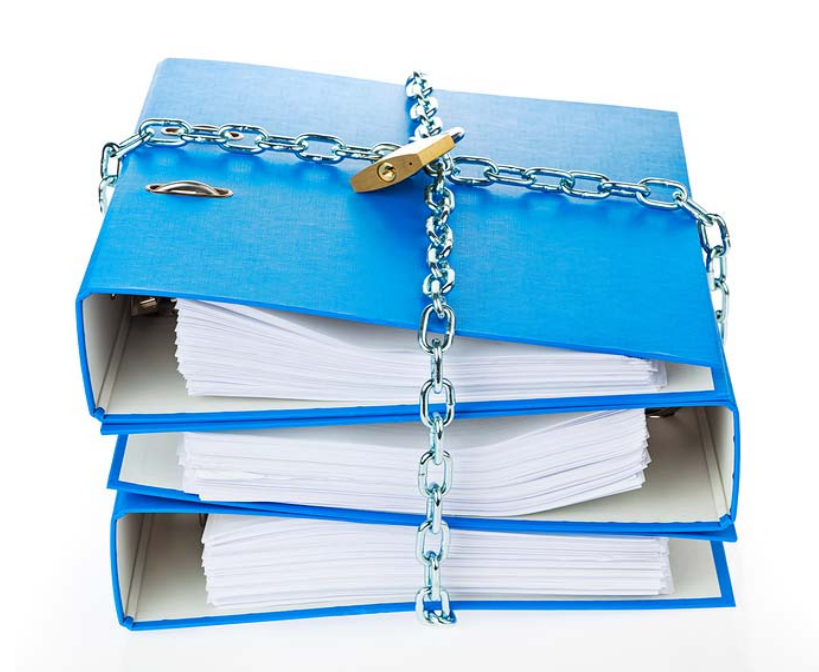


# HOW TO IMPROVE THE BELGIAN PROCESS FOR MANAGED ENTRY AGREEMENTS? AN ANALYSIS OF THE BELGIAN AND INTERNATIONAL EXPERIENCE





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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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- **Finally, this report has been approved by common assent by the Executive Board.**
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## LIST OF ABBREVIATIONS

<b>ABBREVIATION</b>	<b>DEFINITION</b>
AIFA	Agenzia Italiana del Farmaco
CAHT	Clause de chiffre d'affaires annuel hors taxe
CATT-CAIT	Commission for Advice in case of Temporary Reimbursement of a drug – Commissie voor advies in geval van tijdelijke tegemoetkoming voor het gebruik van een geneesmiddel – Commission d'avis en cas d'intervention temporaire dans l'usage d'un médicament
CED	coverage with evidence development
CEPS	Comité économique des produits de santé
CHMP	Committee for Medicinal Products for Human Use
COI	Conflicts of interest
CTG – CRM	Commission for the Reimbursement of Pharmaceuticals – Commissie Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments
EMA	European Medicines Agency
EMI-net	European Medicines Information Network
EU	European
FAGG – AFMPS	Federal Agency for Medicines and Health Products – Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – Agence fédérale des médicaments et des produits de santé
HAS	Haute Autorité de Santé
ICER	Incremental cost-effectiveness ratio
IMA – AIM	Intermutualistic agency
KCE	Belgian Health Care Knowledge Centre
LSE	London School of Economics
MEA	Managed entry agreements
MS	Multiple sclerosis



NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PFS-CPSP	Committee of Pricing for Pharmaceutical Specialties – Prijzencommissie voor de Farmaceutische Specialiteiten – Commission des Prix des Spécialités Pharmaceutiques
PPRS	Pharmaceutical Price Regulation Scheme
PVA	Price-volume agreement
QoL	Quality of life
RIZIV – INAMI	National Institute for Health and Disability Insurance – Rijksinstituut voor Ziekte en Invaliditeitsverzekering - Institut National d'Assurance Maladie-Invalidité.
VWS	Minister of Health, Wellbeing and Sports



## ■ SCIENTIFIC REPORT

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### How to use this document?

This Scientific Report is not intended to be read as a stand-alone document, but as a complement to the Short report of this study. It gives a detailed account of the methods and results of each of the scientific building blocks underpinning the messages rendered in the Short report.

An overview of the results including additional discussion elements as well as the conclusions and recommendations are to be found in the Short report.

The Short report is published as a separate document on our website. It can be accessed from the same referral page as the current document.

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## 1 INTRODUCTION

### 1.1 Background

Rapid access to new potentially beneficial pharmaceuticals may offer perspective to many patients. The challenge is, however, to have sufficient evidence on the intervention's added value versus other alternatives and to bridge the rising gap between unlimited requests for often very expensive innovative pharmaceuticals and limited public resources.

