcomes-based, or a combination of the two. Ten of these deals replaced earlier PASs. The terms of CAAs generally remain confidential. Other types of MEA in use include free stock, dose caps, time caps (i.e., limits on the duration of use), single fixed pricing, and indication-specific discounting, but these approaches are rare. *Figure 1* (Appendix B) shows the frequency of the different types of PASs in England.



SPAIN

Spain negotiated its first MEA in 2010. Thus far, most of the activity has been at the regional or local level, led by the *comunidades autónomas* (autonomous communities) of Andalusia, the Balearic Islands, and Catalonia,

as well as hospitals in Barcelona, Granada, Madrid, and Valencia. Shire, for example, has negotiated risk-sharing deals for more than 20 drugs with more than 100 hospitals (Cepeda Minaya, 2018).

Catalonia has been the autonomous community most active in managed entry: the regional administration has published detailed guidelines on the implementation of risk-sharing agreements. Pharmaceutical companies will need to tailor their managed entry strategies to the different policies of the 17 autonomous communities.

In 2013, Biogen became the first manufacturer to negotiate a national MEA, when it offered the Ministry of Health a treatment initiation agreement for Fampyra™ (fampridine), a treatment for multiple sclerosis (MS). In February 2018, the company concluded another risk-sharing deal with the Ministry of Health, this time for Spinraza® (nusinersen), used in the treatment of spinal muscular atrophy.

One study identified 39 MEAs in Spain as of May 2016. 26 (67%) of these deals were risk-sharing agreements, while the remaining 13 (33%) were expenditure ceilings. MEAs had been negotiated in ten autonomous communities, predominantly at the hospital level. However, all but one of the expenditure ceiling contracts were negotiated nationally. Forty-six per cent of the risk-sharing agreements were in oncology/oncohematology, 12% in progressive inflammatory joint diseases, and 8% in hepatitis C. By comparison, 58% of the expenditure ceiling contracts were in hepatitis C and 25% in oncology/oncohematology (Gimenez et al., 2016).



FRANCE

In recent years, the French healthcare system has made increasing use of a range of managed entry methods to limit expenditure on new medicines:

- price-volume agreements, which reduce prices in inverse proportion to increasing sales volume.
- a policy known as “*remises à la première boîte*” (“discounts on the first box”) reduces a drug’s list price to its net price to prevent parallel exportation.
- agreements with regard to orphan drugs require manufacturers to pay back part of their pre-tax sales if sales of these products exceed specified thresholds.
- the *Comité économique des produits de santé* (CEPS; Health Products Economic Committee) may also impose limits on the daily cost of therapy, dosing or number of units prescribed for a given medicine.

In some cases, a product may be subject to more than one type of MEA, such as a limit on daily cost of therapy to bring its cost in line with that of designated comparators together with a price-volume agreement to ensure that the drug is prescribed only to patients in its target population.

In addition to these financially based managed entry methods, the CEPS can make reimbursement of a new medicine conditional on a *contrat de performance* (OBA). This measure is typically applied to drugs that are given an *amélioration du service médical rendu* (improvement in actual benefit) rating of V (i.e., no improvement), but for which the manufacturer claims a clear advantage over established treatments that can only be proven in the real world. Manufacturers may be required to conduct real-world studies or to monitor outcomes in individual patients, possibly by means of a registry. In 2015, for example, the CEPS required 17 postmarketing studies: nine for new medicines, two for marketing authorization renewals, four for new indications and two for orphan drugs. Manufacturers must bear the full financial risk if postmarketing studies do not confirm a drug's superiority over its comparators. Moreover, companies may face fines if they fail to meet their postmarketing research obligations adequately. In 2013, the French government established the *Comité de suivi des études en vie réelle* (CSEVR; Committee for Monitoring Real-World Studies) to ensure that real-world research meets its exacting standards.

The CEPS reports that, in 2017, MEAs saved the French healthcare system €1.365 billion, an increase of 197% in just five years. The five largest manufacturers in the French market accounted for 57% of these savings and 50% of the cost reduction came from the top ten products. Figure 2 (Appendix B) shows the savings from each of the main types of MEAs in 2017 (CEPS, 2018)

“The CEPS reports that, in 2017, MEAs saved the French healthcare system €1.365 billion, an increase of 197% in just five years.”



GERMANY

Unlike in most other markets, MEAs in Germany typically relate to drugs that have been on the market for several years, rather than new medicines. The first publicly documented MEA in Germany was signed between Eisai/Pfizer and the AOK Bundesverband and AOK Bayern in 2005. The deal was an outcome guarantee for Aricept™ (donepezil), a treatment for dementia. In the following three years, several other companies—led by Novartis—negotiated MEAs with individual health insurance funds (Table 1; Appendix B).

In the last decade, however, there have been few publicly disclosed MEAs in Germany. Birgit Fischer, the Managing Director of the *Verband Forschender Arzneimittelhersteller* (VFA; German Association of Research-based Pharmaceutical Companies), attributes the decline of MEAs to the dominant role played by early benefit assessment of new drugs launched since 2011. This process is mandated by the *Arzneimittelmarktneuordnungsgesetz* (AMNOG; Pharmaceutical Restructuring Act). New drugs are assessed for their level of additional benefit relative to established comparator therapies. According to Fischer, pay for performance is a “fundamental principle” of the AMNOG process, which also makes use of measures such as price-volume agreements (Ärzte Zeitung, 2018a).

Drug manufacturers can negotiate voluntary rebate contracts with individual statutory health insurance funds. Possible options include: price-volume agreements, annual sales volume caps or OBAs. Savings from voluntary rebate contracts have grown steadily, from €800 million in 2009 to €4 billion in 2017. However, branded drugs accounted for only approximately €600 million (15%) of the total savings in 2017 (Pro Generika, 2018). Fischer asserts that central negotiations with the GKV-Spitzenverband (National Association of Statutory Health Insurance Funds) take precedence over local deals (Schüller, 2017).

Within the AMNOG process, the *Gemeinsamer Bundesausschuss* (GBA; Federal Joint Committee) sometimes uses coverage with evidence development (CED) deals to overcome uncertainty associated with certain drugs at the time of their launch. The committee sets time limits for manufacturers to conduct post-marketing research to support a reassessment. At the end of 2017, 56 early benefit assessments (22% of the total completed) had resulted in the imposition of time limits on coverage. In 2017 alone, 14 (29%) of the 49 drugs that were assessed were subject to time limits. The time limits ranged from six months to seven years, with an average of 2.5 years (Storm, 2018).

Failure to meet these deadlines for postmarketing research, or to demonstrate value, is likely to be heavily penalized. According to Wolf-Dieter Ludwig, the German representative at the European Medicines Agency, “if license holders do not provide this additional data after two or three years, we will change our assessment and the price will go down. It’s the only way. We cannot approve drugs with no added therapeutic value, afterward we pay a lot of money for drugs that they do not need” (Fortuna, 2018).

“Unlike in most other markets, MEAs in Germany typically relate to drugs that have been on the market for several years, rather than new medicines.”

In recent months, a number of key stakeholders in the German healthcare system have commented on the possibility of making greater use of managed entry strategies for high-priced new drugs, such as advanced therapy medicinal products. Birgit Fischer believes “it would be interesting to see what would be possible in Germany if lawmakers had the courage to free individual contractual solutions from the Babylonian captivity of the AMNOG” (Schüller, 2017). The *Bundesfachverband der Arzneimittelhersteller* (BAH; Federal Association of Pharmaceutical Manufacturers) “fundamentally welcomes opportunities to promote contractual competition for optimal patient care. One option here is pay-for-performance contracts.” The *Bundesverband der Pharmazeutischen Industrie* (BPI; Federal Association of the Pharmaceutical Industry) is, however, more circumspect: “Pay for performance is successful only if results can be measured by their intended target, namely, a better quality of patient care. Given that there is not yet any scientific consensus regarding the measurement of quality of care, we do not see that it is applicable to the German healthcare system” (Borsch, 2018).

The health insurance funds are also somewhat divided regarding the potential of managed entry for innovative therapies. The National Association of Statutory Health Insurance Funds believes that “pay-for-performance models are among the options to consider” for high-priced technologies, such as cell therapies. On the other hand, the AOK-Bundesverband (Federal Association of General Local Health Insurance Funds) warns that “new price concepts should not be regarded as a panacea because these models can often be implemented only with highly

bureaucratic conditions” (Borsch, 2018).

Despite such reservations from the country’s largest health insurance fund group, Stefan Oschmann, the CEO of Merck KGaA and current President of the European Federation of Pharmaceutical Industries and Associations (EFPIA), would like to see greater use of managed entry strategies in the future: “We have to approach the subject of pricing much more rationally and less emotionally.” Instead of concentrating on the cost per tablet, “reimbursement should much rather focus on outcomes” (Hofmann, 2018).

Oschmann has already taken his own advice. In October 2018, Merck KGaA announced a pay-for-performance agreement with GWQ ServicePlus, a contract service provider for occupational health insurance funds. Under the terms of the agreement, Merck will cover any additional costs incurred if patients on the company’s MS therapy Mavenclad™ (cladribine) do not respond adequately to treatment and have to be switched to an alternative therapy (Ärzte Zeitung, 2018b).

Other companies may also be showing greater interest in MEAs in Germany. In August 2018, Novartis announced its intention to explore innovative payment models—including the option of pay for performance—for its newly approved migraine prophylaxis drug, Aimovig™ (erenumab) (Pharmazeutische Zeitung, 2018).



