Managed Entry Agreements: Lessons from European Payers

AT THE PHARMACCESS LEADERS FORUM ORGANISED BY NEXTLEVEL PHARMA IN LONDON IN APRIL 2018, BRIAN GODMAN, SENIOR RESEARCHER AT THE STOCKHOLM KAROLINSKA INSTITUTE, PROFESSOR AFFILIATED TO SEVERAL UNIVERSITIES AND FORMER MANAGER AT A HEALTHCARE CONSULTANCY, PRESENTED AN OVERVIEW OF MANAGED ENTRY AGREEMENTS (MEAS) FOR HIGH-COST DRUGS FROM THE VIEWPOINT OF EUROPEAN REIMBURSEMENT AGENCIES. AS A PRIVILEGED OBSERVER – ALSO THANKS TO HIS MULTIPLE COLLABORATIONS WITH HEALTH AUTHORITIES –, HE OFFERED VALUABLE INSIGHTS INTO WHAT PHARMACEUTICAL COMPANIES CAN DO TO CONCLUDE SUCCESSFUL MEAS. *FOLLOWING THE MEETING, HE SPOKE TO MARIE-FRANCE COURRIOL OF PPR.*

CURRENT CHALLENGES

Godman presented the position of European payers on managed entry agreements (MEAs) since, in addition to Canada and the US, "most experiences of MEAs are in Europe". From these payers' perspective, the crucial issue today is maintaining free universal healthcare access. MEAs offer an option to meet this objective (see *PPR* January 2014, pp16-19), taking into account the multiple challenges that reimbursement agencies must come to terms with: "unmet medical needs, rising patient expectations, combined with the need to use financial resources as best [they] can", he advised.

Reminding the audience that "healthcare costs represent a large portion of gross domestic product (GDP) (*ie* 10-15% on average across Europe, with the highest rates in Western European countries)", Godman highlighted the fact that "pharmaceuticals are a major burden, and therefore a 'major focus' for payers since they account for a big portion of healthcare costs". In 2012, pharmaceutical spending represented 12% of total healthcare expenditure in the UK, and 19% in Italy and Spain, for example.

"That trend will intensify, notably in Europe where now €20,000 (US$23,600) a month for a new treatment is considered cheap. As an increasing number of biological medicines are coming through, prices go up, putting real pressure on payers. The focus on medicines will also continue because non-communicable diseases are on the rise in Europe". This is exemplified by statins in Scotland, he remarked, where "our volume has jumped fourfold in the last 10 years. Other factors putting pressure on the medicines budget are an ageing population, and rising obesity rates. So how can we manage that as we go forward?" he asked.

EUROPEAN OVERVIEW

At the European level, a series of actions are being taken: "Firstly, health authorities are improving in their management of new medicines entry. Previously, health services were reactive rather than pro-active with pharmaceutical companies (see *PPR* June 2012, pp168-171). Secondly, authorities are getting better at post-launch activities, as shown in Sweden, Catalonia, and Scotland – less so in England. After reimbursement has been granted, they check whether expectations have been met in practice". Godman concludes that this will lead to stricter pricing and reimbursement regulations, and to more market access agreements.

"Nowadays, only about 10% of new medicines are innovative (data for Austria and France); the majority are similar or with a marginal advantage. In the industry, however, every new cancer drug is a 'cure', every new 'orphan' drug is 'a magic bullet'. The trick now for companies is to declare that their new drug is for treating an orphan disease so they can charge another US$30,000 a month. That makes payers more cynical when looking at these agreements. Payers need to check what the true level of innovation is, whether you call the drugs 'orphan' or not, focusing on the substance rather than the hype. When looking for instance at patients' overall survival rates, often new drugs have a limited impact, while we are paying €10,000 euros a month per patient. That is very difficult to sustain", he commented.

"Under value-based pricing, why should we pay more than the current standard by 10 or 20 times, if the current standard is available as a low-cost generic like imatinib?", Godman asked. "Recent studies have shown that the cost of goods of certain cancer drugs can be as low as 1% of the selling price. This was observed in Poland for imatinib following generic availability. This knowledge gives payers leverage when negotiating with the industry. Some of the new products have an exorbitant price. Take the new Hepatitis C drugs, or cancer drugs in the US now averaging US$207,000 per life saved. There is increased prevalence of cancer across Europe, and finite budgets. A health authority must be able to get these new drugs through which are really innovative and pay for them, but also block or reduce the price of those which show little advantage".

Godman acknowledged the need of pharmaceutical companies to recoup costs to re-invest, "but the cost of R&D for an innovative cancer therapy is probably nearer US$100 million rather than the US$1 billion they claim it is.[1] Now that Lipitor (atorvastatin) is open to generic competition, the price has dropped by 99.5%. Because of this reduction – a game-changer –, payers in Scotland have upped the dose at 40mg for high-risk patients".