Available evidence on relative effectiveness and cost-effectiveness of innovative treatments is often insufficient at the time of licensing. Public health authorities and pharmaceutical companies have therefore looked for alternative funding mechanisms, i.e. managed entry agreements (MEA), to share the risks and uncertainties arising from public coverage of pharmaceuticals, whose (cost-)effectiveness is still unknown or for which the budget impact is expected to be very high, but for which early access for the patient is wanted. Rather than to wait for more solid evidence before making a definite reimbursement decisions, MEA should allow to grant early access to pharmaceutical products, while at the same time collecting the relevant data to assess (cost-) effectiveness, controlling the budget impact, monitoring the (rational) use in clinical practice, or generating real life data on effectiveness and use. These data should then allow to make a final reimbursement decision at the end of the MEA.

Confidential MEAs are increasingly also used just to negotiate a lower price for very expensive pharmaceutical products. It was considered beneficial for both the companies and the government. The confidential nature of the conventions is attractive to companies, because it implies that public prices are not reduced, which is important for them in an area where external reference pricing is used to set prices of pharmaceuticals (i.e. countries are looking at public prices in other countries to determine the price they are willing to pay).



In Belgium, these formal agreements are possible since 2010 and have the form of conventions concluded between the pharmaceutical companies and the Minister of Social Affairs and Public Health: the so called 'art. 81 (bis)' conventions. More details on the procedure to obtain such a convention is described in the chapter 3 of this report.

## 1.2 Study objectives and research questions

About 6 years after the introduction of the MEA procedure in Belgium, KCE was asked to assess the strengths and weaknesses of the MEA procedure and to identify the areas where there is room for improvement of the entire process leading to conventions, starting with the standard CTG-CRM procedure up to the end of the convention and the possible renewal.

The initial objective of this study was therefore to better understand the different types of MEAs, to assess their impact and to provide recommendations on how to improve the process. The following research questions were raised:

- What lessons can be learned from the European experience? Based on a review of the literature, the following subquestions were analyzed:
  - What is the potential impact of MEAs? What are their main strengths and weaknesses?
  - Which challenges needed to be overcome and what are the potential solutions?
- What lessons can be learned from the Belgian experience? Based on an evaluation of Belgian conventions, the following subquestions were analyzed:
  - Which kind of conventions were concluded in Belgium up to now and what are the possible practical problems with each type of convention in the Belgian context?
  - Which uncertainties and/or problems were addressed, how were they addressed and to what extent were these uncertainties and/or problems resolved?
  - Which conditions were imposed in the conventions and to what extent were these conditions respected?

- What were the results of the conventions already expired? Were the initial objectives met? What was the impact of these conventions on the reimbursement negotiation process that followed them?

Unfortunately, due to the confidential character of the MEAs, we faced numerous obstacles that impeded complete answers to these questions.

## 1.3 A difficult process due to data confidentiality and threat of legal proceedings

KCE's main priority was to evaluate the existing conventions to provide well-considered advice to the policy makers to improve their policy. The analysis was nevertheless limited by the confidential character of the appendices of the conventions, encompassing the precise outcome of the negotiation process (for instance the exact amounts or percentages of discounts, budget caps, etc.). KCE committed from the beginning of this project to respect the confidential nature of the conventions (with anonymous aggregated reporting and with a final check by the RIZIV – INAMI to verify the respect of the confidentiality and the validity of all observations and statements).

This was nevertheless not approved by the representatives of the pharmaceutical industry. Even after having invited them to participate in the study as external stakeholders, in full transparency, Pharma.be, a Belgian organisation representing part of the (non-generic) pharmaceutical industry, threatened to take legal action against KCE if the study was continued. We unfortunately had no other choice than to stop the collaboration and to base our analysis on public information only. Details on the compensation mechanisms available in the appendices of these conventions could not be used (neither directly, nor indirectly).



Discussions with other stakeholders involved in the negotiations of the MEAs were also hampered by the fact that some people were afraid of possible accusations of having disclosed confidential information (although they were initially enthusiastic to collaborate). Those stakeholders who did participate in our discussion meetings did not give any information directly or indirectly related to the confidential part of the MEAs (neither on the content of the appendices nor on what was discussed within the working groups).