NETHERLANDS

The Dutch government turned to managed entry in 2006 in an attempt to control pharmaceutical expenditure and reduce regional variations in access to medicines. The *College voor Zorgverzekeringen* (CVZ; Healthcare Insurance Board), now renamed the *Zorginstituut Nederland* (National Health Care Institute), experimented with conditional reimbursement based on CED: manufacturers were offered provisional reimbursement of their medicines for four years, in return for which they were required to conduct outcomes research.

From a list of 49 potential candidates for such MEAs, 12 high-priced hospital medicines were selected for conditional reimbursement. However, for five of the drugs, post-marketing research yielded insufficient data to reach conclusions regarding the therapeutic benefit, cost-effectiveness, or appropriate use of the products. Following reassessment, continued reimbursement was recommended for ten of the drugs, but six of these medicines were subject to requirements for additional evidence generation. Recommendations to discontinue the reimbursement of the two other drugs in the pilot program have yet to be implemented (Makady et al., 2018).

In addition to misgivings about the value of

CED, the CVZ was unhappy because it felt that it bore a disproportionate share of the risk in these deals.

Toward the end of 2012, Edith Schippers, the Minister of Health at the time, announced that the Dutch healthcare system would henceforth favor financially based deals over outcomes-based MEAs. Financial arrangements are generally reserved for the following circumstances:

- a drug has an above-average price or projected budget impact.
- the proposed price is deemed unreasonable and unacceptable.
- price competition is likely to be limited, and stakeholders will have insufficient influence on prices (Schippers, 2015).

The use of financial arrangements in the Netherlands has grown steadily in recent years. The number of such deals increased from 16 in 2015 to 25 in 2017. Savings from these arrangements grew from €66.7 million in 2015 to €132 million in 2017 (Bruins, 2018).

sales of approximately SEK4 billion, equivalent to 15% of total pharmaceutical sales in Sweden. The deals relate primarily to TNF- α inhibitors, hepatitis C therapies, and oncology drugs. Details of the terms of these MEAs are not readily available, but they appear to be financially based schemes that reduce prices in response to increased prescription volume (TLV, 2018).

The *Tandvårds- och Läkemedelsförmånsverket* (TLV; Dental and Pharmaceutical Benefits Agency) works with the county councils and pharmaceutical companies to negotiate national MEAs. County councils may negotiate their own MEAs directly with drug manufacturers, but the grant they receive from the government will be reduced the following year if they do so. The Swedish government is keen to maintain a uniform national pricing policy.

The TLV sees a growing role for MEAs in Sweden: “There are major challenges in the pharmaceutical field both in Sweden and internationally. The trend is for new pharmaceuticals to be introduced at an earlier stage, which means that the uncertainties surrounding these pharmaceuticals are often high. In the coming years, it is likely that the factors that increase the cost of pharmaceuticals will be stronger than the cost-cutting effects. However, MEAs will become an increasingly important tool to dampen cost increases, together with generic competition and measures in the form of reassessments and price reductions for products that are older than 15 years” (TLV, 2018).

A rapid increase in the number of MEAs boosted savings from SEK259 million in 2015 to SEK723 million the following year. Savings in 2017 were projected to increase once again, to SEK940 million. In 2015 and 2016, the savings went entirely to the county councils. Beginning in 2017, however, the government received a portion of the savings: 30% in 2017 and 40% in 2018 and



SWEDEN

The first national MEA in Sweden was signed in November 2014. There are currently 22 MEAs covering drugs that have combined

2019. The TLV calculates that MEAs reduce expenditure on the drugs they cover by an average of approximately 25% (TLV, 2018).

Examples of MEAs in Europe

One of the earliest MEAs in Europe was a risk-sharing scheme negotiated between the UK Department of Health and four manufacturers of disease-modifying MS therapies (Bayer Schering Pharma, Biogen, Merck Serono and Teva) in 2002. The deal was prompted by lobbying from the MS community in response to NICE's decision to reject coverage of any of these drugs. The MEA was based on a ten-year observational study and required manufacturers to cut their prices if the research found that their drugs exceeded an incremental cost-effectiveness ratio of £36,000 per quality-adjusted life year (QALY). Because of an underestimation of the complexity of setting up the scheme, it took three years—twice as long as expected—to meet the minimum recruitment target of 5,000 patients. The results of the initial two-year assessment of accumulated disability were not published until 2009, seven years after the MEA was approved. The early evidence suggested the drugs failed to delay disease progression, but results after six years of research were more positive. More than 18,000 patients were eventually enrolled in the scheme, but the MS Society reported in 2013 that fewer than 40% of eligible patients were receiving treatment with one of the drugs in the scheme—a lower percentage than in any other European countries except Poland and Romania. Critics of the agreement have taken issue with its:

- administrative cost,
- complexity,
- governance,
- choice of outcomes measure,
- logistical delays,
- inflexibility, and
- lack of enforceability.

“In July 2018, the Dutch and Belgian Ministries of Health announced a joint CED decision...”

Prices were not cut after disappointing initial study results. In July 2017, NICE announced that it was pausing a review of its earlier multiple technology appraisal of beta-interferons and glatiramer acetate in response to reports that the manufacturers were considering new access agreements for their products. In June 2018, NICE recommended the use of all but one of these drugs (Bayer's Betaferon®) on the explicit basis that the manufacturers had offered the NHS commercial arrangements (NICE, 2018).

Notwithstanding the difficulties of the MS risk-sharing scheme, the NHS did negotiate a number of other OBAs in the following years. One study examined the practical challenges of executing four of these schemes in the field of oncology, for Janssen-Cilag's Velcade® (bortezomib), Pfizer's Sutent (sunitinib), Roche Genentech's Tarceva® (erlotinib) and Merck Serono's Erbitux® (cetuximab). An online survey completed by 31 NHS trusts in England found that the average time needed to process each patient enrollment in an MEA was 17.5 minutes for Tarceva®, 19 minutes for Sutent®, 37.5 minutes for Velcade® and 45 minutes for Erbitux®. 73% of survey participants indicated that they did not have capacity to participate in any more schemes. Respondents expressed a preference for simpler agreements that had fewer requirements for data collection and monitoring. A common complaint was that hospital pharmacy systems were not set up to track patients as required by these schemes, to process claim forms in the time permitted (as little as five days in some cases) and to manage free stock. A key finding was the need for funding to provide dedicated staff time to track and manage MEAs to ensure that claims are not missed. Respondents also

called for future MEAs to have more flexible time allowances—ideally, at least 90 days—to process claims. In addition, the survey found that the development of national templates for PASs would help manufacturers to use “off-the-shelf” schemes that would benefit the NHS (Williamson, 2010).

The existence of a well-defined national system of web-based registries and classification of MEAs has been a major factor in the popularity of OBAs in Italy. For example, the SSN reimbursed Novartis’ Rasilez® (aliskiren), an antihypertensive, only after the establishment of a registry for the drug and its inclusion in the *Registro dei Farmaci Cardiovascolari* (Registry of Cardiovascular Medicines). Using two years of observational data, AIFA decided to extend prescribing from specialists to general practitioners, cut the drug’s price in line with the prices of other antihypertensives and introduce a spending ceiling for the product (based on a budget impact analysis for aliskiren as second-line therapy) (Fondazione Smith Kline, 2018).

In France, Celgene negotiated an outcomes-based MEA for Imnovid® (pomalidomide), a treatment for multiple myeloma. The agreement required the company to establish a dedicated registry to gather real-world efficacy and safety data for all patients prescribed the drug. To ensure the objectivity of the registry, responsibility for running the registry was delegated to a contract research organization, and the outcomes measured were determined by independent experts from the International Myeloma Working Group. In return for a price premium, Celgene agreed to refund the cost of treatment for non-responders (Ducruet, 2015).

The European Union (EU) marketing authorization in 2013 of Gilead Pharmaceuticals’ Sovaldi® (sofosbuvir), an innovative therapy for hepatitis C, prompted several countries to adopt

stringent measures to contain the cost of a medicine that had a potentially enormous budget impact. France, Italy, and Spain all negotiated high-profile MEAs for the drug, albeit with substantially different terms. All three countries imposed price-volume agreements for the drug. In addition, Italy set a fixed cost per patient (AIFA, 2015; Marata & Formosos, 2015). Spain imposed a budget cap for the first year of sales and negotiated a risk-sharing agreement that secured initial discounts pending real-world data (El Global 2014a; El Global 2014b). In France, Gilead had to grant substantial rebates and agree to an outcomes contract based on data from the Hepather database operated by the *Agence nationale de recherches sur le SIDA* (ANRS; French National Agency for Research on AIDS), with treatment costs refunded for non-responders (APM News, 2014).

In July 2018, the Dutch and Belgian Ministries of Health announced a joint CED decision with regard to Biogen’s Spinraza® (nusinersen). Following completion of a collaborative HTA process, the two Ministries of Health began pricing negotiations with Biogen in February 2018. The confidential pricing agreement provides Biogen temporary reimbursement of Spinraza® until December 2020. In the interim, the company will be required to gather real-world data on safety, efficacy and use of the drug in clinical practice, as well as supplementary research on variations in the drug’s effectiveness in four subtypes of the disease. These data will then be used to re-evaluate Spinraza® (Rijksoverheid, 2018; De Block, 2018).