He added: "With my health authority colleagues across Europe, we started thinking about new models for the future, based on three pillars:

- pre-launch: doing horizon scanning to see what the key products are – particularly those addressing unmet needs, or raising concerns with safety or price; building registries
- peri-launch: based on available forecast, having negotiations on pricing and reimbursement, and appraising MEAs
- post-launch: following up, checking registries, quality indicators, and monitoring prescribing, *etc*".

Godman emphasized a critical point: "in most European countries, following outcomes up in patients is very difficult in practice (see *PPR* August 2017, pp224-227). Germany, Austria, France are for example countries with that issue. By contrast, Scotland has some comprehensive, interlinked databases. Catalonia has good IT systems, and has been successful with the monitoring of gefitinib.

"The best data is found in Scandinavian countries, as every individual is given a single number at birth used for driving licences, as social insurance number, and health number; so patients can be tracked well through the system". In that respect, Godman mentioned his collaboration with the Stockholm county council [entity responsible for the day-to-day funding and administration of the health system in the Stockholm area (see *PPR* January 2017, p150)], which works from 'pre-birth' of medicines 2 to 3 years before EMA approval until disinvestment. The early awareness and alert (EAA) activities ensure that councils plan

on the long term, and that the Swedish healthcare system is ready for the introduction of new medicines.

“MEAs are used to facilitate funding and reimbursement through Europe in a situation with many uncertainties, where the pharmaceutical industry is wanting to charge a high price for new medicines, and payers must work within finite budget limits. Most clinical trials are done in perfect patients or as perfectly as possible – that is, very differently from real life. But we know a lot of cancers are not treated as well as they could, and many other diseases are still not treated either. How can we put all this together to have good MEAs?”, he asked.

“Outcome-based and financial-based schemes can be found across Europe, and most will fit into the latter category. Financial-based agreements involve for instance payback, rebates, price caps or supply of free drugs (see *PPR* December 2017, p355).” He nevertheless recognised that there can be some overlap between the two types of agreements.

“Globally we actually observe a decline in outcome-based schemes, a trend which will continue unless we can solve the problem of how to capture patient data as part of routine clinical care. The most challenging scheme is found in Italy where every single new biological drug has a patient access scheme. This implies maintaining a registry for every single cancer or biological medicine, and filling in each single form – which is a nightmare for clinicians (see *PPR* January 2018, pp10-14). They must do it because hospitals only get reimbursed the money for the drug if they fill in the forms. Instead, what you need is just one registry you can interrogate: this is being done in Sweden, and in Scotland we can link databases together. So, unsurprisingly, most schemes across Europe are price-volume and discount-based schemes, just because of the difficulties involved.

“Most schemes rely on confidential discounts. The National Institute for Health and Care Excellence (NICE) has been again recently advocating more discounts via patient access schemes. Basically, if NICE gets a discount, it can easily authorise the treatment within four weeks through the Patient Access Scheme Liaison Unit (PASLU) (see *PPR* January 2012, pp4-6). For more complicated agreements (*eg* including dose caps), it would take much longer. NICE has entered into 140 patient access arrangements with companies. The Scottish Medicine Consortium (SMC) has the same approach, approving 80-90% of medicines, since it can get some ‘decent’ prices through patient access schemes (see *PPR* October 2017, pp298-301). But if they approve 90% of medicines, I would consider NICE and SMC to be more of a pricing agency, and no longer a Health and Technology Assessment (HTA) agency”.

Godman then moved on to MEAs in Central and Eastern Europe, judging that they are given little exposure compared with Western European countries (see Table 1). “Poland led the process in 2012. Most of the MEAs then were price-volume discount schemes, mostly regarding oncology drugs, unsurprisingly due to their high promises”. Remarkably, “risk-sharing arrangements have first been put into law by Poland in May 2011, making it the first of all European countries to define such agreements legally”.

PROS AND CONS

Godman then reviewed the pluses and minuses of financial-based and outcomes-based agreements.

Financial-based Schemes

“Financial-based schemes enhance the possibility of reimbursement of drugs which otherwise would not have been reimbursed, and transfer some of the costs to the pharmaceutical

company rather than to the payer. This is essential where concerns of excessive utilisation exist. If a manufacturer has a finite price volume agreement, they want to make sure that physicians are not overprescribing because that costs them money (see *PPR* January 2016, p22). A company also needs to build in the possibility of dosage creep into any price volume agreement. As mentioned for atorvastatin, while the initial dose was 10-20mg, now the advocated dose for high risk patients in Scotland is 80mg. The same occurred with simvastatin, dosed at 10 and 20mg initially, and now recommended at 40 and 80mg.

"Another concern, particularly with dose capping scheme, is that of patient confidentiality. Issues arose with Lucentis (ranibizumab) around how many injections the patient should receive. But who administers that?"