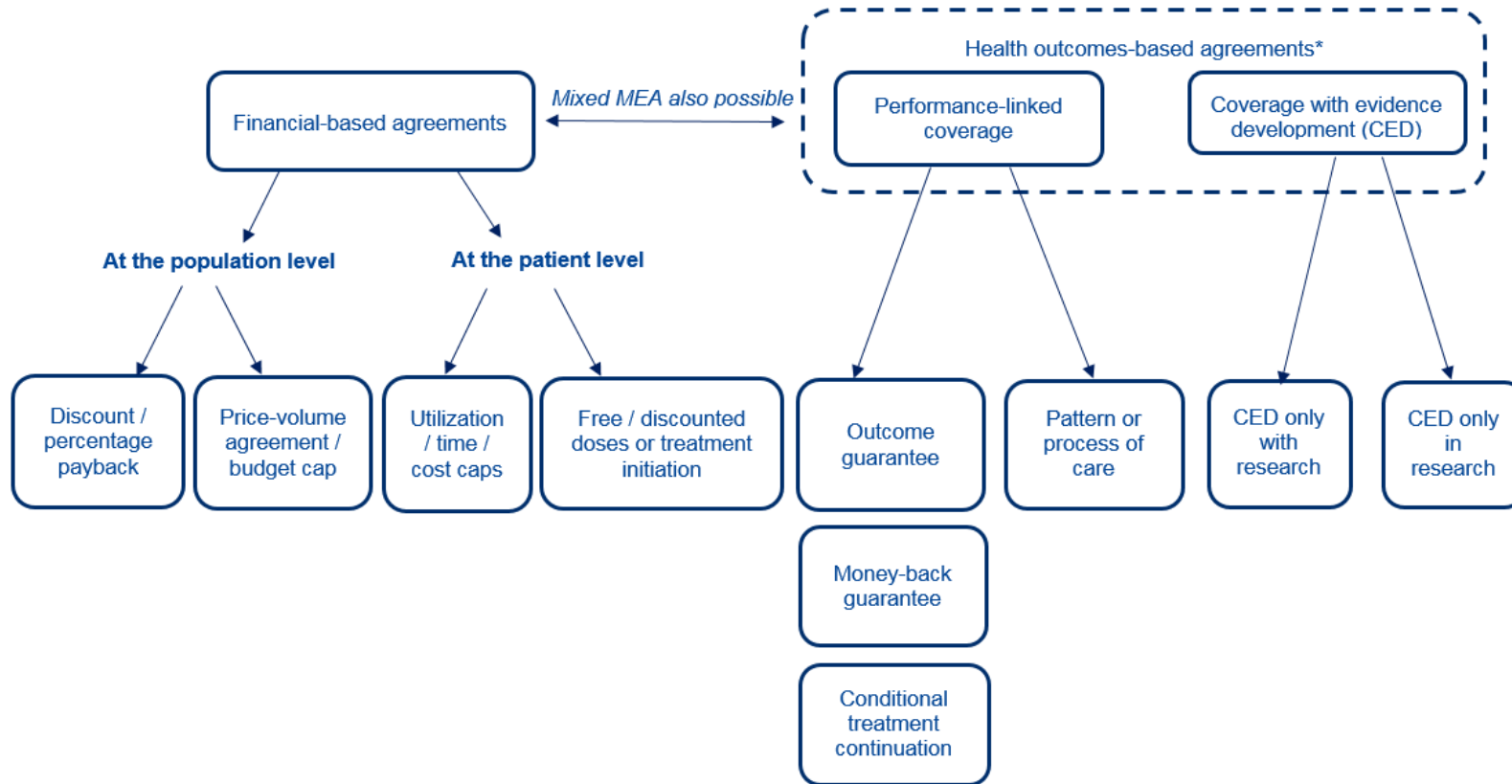
Notwithstanding these limitations and the pressure put on KCE to stop the project, we believe that the analyses of all available non-confidential information and the information from a selection of other countries provides an interesting set of observations and allowed us to formulate valid recommendations (included in the short report). Therefore, it deserves to be published transparently.

#### 1.4 A rapid look at the existing taxonomy

A variety of names have been used to describe these formal agreements, such as managed entry agreements (MEA), risk-sharing agreements, patient access schemes, etc.<sup>1</sup> The first step of this report was therefore to select and define the terms that will be used. The taxonomy used in this report was adapted from different propositions identified during our research of the literature (performed in chapter 1) (see Figure 1 and Table 1). It should be noted that a MEA can be a mix of various schemes, e.g. a performance-linked agreement combined with a financial component. Moreover, concerning financial based agreements, it is possible that the percentage of discounts is based on outcomes estimations.



Figure 1 – MEA taxonomy used in this report



\*Term used in the literature to encompass performance-linked coverage and CED. It should also be noted that some experts also use the term “performance-based agreements” at this level (e.g. OECD 2017 or EC 2011)<sup>2, 3</sup>. Source: adapted from the literature<sup>2-5</sup>