AUSTRALIA

In 2010, the Australian government signed a Memorandum of Understanding (MOU) to extend their pharmaceutical price reform policies including provisions for MEA schemes (Vitry & Roughead, 2014; Wonder, Backhouse, & Sullivan, 2012). The government and the pharmaceutical industry agreed to establish provisions to improve the quality and strength of evidence provided to the Pharmaceutical Benefits Advisory Committee (PBAC) and to improve the chances of listing a new medicine (Wonder et al., 2012). To achieve these objectives, an MEA must address uncertainties associated with new medicines. MEAs in Australia can be either non-outcomes-based (price-volume agreements, discounts, price or dose capping schemes) or outcomes-based (Roughead). Outcomes-based schemes can be at the patient-level, with conditional treatment rules or outcomes guarantees for example, or at the population level, with CED (Roughead).

An outcomes-based MEA proposal will be considered by the PBAC under the following conditions:

- There is high unmet clinical need for the medicine in the requested indication;
- New clinical data will resolve

uncertainty surrounding the clinical effect that would have otherwise prevented a positive recommendation;

- A confidential agreement between the sponsor and government will be used to ensure clear understanding of all obligations; and
- Any subsequent review of the evidence specified in the agreement would also include a consideration of all other relevant evidence at that time (Wonder et al., 2012).

Studies to date show that non-OBAs, particularly price discounts, tend to dominate the managed entry space in Australia (Lu et al., 2015; Robinson & Roughead, 2016). However, in an international context, Australia is amongst the most experienced with MEAs and CED (Lu et al., 2015; Montilva, Degun, & Xue, 2016).

Australia has implemented several OBAs in cases where efficacy was uncertain. In a recent review of 170 MEAs implemented from January 2012 to May 2016 in Australia, which included financial as well as outcomes agreements, it was found that 5% of MEAs were outcomes-based (Robinson, Mihalopoulos, Merlin, & Roughead, 2018).

“In an international context, Australia is amongst the most experienced with MEAs and CED...”

There was substantial variety in how these agreements were established and implemented to address product specific needs and questions. Examples of outcomes-based MEAs in Australia are summarized in Table 2 (Appendix B).



CANADA

Unlike other markets with national pharmaceutical coverage systems, reimbursement in Canada takes place in a “patchwork” of federal, provincial, territorial (F/P/T) public drug plans alongside private drug plans.

The acceptance of MEAs (referred to as PLAs in Canada) was primarily driven by the Ontario (Canada’s largest province) government’s passing of Bill 102, the *Transparent Drug System for Patients Act* in 2006. This legislation granted Ontario the ability to negotiate MEAs with manufacturers, including confidential financial terms, to achieve better value for the publicly funded system (Ontario Ministry of Health and Long Term Care, 2006). Around the same time, but through separate initiatives, several other provincial drug plans also began pursuing MEAs.

With the perceived initial success of MEAs in Canada coupled with the increasing entry of high cost drugs in 2010, the Council of Federation, a congress comprised of territorial and provincial premiers, announced their intention to assess

the feasibility of joint negotiations with participating drug plans. The success of this initial pilot led to the eventual establishment of the pan-Canadian Pharmaceutical Alliance (pCPA) in 2013/14. The pCPA now leverages the combined negotiating power of all the public drug plans to “achieve greater value for publicly funded drug programs and patients” (pan-Canadian Pharmaceutical Alliance).

As of October 31, 2018, the pCPA had completed 216 joint negotiations with 57 negotiations underway, the highest number of active negotiations on record (See *Table 3*; Appendix B). A total of 27 files have been closed without reaching a successful conclusion.

On average the pCPA initiated 5.6 negotiations, completed 4.2 negotiations and closed 0.9 negotiations per month between January 2017 and October 2018.

The terms of most MEAs are considered confidential, with the result that little information is publicly available beyond the number of such deals that have been negotiated. However, in April 2018 the pCPA Office, dedicated staff to support the work of the pCPA, confirmed in a public forum that there are several negotiations where the pCPA has or is exploring outcomes-based MEAs (2018 CADTH Symposium). In November 2018, an industry representative also confirmed successful negotiation of an OBA with the pCPA for a drug for the treatment of a rare disease. In addition, according to a 2016 report, industry experts revealed that manufacturers have negotiated six OPRAs (Avalere, 2016). In another study, conducted by Toumi et al. (2013), researchers identified the six Canadian agreements, most likely undertaken pre-pCPA, including: clozapine, docetaxel, finasteride, donepezil, rivastigmine, galantamine.

One of the key challenges in Canada surrounding development of outcomes-based MEAs is comprehensive national RWE

“On a national level, a proposed supplemental process for expensive drugs for rare diseases (DRDs) is under consultation, incorporating the use of RWE requirements (when applicable) and the use of MEAs.”

data sources. In October 2018, the Canadian Association of Population Therapeutics (CAPT) hosted a full-day workshop to discuss recent advances in the dialogue on RWE in Canada from a regulatory, HTA and reimbursement perspective. The day was attended by participants invited from various stakeholder groups, including Health Canada, CADTH, provincial cancer agencies, provincial drug plans, the pCPA, researchers/clinicians, patient stakeholder groups, and the pharmaceutical industry.

It was noted at this workshop that critical to success of RWE data collection is transparent and ongoing dialogue focused on factors to consider for each product’s unique situation, practical implementation approaches,

proactive-versus-reactive stance, and ensuring a healthcare system approach. It was discussed that patient support programs could potentially be a source of credible and rich data to inform outcomes-based agreements and ongoing decision making. This assumes patient support programs are properly structured to ensure data are collected with a degree of rigor and quality that instills confidence for all stakeholders involved in this exercise.

On a national level, a proposed supplemental process for expensive drugs for rare diseases (DRDs) is under consultation, incorporating the use of RWE requirements (when applicable) and the use of MEAs. Continued reimbursement would be contingent on the evaluation of RWE based on predetermined targets. This proposed change in policy may serve to facilitate the use of more OBAs in Canada to support access to specialized high-cost drugs. Such initiatives may form the cornerstone of obtaining the necessary data to negotiate and implement outcomes-based MEAs in Canada in the future.



UNITED STATES

The US healthcare system is uniquely complex in its structure, with residents covered by a range of private and government-sponsored insurers, and pharmaceutical market access governed by a wide variety of stakeholders, including the Centers for Medicare and Medicaid Services (CMS), state Medicaid agencies, employers, managed care organizations (MCOs), accountable care organizations (ACOs) and pharmacy benefit management companies (PBMs).

In 2017, 217 million US residents (67.2% of the population) had some form of private health insurance: 181 million (56%) had employment-based benefits and 51.8 million (16%) had direct-purchase health insurance. In addition, 122 million (37.7%) received government-sponsored health benefits—62.5 million (19.3%) from Medicaid (the state-sponsored program that covers low-income residents), 55.6 million from Medicare (the federal program that covers elderly and disabled residents), and 15.5 million (4.8%) from military healthcare programs. Some residents received health benefits from more than one type of health plan (e.g., an employer-sponsored health plan plus Medicare, Medicaid plus

Medicare). On the other hand, 28.5 million (8.8%) were uninsured—down substantially from a peak of 50 million (16.3%) in 2010 (US Census Bureau, 2018).

The United States is also unusual in allowing pharmaceutical companies a (theoretically) free hand in setting prices for prescription drugs. In practice, manufacturers generally have to offer MCOs or their PBMs substantial discounts or rebates to secure favorable formulary status. In addition, pharmaceutical companies have to give specified discounts to Medicaid, the 340B drug discount program (which offers savings to more than one third of US hospitals and clinics that treat low-income patients), and the Medicare Part B program (which covers inpatient treatment for Medicare beneficiaries).

The US market presents some particular challenges to managed entry. Patterns of health insurance coverage are much less stable than in most other advanced economies. For example, people who have employer-sponsored health benefits (the majority of the population) change their health plans when they switch employers; the limited average enrollment period of members is a disincentive to health plans to abandon the short-term advantages of discounts and rebates for the promise of long-term gains from MEAs. In addition, the PBMs that currently play a key role in negotiating discounts and rebates on prescription drugs have little or no involvement in managing medical benefits, making it difficult for them to contribute to managed entry strategies.

Growth of Value-Based Contracts (VBCs)

In the United States, “value-based contracts” (VBCs) are the most common designation for MEAs. The Pharmaceutical Research and Manufacturers of America (PhRMA), the association that represents the US pharmaceutical industry, maintains a database of VBCs whose existence has been publicly disclosed, although the terms of

these deals almost always remain highly confidential (Pharmaceutical Research and Manufacturers of America, 2018). From 2009 through the first half of 2018, 43 VBCs were mentioned in public statements, but there may have been many more agreements that were not disclosed. The PhRMA analysis indicates that the frequency of VBCs has increased in recent years (*Figure 3*; Appendix B).

According to PhRMA, AstraZeneca, Amgen, Biogen, Novartis, Eli Lilly, and Merck are the drug manufacturers that have negotiated the most VBCs in the United States (*Figure 4*; Appendix B).

Among payers, Harvard Pilgrim Health Care has negotiated the greatest number of VBCs with drug manufacturers. Cigna and Prime Therapeutics have also been particularly active in striking deals with pharmaceutical companies (*Figure 5*; Appendix B).

Endocrinology, cardiology and neurology are the therapeutic areas that have been the focus of the most intense activity in negotiating VBCs. *Figure 6*; Appendix B shows that there have been nine VBCs for diabetes drugs, seven for MS therapies, six for treatments for familial hypercholesterolemia, and three each for treatments for cardiovascular disease, heart failure, and hepatitis C.