"Chasing companies if the payer wants discounts and rebates can be a headache. Now, pharmaceutical companies may help on early access schemes, as they can be complex to administer. Having a more IT approach may help with that".

As also discussed by Godman, co-payments are an issue "especially in Central/Eastern Europe where you have 30 to 70% level co-payments – less so in Western European countries. That is a real disaster for the biological medicines. If a co-payment is based on the list price rather than on the discounted price, it is a huge burden for the patient. Looking at the management of inflammatory bowel disease in Serbia, we found very little use of the biologicals (including anti-tumour necrosis factor [TNF] alpha) because patients just could not afford them. This is something to be careful about when hearing claims of 'giving greater access to medicines'".

Outcomes-based Schemes

In Godman's view, an advantage of such schemes is that patient population can be targeted and the agreements can be monitored in practice – provided there is good patient-level data available.

He nonetheless raised other concerns: "What is the objective of these schemes? Is that fully transparent? Who will end up funding the databases and registries? Who pays for putting up a new IT system: is that the health authority, is that the pharma company? If there is a paper-based scheme, like in the Netherlands, do you ask a busy commission to fill in forms, as we did in the UK in 2002 with multiple sclerosis drugs [under a risk-sharing scheme whose monitoring reportedly cost £1 million/year to the Department of Health and the four drug companies that were funding it]? Basically, the government was under pressure to accept these new interferons, so they requested the busy neurologists to fill in all these complex forms; this really brought down the number of patients".

Godman added to that "the length of follow up, particularly if it's not decided at the outset. In fact, multiple schemes were started, where it appeared they were not that beneficial". When an authority decides to extend a scheme when the first set of data is inconclusive, it can last an excessive amount of time, at the agreed price rather than at the value price, "which is – or should be – frightening for payers".

Lastly, Godman addressed media pressure (see also *PPR* January 2014, pp16-19). "Let me take the example of the Netherlands and the enzyme replacement therapy with alglucosidase alfa in Pompe disease (see *PPR* August 2016, pp230-231). From a payer's point view, it was known that it did not really work. In 2012, the Dutch Health Care Insurance Board (*College voor Zorgverzekeringen* [CVZ]) passed on a negative decision to the government. The draft advice was leaked to the press, as a result triggering all this debate of 'how much is a life

worth?'. The Dutch government, following pressure from the press, ignored the CVZ's advice and funded the medicine, up to €15 million per quality-adjusted life year (QALY) for the non-classic form of Pompe disease. In a publicly-funded healthcare system, in my opinion, this is immoral.[2] Of course, nobody wants to be a disinvestment group, everybody wants to be an investment group. That is the problem health authorities have: how do they disinvest in a product if they find the price is not worth it in practice? This is an issue with so many schemes as well", he noted.

GUIDANCE FOR PHARMA

Godman believes that MEAs "are here to stay and will accelerate. So what pharmaceutical companies can do is help to ensure that payers have more accurate data, in order to move forward in a solid fashion.

"Companies could be more transparent on the true costs of goods", he added. "Payers can also look together with companies at alternative funding models, *eg* transparent value framework for orphan diseases; that could be one way of going forward – talking about the levels of uncertainty".

One piece of advice for manufacturers willing to enter into talks with health authorities is to start early, "three years before the likely European Medicines Agency (EMA) approval (see Figure 1); and then to go on with pricing".

Furthermore, for companies to get into discussions with payers beyond the question of savings, one suggestion from Godman is for manufacturers to provide "markers which can help agencies identify patients in whom the drug might be particularly effective. When reimbursement bodies have a strict budget, and 10 patients they can fund, they want to fund all 10 where it is going to work". He related the example of Velcade (bortezomib) in the UK: "NICE rejected it initially (see *PPR* January 2014, p24), because of its high price, then Janssen-Cilag mentioned that they had a scheme which enabled them to target patients for whom the treatment would be beneficial. If Janssen-Cilag had proposed that initially, they may have obtained a high price.

"The same happened with AstraZeneca's lung cancer drug Iressa (gefitinib). Only afterwards did the company say that they had a relevant efficiency marker. The issue is that Iressa had been launched in Japan in 2002 with a high dose and caused fatal side effects [in over 600 patients] – the reason why it was taken off the market. If AstraZeneca had targeted those patients for whom the drug could work best, then their drug would probably have remained on the market and not be withdrawn to be later re-launched with markers. They might not have got as much money as they had expected, but they would have benefitted by remaining on the market. And probably in the long run they would have got greater returns".

Another winning argument for manufacturers would be to offer to help monitor patients: "you can get a reasonable price for that. Generally, if you propose value-based pricing and propose to target the patients for an innovative therapy or excellent therapy, then you will be very successful. Or should be successful". Godman then concluded: "Payers want to do more worthwhile MEAs because they want more new drugs that work to address continuing unmet need".