**Table 1 – Definitions of managed entry agreements**

Financial-based agreements	Health outcome-based agreements*
<p><b>At the population level:</b></p> <ul style="list-style-type: none"><li>Discount on the price / percentage payback: percentage reduction of the price / percentage of the real turnover that must be refunded.</li><li>Price-volume agreement (PVA) / Budget Cap: the unit price is linked to the expenditure (volume). One or various thresholds of expenditure (volume) can be defined (i.e. preset budget(s)). A compensation mechanism is given once a threshold is passed (payback/refund, discount). A variant of these MEA are budget caps, i.e. no refund until a predefined level of turnover and 100% of refund after.</li></ul> <p><b>At the patient level:</b></p> <ul style="list-style-type: none"><li>Utilisation or time or cost capping schemes: maximum doses, time, or cumulative cost of treatment per patient after which the manufacturer pays (at least partly) for any additional doses required.</li><li>Free (or discounted) doses / Free (or discounted) treatment initiation: the therapy is free (discounted) up to a certain number of doses or treatment cycles.</li></ul>	<p><b>Performance-linked coverage: link the performance of the product (measure of clinical outcomes) to payment or reimbursement.</b></p> <ul style="list-style-type: none"><li>Outcomes guarantee**: payment for responders only, i.e. the manufacturer is only paid if the product meet an agreed outcome target.</li><li>Money-back guarantee: refund for non-responders, i.e. the manufacturer provides refunds if the product does not meet an agreed outcome target.</li><li>Conditional treatment continuation: payment / reimbursement for continued use only for patients reaching a pre-defined intermediate treatment milestone. Pattern or process of care: payment / reimbursement is linked to practice patterns (e.g. adherence of the patient to the treatment) or is granted only for patients that satisfy eligibility criteria for example as a result of a genetic test.</li><li>Pattern or process of care: payment / reimbursement is linked to practice patterns (e.g. adherence of the patient to the treatment), is granted only for patients that satisfy eligibility criteria for example as a result of a genetic test, or is limited to reference centre.</li></ul> <p><b>Coverage with evidence development: the coverage decision is temporary and is conditioned upon the collection of evidence.</b> The use must therefore be done under controlled circumstances (e.g. through RCT or evidence-providing registries).</p> <ul style="list-style-type: none"><li>Only with research: evidence collection only for a sample of patients, i.e. only a sample of patients must be involved in the study while all patients are covered.</li><li>Only in research: evidence collection for all patients, i.e. only patients participating in the study are covered.</li></ul>

*\*Term used in the literature to encompass performance-linked coverage and CED. It should also be noted that some experts also use the term “performance-based agreements” at this level (e.g. OECD 2017 or EC 2011)<sup>2, 3</sup>. Source: adapted from the literature<sup>1, 3-6</sup>*





## 2 A REVIEW OF THE LITERATURE ON MANAGED ENTRY AGREEMENTS: WHAT CAN BE LEARNED FROM THE CURRENT EUROPEAN EXPERIENCE?

### 2.1 Introduction

Based on a structured literature review, the aim of this section is to provide an overview on the potential impact that MEAs could have (both financial and clinical impact), the most common advantages and disadvantages they offer, as well as on potential solutions available to deal with the challenges they currently pose.

### 2.2 Methods

A project funded by the European Commission (EMINet project) assessed these formal agreements and concluded that despite the no negligible number of agreements already implemented in European countries, little information is available on the impact of these schemes and whether they are meeting their objectives. They added that the confidentiality nature of most of the information linked to these MEAs hampers cross-country learning.<sup>1</sup> This review was taken as a starting point. Their search strategy covered literature published up to October 2011. An update of their search (described in an appendix) was carried out by the KCE team in Medline (through OVID), EMBASE and SCOPUS. In addition to this, a search for grey literature was performed in google and google scholar using the same terms of the search performed in Medline. The search was performed in February 2016 and focused on European health systems, in order to ensure consistency with the geographical scope of the review used as our departing point. Studies on MEAs for medical devices or procedures were excluded from this review, since at present, in Belgium only pharmaceutical products can be the subject of such MEAs. Language inclusion criteria were English, French, Dutch, Spanish, Italian, Portuguese and German.

To identify potentially relevant studies for our analysis, we first went through all titles and abstracts in order to exclude any obvious studies that did not match our research question.

Full texts were obtained for all studies that appeared to be interesting, or for which there were some doubts, in order to select those relevant for inclusion in our review. Reference lists of the selected studies found via our search were checked for additional references worth adding to our analysis.

To update results of identified studies, we also contacted experts in France, UK, Italy and the Netherlands (i.e. countries identified both from our literature research and in the EMINet report as having an interesting experience in MEA) in order to obtain any more recent studies or findings on this topic. Experts contacted are also included in the appendix to this chapter.

Study selection was completed by one researcher but any doubts that came up during the exercise were discussed and solved in collaboration with a second reviewer.

Publications in the form of letters, editorials or notes and abstracts were excluded, unless they covered “impact evaluations” or offered specific “good” or “bad” examples of MEAs. Although overall, these types of short publications do not offer enough detail to draw clear conclusions, the authors of this review were conscious of the scarcity of impact evaluations and decided to be as inclusive as possible in this regard (see Table 2 for selection criteria).