“The US government has recently expressed its support for innovative approaches to pricing as a means to reduce the cost of prescription drugs in the US.”

Stakeholder Attitudes Toward VBCs

Payers' Attitudes

An online survey of health plans with a total of 183 million covered lives, conducted by Avalere Health in April 2017, found that

70% of respondents had a favorable attitude toward VBCs. Twenty-four per cent of plans already had a VBC in place, including 12% that had negotiated more than five such contracts. A further 30% of plans were in the process of negotiating their first VBC(s) at the time of the survey, whereas 29% did not intend to undertake value-based contracting, and 16% were unsure (Avalere Health, 2017).

Despite the strong interest in VBCs, payers will reject proposals for such deals for a variety of reasons. A survey of 25 pharmacy directors from health plans, health systems, and PBMs, conducted by Precision Value & Health in March 2018, found several common reasons for rejecting VBC proposals, summarized in *Figure 7*; Appendix B.

Pharmaceutical Companies' Attitudes

Although only a limited number of drug manufacturers have negotiated VBCs to date, companies that have signed such deals are generally positive about their benefits. A 2017 survey by PwC of 101 pharmaceutical executives from 97 companies found that respondents from 24 companies had participated in a VBC. Seven of these companies had reportedly negotiated more than 20 VBCs, indicating that many of these deals were not in the public domain. Eighty per cent of the respondents from companies that had undertaken VBCs judged these deals to have been somewhat or very successful, and 92% indicated that their companies were somewhat or very likely to renew current VBCs (PwC, 2017).

The PwC survey found that 34% of VBCs were established at the pre-commercial stage (i.e., prior to regulatory approval), 28% at launch (i.e., following regulatory approval), and 18% at least one year after launch. Pharmaceutical executives identified the challenge of reaching agreement with partners regarding metrics for the evaluation of drug performance and patient outcomes as the greatest obstacle to negotiating

VBCs, cited by 29% of respondents. Seventeen percent reported difficulties in the management of drug performance monitoring, data collection or analysis, 16% expressed concern about the financial risks associated with poor patient outcomes or underperforming products, and 15% perceived a lack of clear financial incentive to participate in VBCs. Survey respondents also worried about some regulatory barriers, especially concerns about the risk of violating “best-price” regulations and restrictions on the communication of off-label information (PwC, 2017).

US Government’s Attitude

The US government has recently expressed its support for innovative approaches to pricing as a means to reduce the cost of prescription drugs in the United States. In May 2018, the government published a document entitled *American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs*. Among a wide range of proposals, the blueprint identified “considering further use of value-based purchasing in federal programs, including indication-based pricing and long-term financing” as one of the opportunities for pricing reform. The document also mentioned the possibility of “removing government impediments to value-based purchasing by private payers” (Department of Health and Human Services, 2018).

The Trump blueprint poses the following questions with regard to value-based purchasing of prescription drugs:

- “What benefits would accrue to Medicare and Medicaid beneficiaries by allowing manufacturers to exclude from statutory price reporting programs discounts, rebates, or price guarantees included in value-based arrangements?”
- How would excluding these

approaches from Average Manufacturer Price (AMP) and Best Price (BP) calculations impact the Medicaid Drug Rebate program and supplemental rebate revenue?

- How would these exclusions affect Average Sales Price (ASP) and 340B Ceiling Prices?
- What regulatory changes would Medicaid Managed Care organizations find helpful in negotiating VBP supplemental rebates with manufacturers?
- How would these changes affect Medicare or the 340B program?
- Are there particular sections of the Social Security Act (e.g., the anti-kickback statute), or other statutes and regulations that can be revised to assist with manufacturers’ and states’ adoption of value-based arrangements?”

Although the government has yet to answer these questions, the mere fact that it has posed them reflects a broadly positive attitude toward the concept of value-based contracting. Moreover, in June 2018, FDA Commissioner Scott Gottlieb disclosed that “we have heard from some manufacturers that, in the absence of clear guidance from the agency, they were inhibited from sharing certain economic and other information and, potentially, even from generating additional rigorous data for payors to evaluate in determining the value of a product to their health plans and their beneficiaries, and then to tie value-based contracts to these measures.” However, new FDA guidance includes recommendations that are, according to Gottlieb, “designed to enable truthful, non-misleading and appropriate company communications with insurers across a product’s lifecycle.” In particular, the FDA has clarified that VBCs are exempt from its price reporting requirements (Food and Drug Administration, 2018).

Commissioner Gottlieb also believes that the Trump blueprint advances the principle that “prices should be able to adjust to reflect the value in how medicines are prescribed and the outcomes they deliver, to control rising spending and reduce the burden of drug costs for consumers. To achieve these goals, selling models should be able to tie the price of drugs more closely to the usefulness of the clinical setting in which they are prescribed. We want to encourage competitive contracting based on measures of value that matter most to purchasers and patients, not get in the way of these competitive negotiations” (Food and Drug Administration, 2018).

A regulatory environment that is more explicitly conducive to value-based contracting should give all stakeholders greater incentive to pursue such agreements in the future.



CHALLENGES TO NEGOTIATING OUTCOMES-BASED MEAs

The negotiation of outcomes-based MEAs pose considerable challenges for public and private payers alike. Moreover, these barriers prove largely universal to the jurisdictions described within the previous sections.

Cost - The resources and time required to establish and execute an outcomes-based MEA can prove administratively burdensome. As a result, some payers question the utility of innovative agreements in relieving budgetary pressures to the extent that was initially believed. Furthermore, in interviews with payers, PBMs, and economic experts in the US, researchers noted mention of cases where rebates received for unmet outcomes ultimately failed to offset the costs incurred of implementing the agreement itself (Seeley & Kesselheim, 2017). In a 2015 study

conducted by Garrison and colleagues, 33% and 27% of key reimbursement stakeholder respondents ranked “significant additional effort” as the first or second most critical barrier to using OBAs, respectively (Garrison et al., 2015).

Data infrastructure - Countries in which flexible and comprehensive infrastructures are available to collect data, especially when present in a single-payer or closed-setting system, are most likely to be successful in negotiating outcomes-based MEAs. Conversely, countries with limited or inappropriate infrastructure in place are at a disadvantage in capturing outcomes at the individual patient level and/or in the long-term. Similarly, jurisdictions such as Canada, experience added difficulty in negotiating

collectively because provincial/territorial payers operate different data systems. Respondents in the aforementioned Garrison study, ranked “inadequate data infrastructure” as a major barrier in negotiating OBAs (2015).

Performance metrics selection - Selection and the ability to capture the most appropriate performance metric of a

product’s effectiveness for inclusion in an outcomes-based scheme can also prove difficult. Specifically, the limitations within many jurisdictions’ systems often results in high-quality patient health outcomes being inaccessible. Instead, decision makers may be forced to rely on more easily accessed claims records, which can only reflect less-desirable surrogate markers rather than outcomes.



KEY QUESTIONS TO ADDRESS WHEN CONSIDERING AN OUTCOMES-BASED MEA

Before undertaking an outcomes-based MEA, payers and manufacturers need to clearly understand their objectives for pursuing such a deal. They also need to ensure that the other party's expectations are broadly compatible with their own. In laying the groundwork for an OBA, payers and manufacturers need to address the following questions:

Will further research address uncertainty regarding a drug's clinical or economic benefits?

For instance, if marketing authorization was granted based on improvements in

intermediate or surrogate endpoints, would further research help to determine whether the drug improves survival and/or quality of life? In oncology, for example, clinical trials are often terminated when it is evident that a drug offers superiority in delaying disease progression, but real-world data may provide valuable insights with regard to the reliability of the delay to disease progression.

Are the chosen outcomes appropriate and measurable?

Outcomes-based MEAs typically seek to measure the relative clinical effectiveness of a new drug relative to the current standard of

care, or in specific patient sub-populations. If the agreement is based on patient response, it must be relatively simple to measure this response. A decision-analytic model can help to identify the key determinants of costs and benefits, which ultimately govern a drug's cost-effectiveness.

Are the timelines realistic and understood by all parties?

Two timelines must be considered: the time needed to initiate an agreement and the time required to conduct research. It may take considerable time to enlist the support of the wide range of participants involved in some schemes—the payer, the manufacturer, medical associations, hospitals, individual healthcare professionals and patients. In particular, the challenges of patient recruitment can lead to substantial delays. The time allowed for research needs to be long enough to gather the required data, but not so long that the assumptions that underpin the research are superseded. For example, the election of a new government could lead to a shift in policy, or the standard of care may change as a consequence of the launch of new technologies or procedures. The accepted wisdom is that the follow-up period should generally not exceed three years, though a longer timeline may be needed in the case of therapies that offer the promise of a cure in the long term.

Are the costs acceptable?

The costs of a scheme to a healthcare system must be in proportion to the potential benefits.

Is it clear who will fund the research?

Although manufacturers will often be expected to bear the cost of data collection, national or regional government departments or agencies may provide funding in some cases.

Who will collect and analyze the data?

Much will depend on the nature and setting of the study. Will the data come from a randomized clinical trial, a pragmatic clinical trial, an observational study, a registry, claims data, laboratory and pharmacy data, patient support program data, or hospital and electronic medical records? What safeguards need to be in place to protect patient confidentiality? Can data collected through patient support programs be used as the basis of these agreements?