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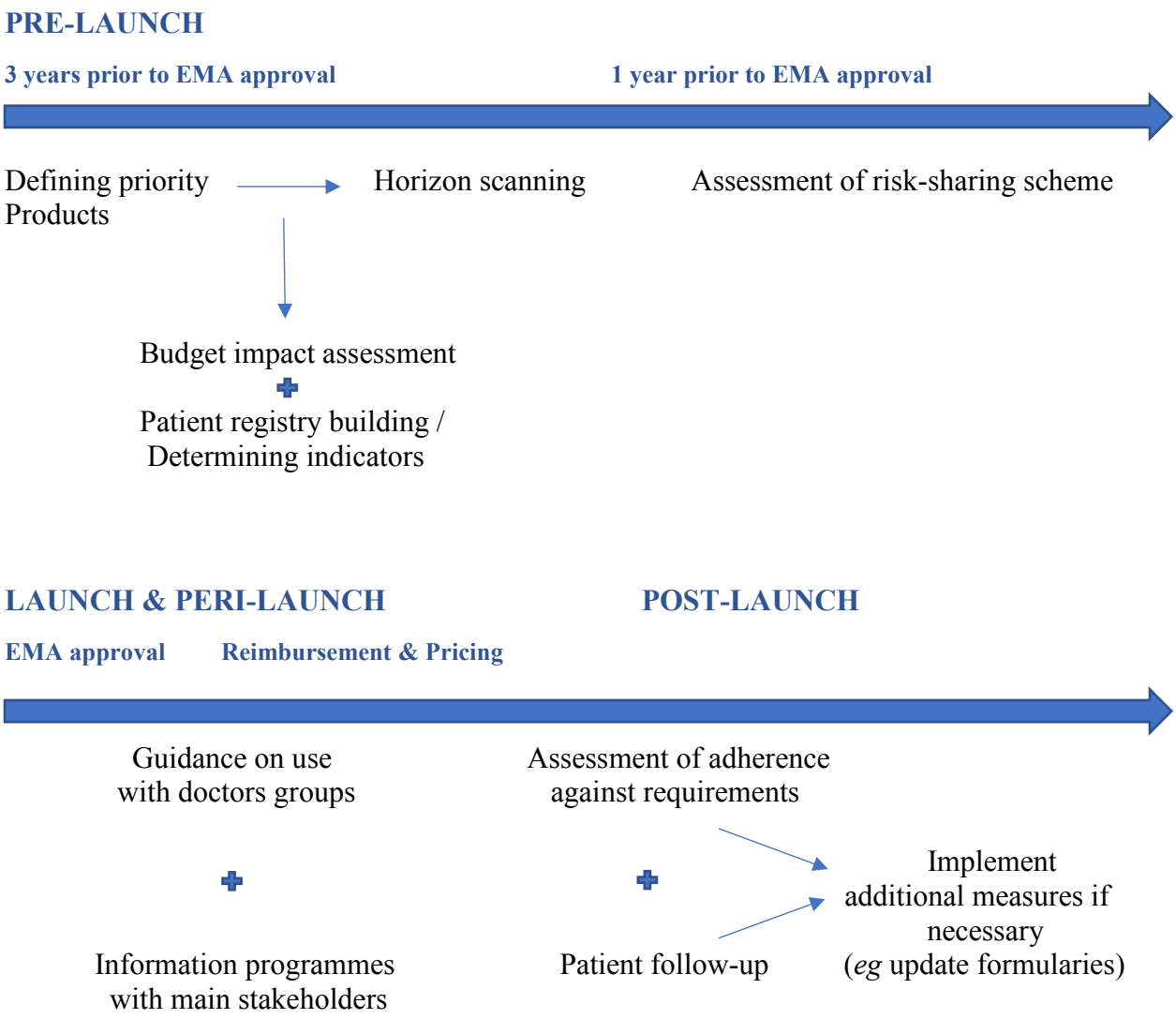
Table 1: MEAs in Central and Eastern Europe (as of February 2017)

Country	**Date of First MEA**
Albania	no MEA
Bosnia and Herzegovina	unknown
Bulgaria	2015
Croatia	2009
Czech Republic	2013
Estonia	2014
Kosovo	no MEA
Latvia	2013
Lithuania	2008
Hungary	2006
Poland	2012
Romania	2015
Russia	no MEA
Serbia	2016
Slovakia	no MEA
Slovenia	2005

Note: Other Central and Eastern European countries were either not part of the survey or information was unavailable.

Source: Brian Godman, adapted from [3].

Figure 1: Timescale for Implementation of Outcomes-based Schemes



Source: Brian Godman, adapted from [2], [4] and [5].