**Table 2 – Selection criteria for the update on the European review by Ferrario et al. (EMINet Project)**

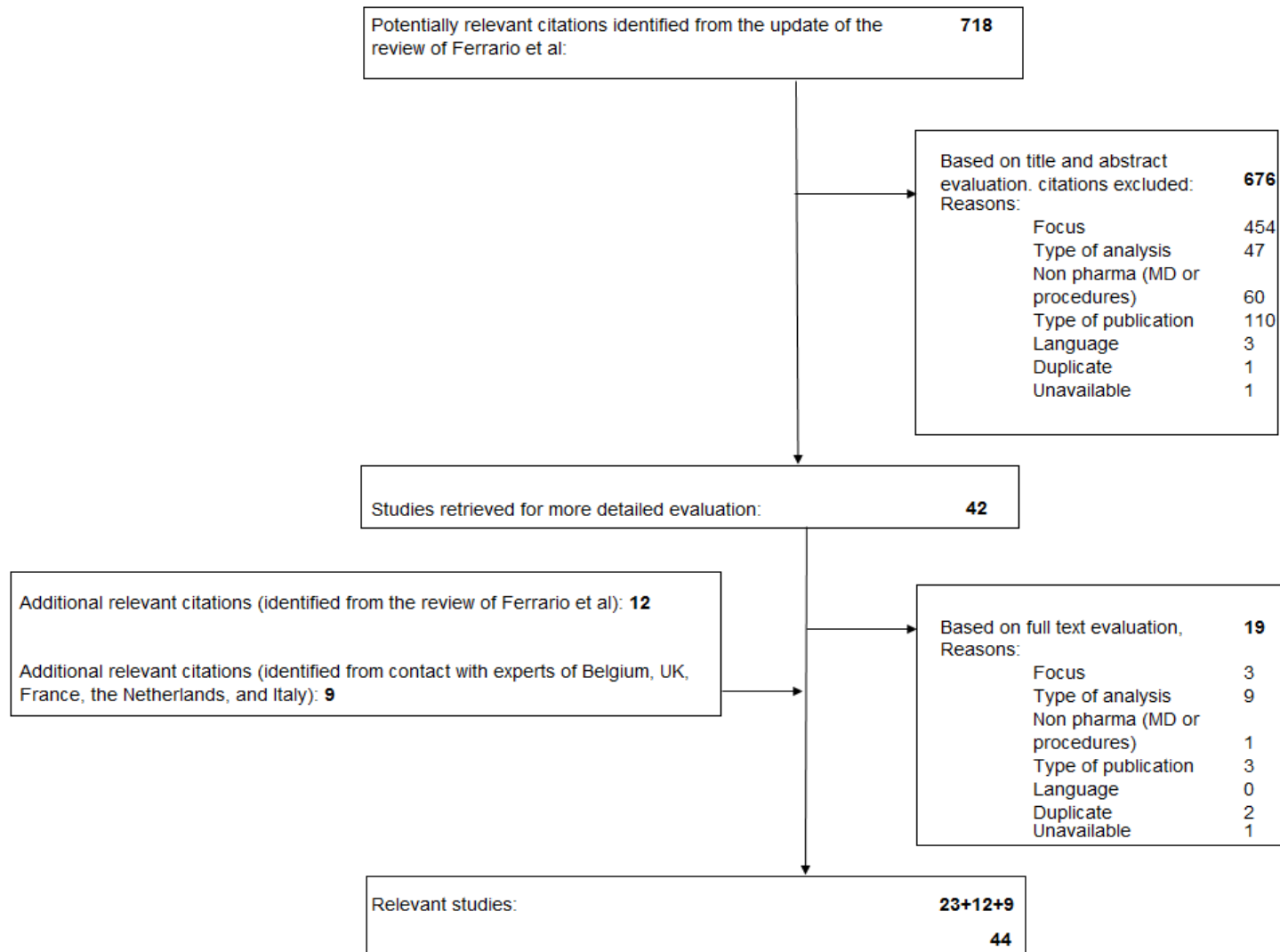
Selection criteria	Inclusion criteria	Exclusion criteria
<b>Mean focus of study/review</b>	Primary studies or reviews in which MEAs (any type) are the main focus	MEAs are not the main focus of the primary study or review
<b>Scope</b>	Primary studies or reviews in European health systems	Primary studies or reviews in non-European countries
<b>Type of analysis</b>	Impact studies, detailed reviews or descriptions of strengths, weaknesses and/or potential solutions to overcome the challenges of MEAs	Simple descriptions. No analysis on impact or detailed descriptions of challenges, strengths or weaknesses of MEAs
<b>Focus of the MEA</b>	MEAs for pharma products	MEAs for medical devices or procedures (Medical devices not yet subject to MEAs in Belgium)
<b>Type of publication</b>	Primary studies or reviews. Abstracts, letters, editorials or notes included only if "impact" evaluations	Abstracts, letters, editorials or notes (if no impact analysis or specific MEA examples presented)
<b>Language</b>	English, French, Dutch, Italian, Spanish, Portuguese and German	Any other languages

Our search returned 718 citations, after eliminating duplicates (see Figure 2 for details). Of those, 676 did not meet our inclusion criteria based on a review of their title and/or abstract. Of the 42 citations left, 19 were excluded after reading their full text because of their main focus<sup>7-10</sup> (not specifically on MEAs, non-pharma, or focused on non-European health systems); the type of publication<sup>11-13</sup> (abstracts, letters or opinion letters, with no impact evaluation); the type of analysis<sup>5, 14-21</sup> (mere description, no analysis of impact or evaluation of challenges, strengths or weaknesses of MEAs); or duplication<sup>22, 23</sup> (evaluation whose results are already covered in a more recent publication by the same author). Finally the full text of 1 publication could not be found,<sup>24</sup> and although the author was contacted no response was obtained within the timelines of our project. This left us with 23 relevant recent studies, which added to the 12 references originally used in Ferrario et al. in their SWOT analysis, (no impact evaluations had been identified by the LSE at the time of their publication).