How will research findings impact pricing and reimbursement?

If possible, the terms of the agreement should clearly specify targets and the procedure for potentially altering a drug's price or reimbursement status. Clarity in this regard is likely to be greater in healthcare systems that have a specified cost-effectiveness threshold for reimbursement than in systems that rely on less-explicit methods of negotiation.



OUTLOOK AND IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY

Given the commercial sensitivities associated with outcomes-based MEAs, it is not surprising that the existence of some of these deals—let alone the precise terms of the agreements—is not publicly known. Data on the results of MEAs are even more elusive. However, government-administered programs in some countries do provide information on the impact of these initiatives as a whole, though no insights into individual schemes. As discussed previously, official data from France, Italy, the Netherlands, and Sweden show that financially based MEAs can deliver significant—and growing—savings for healthcare systems. These results will encourage governments to continue, and expand, such initiatives.

On the other hand, the aforementioned data from France and Italy suggest that savings from OBAs may be much more modest, perhaps raising questions about whether they are always worth the considerable effort they entail. The Dutch government took the decision in 2012 to move away from outcomes-based MEAs to financial arrangements, and the NHS in England and the pCPA in Canada have similarly favored simple discounts in recent years. However, both NHS England and the pCPA now appears more receptive to OBAs for certain medicines, and payers in other countries have expressed interest in exploring the potential of such deals. For example, health insurance funds in Germany are willing to consider pay-for-performance contracts as an option for high-

priced new drugs, the national government and regional administrations in Spain are negotiating new risk-sharing deals, and the Swedish government has identified a role for MEAs in overcoming the uncertainty associated with some new medicines at launch.

“In the years ahead, payers and manufacturers will need to tailor MEAs to the growing pipeline of advanced therapy medicinal products—medicines based on genes, tissues or cells that are also referred to as regenerative curative therapies.”

Significantly, the US government sees VBCs as a way to reduce the cost of new prescription drugs. At present, these deals are all in the private sector, but in August 2017, CMS announced plans for an outcomes-based contract with Novartis for Kymriah® (tisagenlecleucel), a revolutionary new chimeric antigen receptor T-cell (CAR-T) therapy for B-cell acute lymphoblastic leukemia with a list price of \$475,000. CMS subsequently canceled this plan in the face of criticism of the way it conducted its negotiations with Novartis, but the agency remains committed to “moving to value-based payment for high-cost drugs and therapies” (Karlin-Smith & Pittman, 2018; Sagonowsky, 2018).

For managed entry strategies to be successful for all stakeholders, payers and pharmaceutical companies need to understand—and agree—which types of deals are suitable for which drugs. Broadly speaking:

- **financially-based MEAs** are relatively simple to administer and can be useful for drugs that are expected to have a significant budget impact and a potentially unpredictable and

- growing patient population;
- **patient-level outcomes-based MEAs** can be used to reduce payers’ risk in reimbursing a drug by ensuring that they have to pay only for patients who meet specified outcome targets; and
- **population-level outcomes-based MEAs** can be used as the basis for CED to overcome uncertainty surrounding a drug at launch.

CED is likely to become much more important in the future as growing numbers of drugs qualify for accelerated regulatory approval through mechanisms such as adaptive pathways in Europe, regulatory and HTA alignment of reviews in Canada, and breakthrough therapy status in the United States. Faster marketing authorization benefits patients by giving them earlier access to promising new therapies, but it may also leave more questions unanswered at the time of launch. MEAs can play a crucial role in overcoming such uncertainty. However, manufacturers must be prepared for the possibility that disappointing results from postmarketing research could lead to price cuts and/or less-favorable reimbursement terms.

Increasing use of outcomes-based MEAs could present a further significant challenge, namely, insufficient capacity to keep up with demand. Healthcare professionals are often already under considerable pressure and may struggle to find the time needed to perform additional administrative tasks. The healthcare infrastructure may also need to be improved to cope with an expansion of MEAs. The introduction of electronic medical records in many countries would likely be of considerable help in compiling the necessary data. The burgeoning use and sophistication of patient support programs for specialty drugs may also provide a cost-effective means for data collection. Governments might also consider following Italy’s example in establishing a comprehensive network of

online registries to support MEAs.

Pharmaceutical companies need to prepare for the increasing role that digital health technology will play in their businesses, including MEAs. Some of the most promising opportunities are likely to come from the intersection of mHealth—the use of mobile and wireless technologies to support the realization of health objectives—and big data. New devices and apps will give life sciences companies, payers, healthcare providers and patients unprecedented access to data on patients' health status. The boundaries between drugs, devices and procedures are likely to become increasingly blurred.

Some manufacturers are already seeking to capitalize on the opportunities presented by digital health technology. For example, Joe Jimenez, the former CEO of Novartis, sees a role for so-called “beyond-the-pill” strategies in “creating value by embedding products into a holistic offering with the aim to improve patient outcomes and provide tangible competitive advantages” (Sagonowsky, 2018). Clemens Kaiser, the Head of Sanofi in Germany, sees a need to “separate ourselves from conventional clinical endpoints. In the future, it will be all about outcomes, that is, what really helps the patient. To that end, apps and smartphones are very important—as information databases for patients, who participate in their therapy. And naturally as a bridge between the patient and a system that says: ‘The treatment worked, and success will now be rewarded’” (Woratschka, 2016).

In the years ahead, payers and manufacturers will need to tailor MEAs to the growing pipeline of advanced therapy medicinal products—medicines based on genes, tissues or cells that are also referred to as regenerative curative therapies. These drugs—or drug/device combinations, in some cases—are expected to be far more expensive than established medicines.

An additional challenge in funding some of these products is that they may be dosed just once but have effects that potentially last for many years. At present, healthcare reimbursement systems that typically work on annual budgets are not designed for therapies that have enormous initial costs with benefits that extend over many years. MEAs will need to be adapted to accommodate this different funding model.

Pharmaceutical companies will also have to adjust to a growing range of partners for MEAs. Although many agreements will be negotiated at national level, in some countries, manufacturers may have to deal with local hospitals or regional administrations. In the future, companies may also have to negotiate MEAs with payers from two or more countries working together. As noted earlier, in July 2018, the Dutch and Belgian Ministries of Health announced a joint CED decision with regard to Biogen's Spinraza® (nusinersen). These two countries have taken the lead in a cross-border pricing and market access collaboration known as the BeNeLuxA Initiative, which now includes Luxembourg, Austria and Ireland. Across Europe, organizations from at least 29 countries participate in nine different cross-border market access collaborations of various kinds. In the future, some of these alliances may seek to negotiate international MEAs (Grubert, 2018).

Whoever is on the opposite side of the negotiating table, pharmaceutical companies will have to convince them that they (the manufacturers) are interested in a genuine collaboration. Although payers' and manufacturers' objectives will never align completely, both parties ultimately have a common interest: to ensure that patients have timely and affordable access to innovative medicines. MEAs can play a crucial role in achieving that goal.

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APPENDIX A - LIST OF ACRONYMS AND ABBREVIATIONS

AAR - Accelerated Access Review
 AIFA - Agenzia Italiana del Farmaco
 ANRS - Agence Nationale de Recherches sur le Sida
 CAA – Commercial access agreement
 CADTH - Canadian Agency for Drugs and Technologies in Health
 CED - Coverage with evidence development
 CEPs - Comité Économique des Produits de Santé
 CMS - Centers for Medicare & Medicaid Services
 CTC - Conditional treatment continuation
 CVZ - College voor Zorgverzekeringen
 DRD - Drug for Rare Disease
 EMA - European Medicines Agency
 EU - European Union
 FDA - Food and Drug Administration
 GBA - Gemeinsamer Bundesausschuss
 HTA - Health technology assessment
 ISPOR - International Society for Pharmacoeconomics and Outcomes Research
 MACRA - Medicare Access and Chip Reauthorization Act
 MEA - Managed entry agreement
 MOU- Memorandum of understanding
 MS - Multiple sclerosis

NHS - National Health Service
 NICE - National Institute for Health and Care Excellence
 OBA - Outcomes-based agreement
 OPRA - Outcomes-based pricing and reimbursement arrangement
 PAES - Post-authorization efficacy study
 PAS - Patient access scheme
 PASLU - Patient Access Scheme Liaison Unit
 PBRSA - Performance-based risk-sharing agreement
 PBAC - Pharmaceutical Benefits Advisory Committee
 PBS - Pharmaceutical Benefits Schedule
 pCPA - pan-Canadian Pharmaceutical Alliance
 PLA - Product listing agreement
 QALY - Quality-adjusted life year
 RCT - Randomized controlled trial
 RE - Relative effectiveness
 RWE – Real-world evidence
 SSN - Servizio Sanitario Nazionale
 TLV - Tandvårds- och Läkemedelsförmånsverket
 VBC - Value-based contract

APPENDIX B – FIGURES AND TABLES

Figure 1. Patient access schemes negotiated with NICE in England (Status as of October 8, 2018).
NICE Patient Access Schemes Liaison Unit