It should also be noted that after contact with experts of UK, France, the Netherlands, and Italy, as well as Belgian stakeholders, 9 additional reports<sup>3, 25-32</sup> were included in the analysis, resulting in 44 references included in this review (see Table 3 for full references).



**Figure 2 – Update of the review of Ferrario et al:<sup>1</sup> Flow chart selection of studies and reasons for inclusion**



**Table 3 – References included in this review****References****Studies included in the SWOT analysis by Ferrario et al.<sup>1</sup>**

**Adamski, B**, B Godman, G Ofierska-Sujkowska, B Osińska, H Harholz, K Wendykowska, O Laius, S Jan, C Sermet, C Zara, M Kalaba, R Gustafsson, K Garuolienė, A Haycox, S Garattini, and LL Gustafsson. 2010. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Services Research* 10 (153):1-16.<sup>33</sup>

**Carlson, JJ**, LP Garrison, and SD Sullivan. 2009. Paying for Outcomes: Innovative Coverage and Reimbursement Schemes for Pharmaceuticals. *Journal of Managed Care Pharmacy* 15 (8):683-687.<sup>34</sup>

**Carlson, J. J.**, S. D. Sullivan, L. P. Garrison, P. J. Neumann, and D. L. Veenstra. 2010. Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy* 96 (3):179-190.<sup>4</sup>

**Cook, JP**, JA Vernon, and R Manning. 2008. Pharmaceutical Risk-Sharing Agreements. *Pharmacoeconomics* 26 (7):551-556.<sup>35</sup>

**de Pourville, G**. 2006. Risk-sharing agreements for innovative drugs. A new solution to old problems? *European Journal of Health Economics* 7 (3):155-157.<sup>36</sup>

**McCabe, C**, L Bergmann, N Bosanquet, M Ellis, H Enzmann, M von Euler, B Jönsson, KJ Kallen, D Newling, B Paschen, R de Wilde, N Wilking, C Teale, H Zwierzina, and Biotherapy Development Association. 2009. Market and patient access to new oncology products in Europe: a current, multidisciplinary perspective. *Annals of Oncology* 20 (3):403-412.<sup>37</sup>

**Russo, P**, FS Mennini, PD Siviero, and G Rasi. 2010. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. *Annals of Oncology* 21 (10):2081-2087.<sup>38</sup>

**Stafinski, T**, CJ McCabe, and D Menon. 2010. Funding the Unfunderable. Mechanisms for Managing Uncertainty in Decisions on the Introduction of New and Innovative Technologies into Healthcare Systems. *Pharmacoeconomics* 28 (2):113-142.<sup>39</sup>

**Towse, A**. 2010. Value based pricing, research and development, and patient access schemes. Will the United Kingdom get it right or wrong? *British Journal of Clinical Pharmacology* 70 (3):360-366.<sup>40</sup>

**Towse, A**, and LP Garrison. 2010. Can't Get No Satisfaction? Will Pay for Performance Help? Toward an Economic Framework for Understanding Performance-Based Risk-Sharing Agreements for Innovative Medical Products. *Pharmacoeconomics* 28 (2):93-102.<sup>41</sup>

**Trueman, P**, DL Grainger, and KE Downs. 2010. Coverage with Evidence Development: Applications and issues. *International Journal of Technology Assessment in Health Care* 26 (1):79-85.<sup>42</sup>

**Willis, M**, U Persson, Y Zoellner, and B Gradl. 2010. Reducing Uncertainty in Value-Based Pricing Using Evidence Development 150 Agreements. The Case of Continuous Intraduodenal Infusion of Levodopa/Carbidopa (Duodopa) in Sweden. *Applied Journal of Health Policy* 8 (6):377-386.<sup>43</sup>

**Studies identified via the update of Ferrario et al.<sup>1</sup>**

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**Bishop D**, et al. 2013 *BMC Health Services Research* 13(88) - Politics and its intersection with coverage with evidence development: a qualitative analysis from expert interviews.<sup>45</sup>

**Boon W**, et al. 2015 *Health Policy* 119(2):180-185 - Governance of conditional reimbursement practices in the Netherlands.<sup>46</sup>