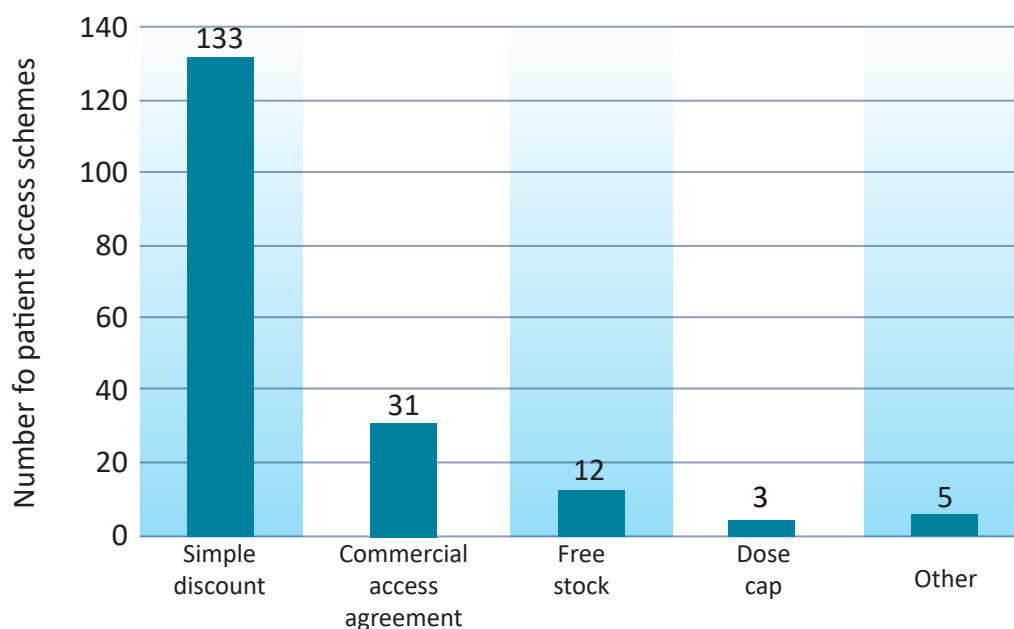


Figure 2: Savings to the French Healthcare System from Managed Entry

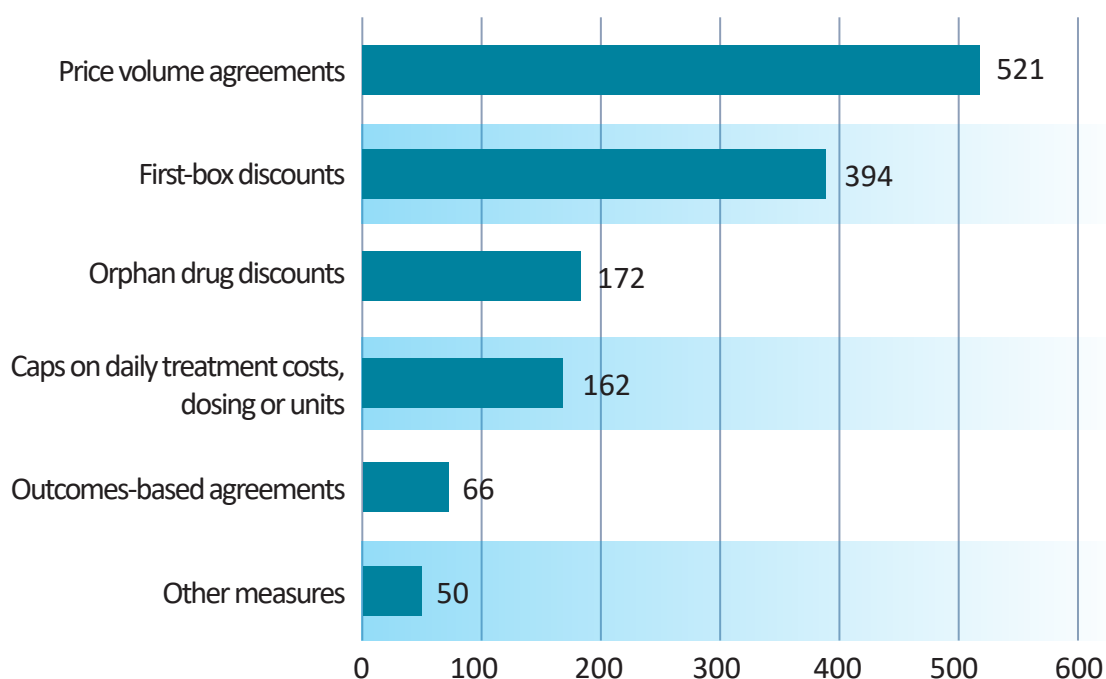


Table 1: Managed Entry Agreements in Germany, 2005-2008 (Schremser et al. 2017).

	Manufac- turer	Health Insur- ance Funds	Drug	Indication	Type of Agreement	Terms
2005	Eisai/Pfizer	AOK Bundes- verband, AOK Bayern	Aricept (done- pezil)	Dementia	Outcomes guarantee	N.A.
2007	Janssen-Cilag	AOK Rhein- land/Hamburg	Risperdal (risperidone)	Schizophrenia, severe behavioral disturbance	Price-volume agreement	N.A.
2007	Eli Lilly	Multiple	Zyprexa (olan- zapine)	Schizophrenia, moderate-to-se- vere manic episodes	Price-volume agreement	N.A.
2007	Novartis	AOK (7 state funds)	Lucentis (ran- ibizumab)	Age-related macular degener- ation	Budget cap	Total expenditure limited to €315 million per year
2008	Novartis	DAK	Sandimmun Optoral (cyclo- sporin)	Renal transplan- tation	Outcomes guarantee	Reimbursement of thera- py costs if donated organ is rejected within one year of surgery
			Myfortic (my- cophenolate mofetil)			
			Certican (ever- olimus)			
2007	Novartis	DAK, BEK	Aclasta (zole- dronate)	Osteoporosis	Outcomes guarantee	Reimbursement of ther- apy costs if patient expe- riences a fracture within one year of treatment
2007	Pfizer	Deutsche BKK	Sortis (atorvas- tatin)	Dyslipidemia	Price-volume agreement	N.A.
2007	Roche	Multiple	Avastin (beva- cizumab)	Metastatic breast cancer	Utilization cap	Partial or complete refund of drug costs if a specified total dose is exceeded
			Avastin (beva- cizumab)	Metastatic renal cell carcinoma		
2008	AstraZeneca	Deutsche BKK	Nexium Mups (esomeprazole)	Acid reflux	Integrated care program and outcomes guarantee	Integrated care program, rebates and coverage of unexpected additional treatment costs
2008	Wyeth Phar- ma	Taunus BKK and others	Enbrel (etaner- cept)	Rheumatoid arthritis	Outcomes guarantee	N.A.

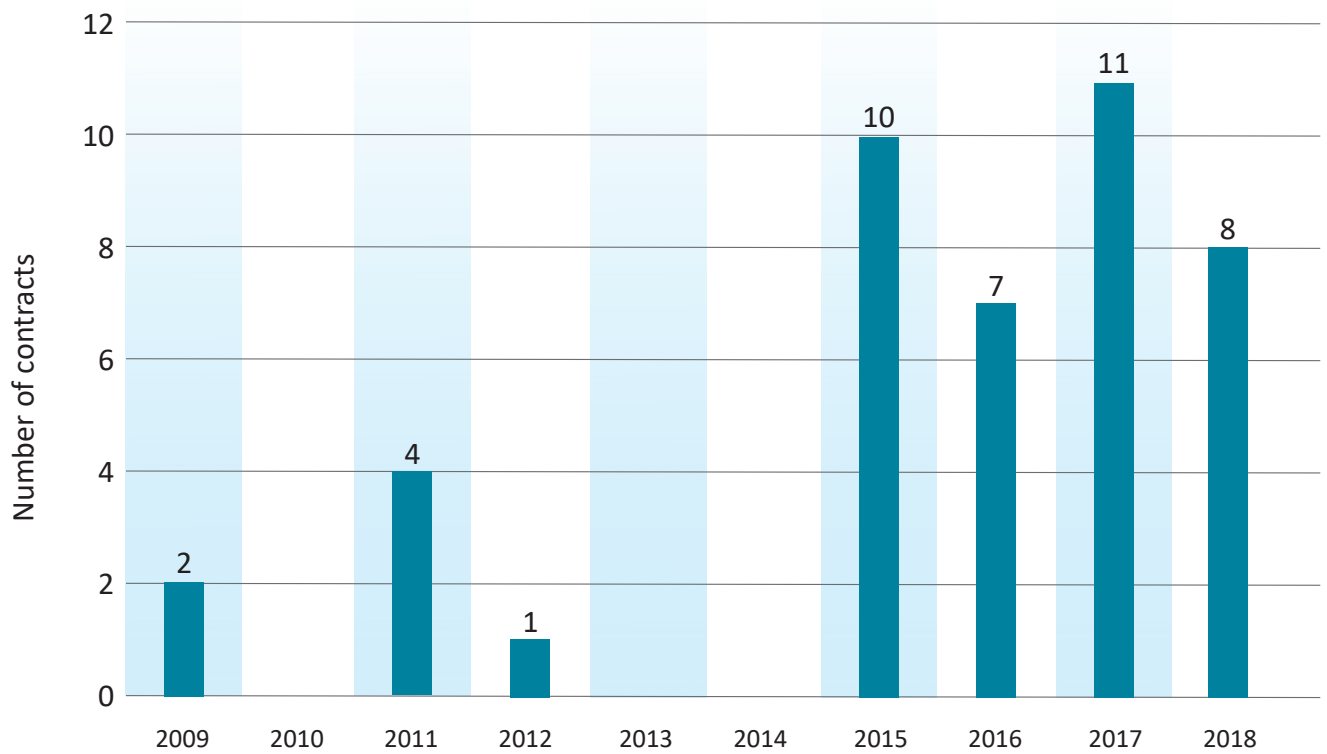
Table 2. Managed Entry Agreements in Australia (Robinson et al., 2018, Tuffaha & Scuffham, 2018, & Roughead).

Drug	Indication	Description of Agreement	Results of Agreement
Bosentan	Pulmonary hypertension	Establishment of a patient registry and a price reduction would be required if mortality rate was higher than in the submission.	Observed mortality was higher than in the trial and a comparator was later listed at a 15% lower price so bosentan price was also lowered to this level.
Cinacalcet	Secondary hyperparathyroidism & hypercalcaemia	Manufacturer was required to provide all on-going data on efficacy and cost-effectiveness. Data from the EVOLVE trial would determine the reimbursement of cinacalcet.	New evidence from the trial showed it was not cost-effective and a significant price reduction was needed to restore the cost-effectiveness.
Crizotinib	Non-small cell lung cancer	There was uncertainty surrounding survival gain so a rebate with interest was required should the drug not deliver claimed benefit (no option for price increase). Registry of first 50 patients to start therapy who were alive after 365 days of starting therapy.	Updated survival outcome was consistent with the initial evidence and the requirements were fulfilled. Crizotinib price remained at initial entry price.
Ipilimumab	Melanoma	Manufacturer was required to rebate the cost of any difference in performance between observed and predicted benefits of ipilimumab.	Not available.
Ivacaftor	Cystic fibrosis	Manufacturer was required to collect data in all patients receiving the drug and provide 100% rebates for patients who were assessed as not responding.	Not available.
Pembrolizumab	Melanoma	There was uncertainty surrounding the extent and duration of benefit and noted major issues with the economic model. Evidence from the ongoing KN-006 trial was required to inform on effectiveness and inform an updated economic model which could result in a revised price.	The updated survival results were similar to those initially presented, however, the PBAC considered that the manufacturer did not comply with all conditions of the agreement. The MEA was closed; the PBAC rejected a request to increase the price but did not recommend a change in the PBS listing.
Trametinib	Melanoma	There was uncertainty surrounding the magnitude of the effect. An MEA was employed to address the uncertainty surrounding the magnitude of effect while providing early access. The initial entry price was given but a rebate with interest was required if trametinib failed to deliver on the expected benefit.	Increased hazard ratios were reported which indicated that the clinical effect was less than the initial submission. Trametinib price was reduced and the PBAC recommended continuation of the listing along with the risk-sharing arrangement.

Table 3. Status of pCPA Negotiations as of October 31, 2018 (pan-Canadian Pharmaceutical Alliance).

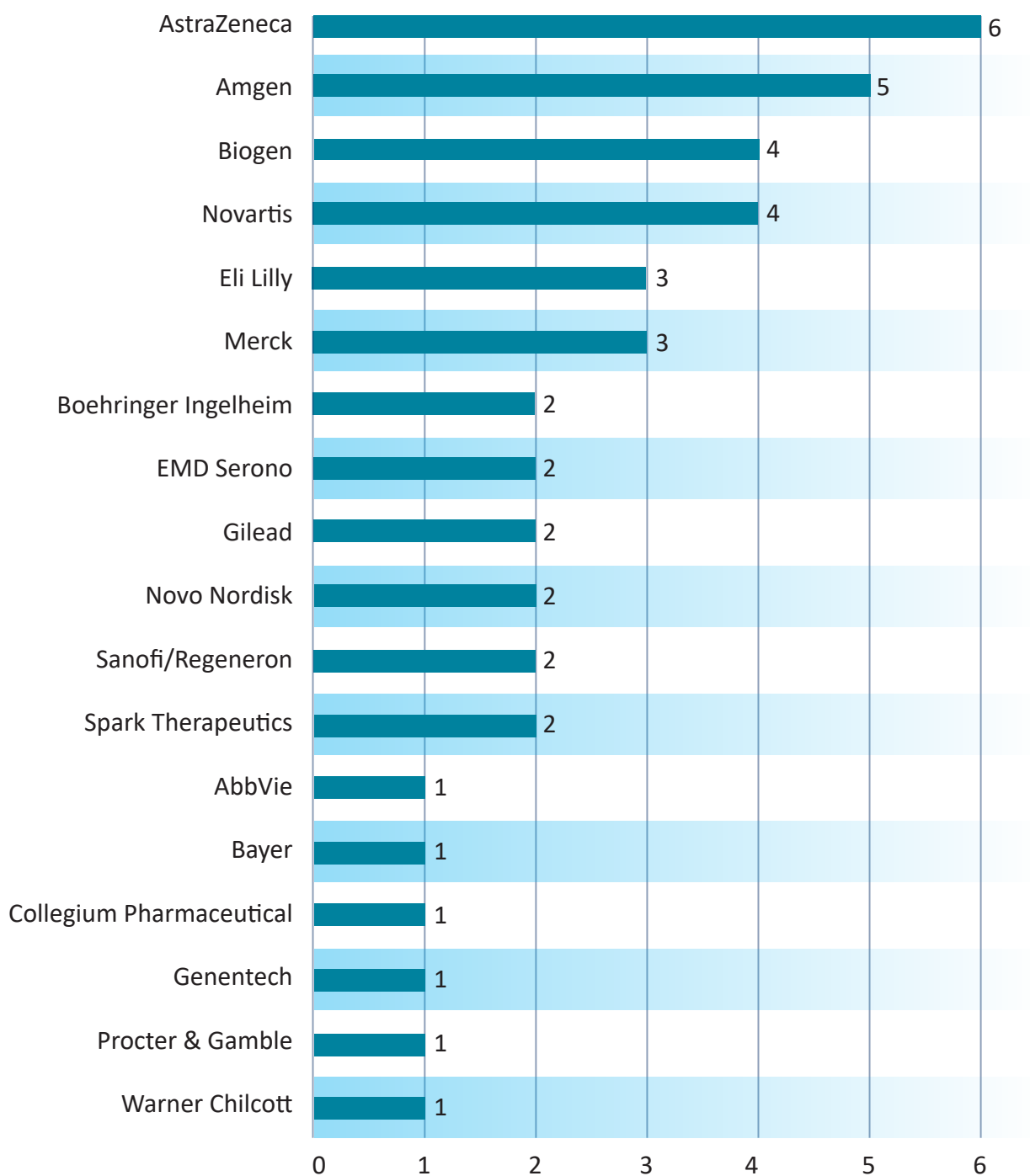
pCPA	Completed	Closed	Active	No pCPA Negotiation
Number of Negotiations	216	28	57	54

Figure 3: Number of Publicly Disclosed Value-Based Contracts in the United States, 2009 Through First Half of 2018 (Pharmaceutical Research and Manufacturers of America).



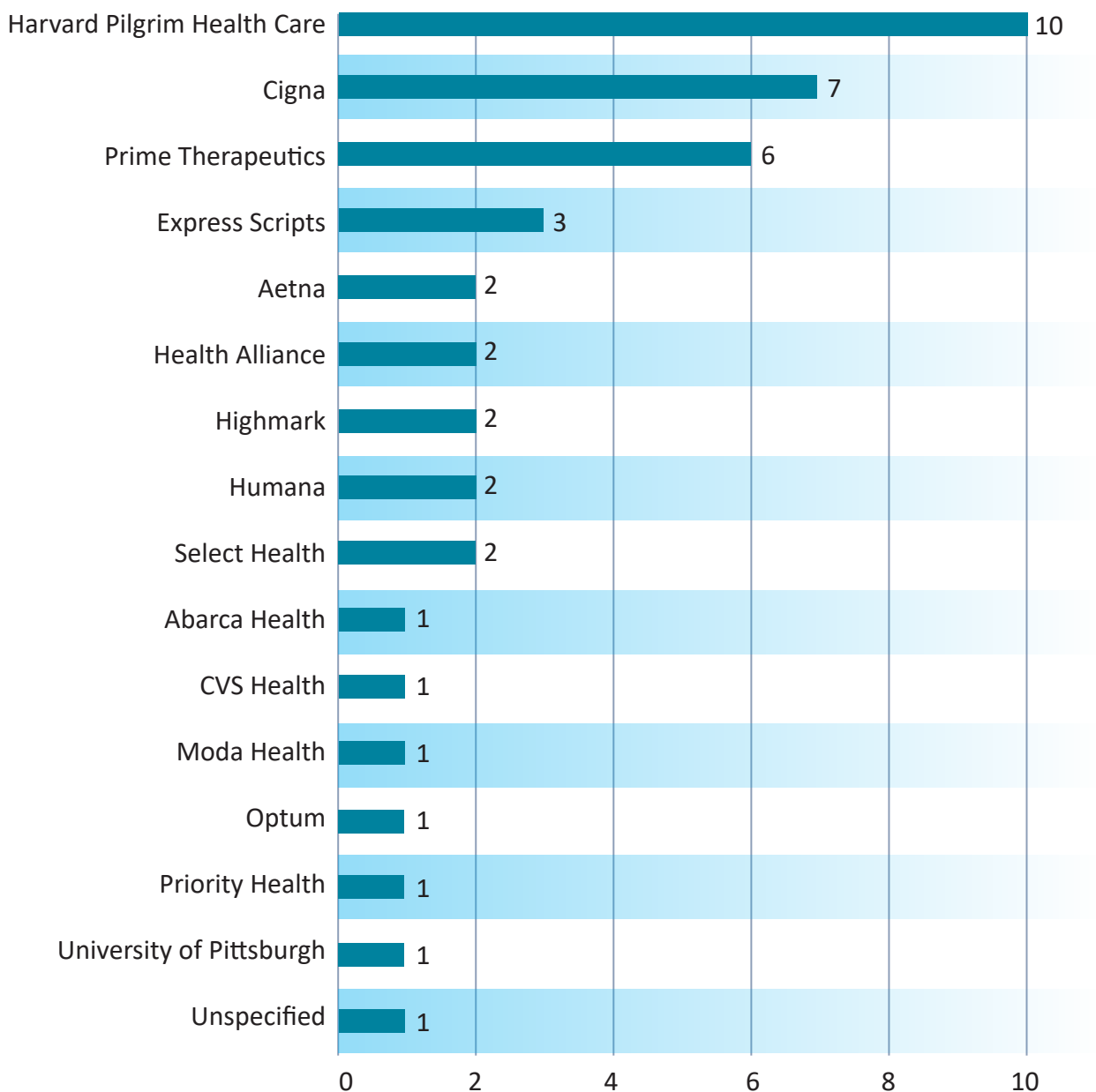
*Data related to the first six months of the year.