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- Brugger U**, et al. 2015 *BMJ Open* 5(3):e007021 - Health technology assessment in Switzerland: a descriptive analysis of "Coverage with Evidence Development" decisions from 1996 to 2013.<sup>47</sup>
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- Campillo-Artero C**, et al. 2012 *Farmacia Hospitalaria* 36(6):455-63 - [Risk sharing agreements: with orphan drugs?].<sup>48</sup>
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- Carlson JJ**, et al. 2014 *Applied Health Economics and Health Policy* 12(3):231-238 - Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers.<sup>49</sup>
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- Fasci A**, et al. 2015 *Value in Health* 18(7):A505 - Conditional agreements for innovative therapies in Italy: The case of pirfenidone.<sup>50</sup>
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- Garattini L**, et al. 2015 *European Journal of Health Economics* 16(1):1-3 - Italian risk-sharing agreements on drugs: are they worthwhile?<sup>51</sup>
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- Garrison Jr LP**, et al. 2013 *Value in Health* 16(5):703-719 - Performance-based risk-sharing arrangements - Good practices for design, implementation, and evaluation: Report of the ISPOR good practices for performance-based risk-sharing arrangements task force.<sup>6</sup>
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- Gaultney JG**, et al. 2015 *Health Policy* 119(2):186-194 - Experience with outcomes research into the real-world effectiveness of novel therapies in Dutch daily practice from the context of conditional reimbursement.<sup>52</sup>
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- Kornfeld A**, et al. 2013 *Value in Health* 16(7):A487-A488 - Coverage with evidence development in Sweden - Formality or effective way to reduce uncertainty?<sup>55</sup>
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- Mortimer D**, et al. 2011 *Health Economics, Policy, & Law* 6(4):509-27 - Breaking up is hard to do: the economic impact of provisional funding contingent upon evidence development.<sup>60</sup>
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- Navarria A**, et al. 2015 *Value in Health* 18(1):131-6 - Do the current performance-based schemes in Italy really work? "Success fee": a novel measure for cost-containment of drug expenditure.<sup>61</sup>
- 
- Neumann PJ**, et al. 2011 *Health Affairs* 30(12):2329-37 - Risk-sharing arrangements that link payment for drugs to health outcomes are proving hard to implement.<sup>62</sup>
- 
- Simon S**, et al. 2015 *Value in Health* 18(7):A492 - Evaluation of a payment by results scheme in a Catalan cancer center: Gefinitib in EGFR mutation-positive advanced non-small cell lung cancer.<sup>63</sup>
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- Zizalova J**, et al. 2015 *Value in Health* 18(7):A567 - The relation between real costs of drugs temporarily reimbursed in mode of coverage with evidence development and budget impact analysis submitted as a mandatory requirement of the application.<sup>65</sup>
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**Studies identified via experts**

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CEPS 2016 - Rapport d'activité 2015.<sup>26</sup>

Department of Health 2015 - Guidance. Pharmaceutical price regulation scheme 2014 (update of December 2015).<sup>27</sup>

Garattini L, et al. 2016 Pharmacoeconomics 2016;34(10):967-9 - Performance-Based Agreements in Italy: 'Trendy Outcomes' or Mere Illusions?<sup>28</sup>

Ministerie van Volksgezondheid 2016 - Voortgangsbrief financiële arrangementen geneesmiddelen<sup>29</sup>

NICE 2017 - List of technologies with approved Patient Access Schemes.<sup>30</sup>

OECD 2017 - New Health Technologies. Managing Access, Value and Sustainability.<sup>3</sup>

Toumi M, et al. 2016 Rethink, Reinvent & Optimize Medicines, Improving Patient Health & Access. Marseille: Creativ-Ceutical.<sup>31</sup>

Toumi M, et al. 2017 Applied health economics and health policy 15(1):5-11 - The Use of Surrogate and Patient-Relevant Endpoints in Outcomes-Based Market Access Agreements : Current Debate.<sup>32</sup>

## 2.3 Results

Globally, the literature provided a very limited description or evidence on the real impact linked to the implementation of MEAs. Most studies gave general information on the perceived advantages and disadvantages of MEAs, with few offering some specific “good” or “bad” examples of MEAs for illustrative purposes and only 12 measured different aspects of their impact.<sup>26, 28, 29, 31, 46, 47, 50, 51, 55, 61, 63, 64</sup> Five of them were identified via contact with experts of the countries.

### 2.3.1 Strengths of MEAs

#### 2.3.1.1 General strengths of MEAs

MEAs were usually perceived as helpful tools to:

- **Improve access to innovative treatments:** General agreement in the literature that MEAs can facilitate rapid patient access<sup>40</sup> and help to address post-launch uncertainty for innovative treatments, avoiding possible coverage rejections purely based on insufficient evidence.<sup>38, 43</sup>
- **Expand time horizon for data capturing:** They also prolong the time for data capturing on effectiveness, safety, cost-effectiveness and budget impact under “real” conditions (ie outside of an “ideal” clinical research context). This offers an opportunity for collecting more reliable and pragmatic, post-market entry information that can then be used to develop clinical and economic evaluations.<sup>48</sup>
- **Influence R&D decisions:** Furthermore, it has been argued that MEAs may send signals to the manufacturers on what are the most important value-adding areas for specific therapeutic indications from a health system or societal perspective, which in turn could inform future R&D

decisions,<sup>48</sup> but less agreement exists on whether they offer incentives for innovation, with some authors arguing that they do so by facilitating financial predictability (eg price during the whole MEA period is known and financial rewards can be estimated)<sup>36</sup> or improving return on R&D.<sup>39</sup>