Figure 4: Pharmaceutical Companies That Have Negotiated Publicly Disclosed Value-Based Contracts in the United States, 2009 Through First Half of 2018 (Pharmaceutical Research and Manufacturers of America).



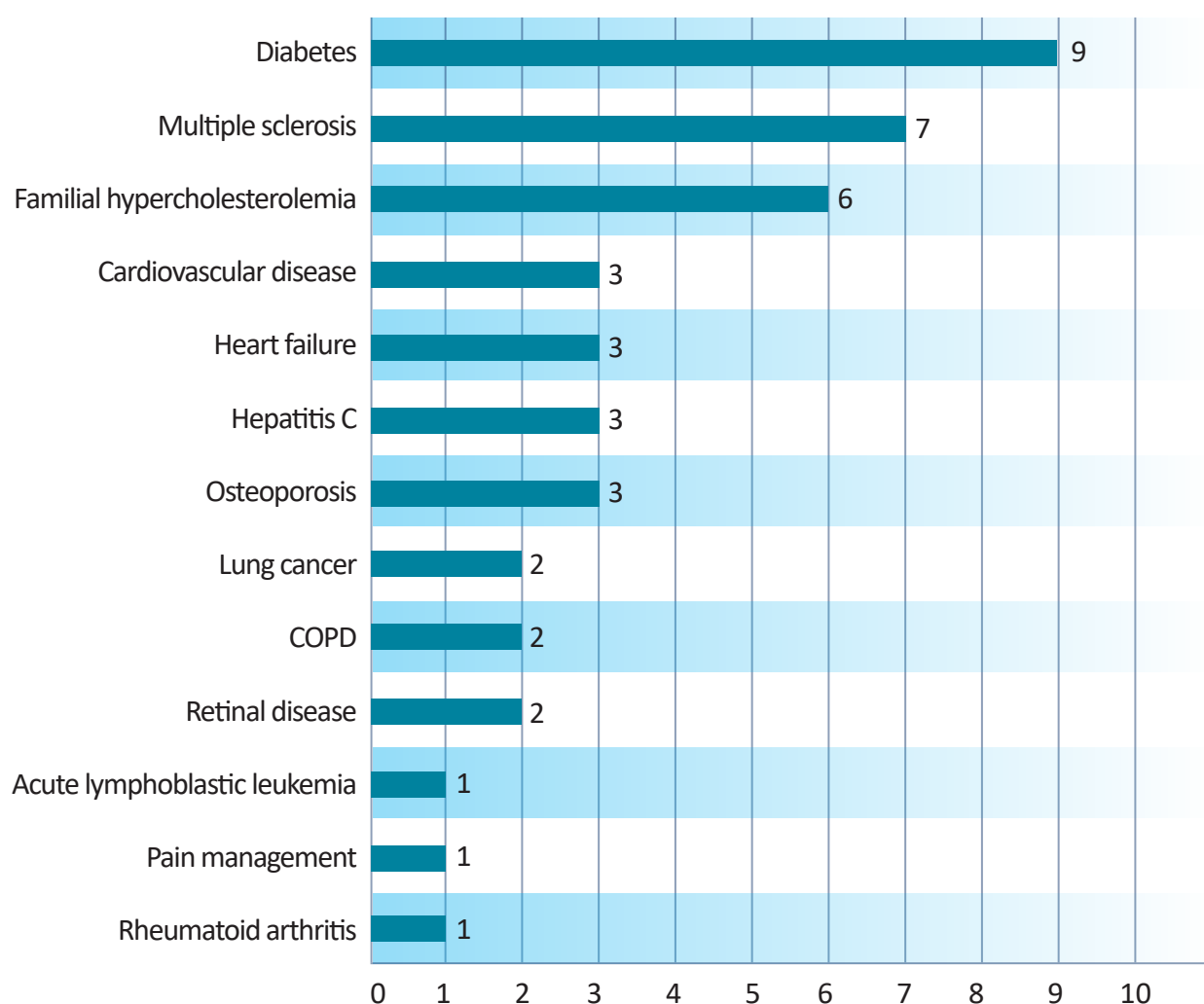
* Data related to the first six months of the year.

Figure 5: Healthcare Payers That Have Negotiated Publicly Disclosed Value-Based Contracts in the United States, 2009 Through First Half of 2018 (Pharmaceutical Research and Manufacturers of America).



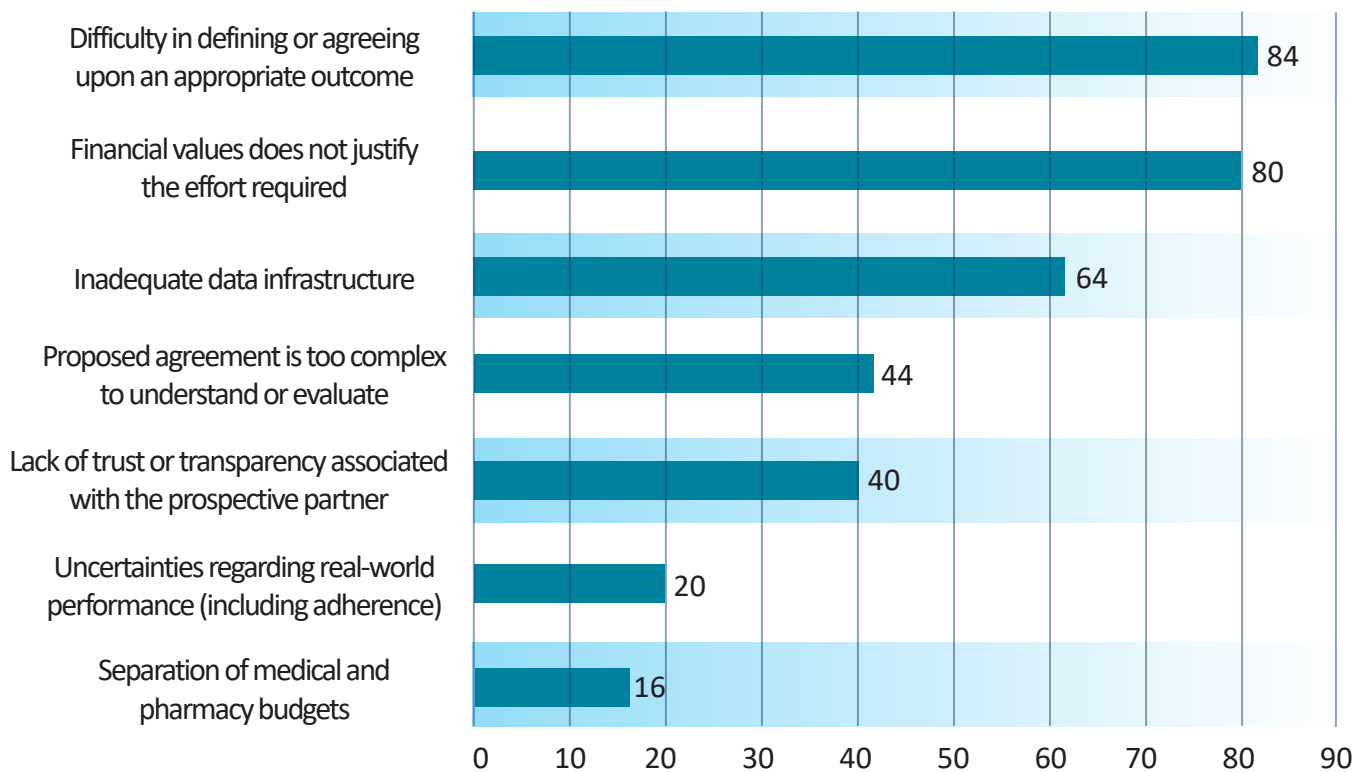
* Data related to the first six months of the year.

Figure 6: Disease Areas Covered by Publicly Disclosed Value-Based Contracts in the United States, 2009 Through First Half of 2018 (Pharmaceutical Research and Manufacturers of America).



* Data related to the first six months of the year.

Figure 7: US Healthcare Payers' Reasons for Rejecting Value-Based Contract Proposals (Buyse, Carter, & Sarnatoro, 2018).



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