### 2.3.1.2 *Main strengths per type of MEA*

Regarding the different types of MEAs and their specific advantages:

#### **Financial-based schemes**

Financial-based schemes offer a simpler and less administratively heavy alternative to health outcome-based schemes (and in particular to coverage with evidence development - CED MEAs), while still helping to contain costs and, by doing so, improve cost-effectiveness. From a manufacturer's perspective, the confidentiality nature of MEAs, and in particular of discount MEAs, helps manufacturers to do price differentiation in an environment with external reference pricing.<sup>49</sup>

#### **Health outcome-based agreements**

Health outcome-based agreements present the main advantage of focusing on those patients likely to benefit the most from a specific treatment strategy. Within these MEAs, those performance-linked coverage schemes using reasonable proxies for clinical outcomes and utilizing existing administration systems (e.g. routine data from patient files) are perceived by some authors as an "ideal" compromise between financially driven discount schemes and CEDs, since they are not as expensive as CEDs but still take into consideration patients' response (unlike financial schemes).<sup>49</sup>

### **Box 1 – Example from Italy: A performance-linked agreement**

An example of a performance-linked MEA was studied by Navarra et al.<sup>61</sup> In their review, the authors support a new Italian system named "success fee", used at the time of their publication for only one drug, pirfenidone, a highly-priced innovative treatment for idiopathic pulmonary fibrosis. The scheme is presented as a less resource intensive and more effective alternative to the previous "registry-based" Italian system.

Pirfenidone is provided by the company at no initial cost for the health system. Between therapy day 165 and 195, the prescribing centre certifies the success or failure of the treatment (failure defined as a decline in forced vital capacity that overcomes a specific absolute value after the first six months of therapy), and gives notice to the manufacturers. Then the company gets a refund only for patients benefiting from the drug. It should also be noted that a failure (of any nature) in delivering the certificate to the Company was interpreted as a successful treatment and had to be paid to the manufacturer.

This system is thought to address a weakness of the previous "registry" system in which the refund by manufacturers to the payer came a posteriori, while offering important benefits (i.e. improved adherence and persistence rates compared to those seen in other EU countries). At the time of re-negotiation of the MEA, new data from phase III trials and clinical practice were available to support a more definitive payers' decision on the reimbursement of the product.<sup>50</sup>

This 'success fee' agreement was ended in October 2015 and a new success fee agreement was concluded for another product (for relapsed and refractory multiple myeloma).



### Box 2 – Examples from the UK and France: A performance-linked MEA (using “proxies” for outcomes), with a financial component (fixed cost per patient in UK and a PVA in France)

In the UK: the example of gefitinib, covered in a recent international review<sup>49</sup> serves as an illustration. A MEA scheme was set up in order to provide gefitinib for patients with locally advanced or metastatic non-small cell lung cancer. Under this MEA, the manufacturer suggested to provide gefitinib at a single fixed cost of £12 200 per patient (~5.6 months of therapy at list price), independently of the overall treatment duration. The UK Department of Health did not offer any reimbursement until the third month of treatment was supplied. Thus, patients receiving less than three months of treatment with the agent did not incur a charge to the system. This scheme used the length of treatment as a proxy for progression-free survival. This is generally accepted in cancer, since most drugs are provided on the basis of “treat-to-progression or unacceptable toxicity”. If patients benefited from gefitinib (i.e. stable and tolerating treatment well after three months), they could continue receiving the drug, and only then, payers paid the fixed cost per patient previously mentioned. Fixed costs help protecting payers and the system from the high costs that could be linked to long-term use. This arrangement was thought to bring benefits to all parties involved: early patient access, management of subgroup uncertainty and low administrative burden.

Under this scheme, although for some specific cases payers would lose money (e.g. those on 4 months do receive the full amount), evidence from the IRESSA Pan-ASian Study, for the target population showed a mean treatment duration of 6.4 months.<sup>66</sup>

In France, a performance-linked MEA was signed in 2014 with Gilead for Sovaldi® and Harvoni®, both indicated in the treatment of hepatitis C.

For Sovaldi, the French “Comité économique des produits de santé” (CEPS) negotiated clawback payment clauses (percentage refunds) associated with sales volumes (beyond a certain amount set at €450 million for 2014 and at €700 million for 2015) and with product performance, monitored in real-world conditions on the basis of a single indicator (i.e. eradication of the viral load) in a large cohort of patients (12 000). Clawback payments were adapted according to the positive or negative viral load eradication result. For the 2014 financial year, clawback payments due for this new mechanism were €76.5 million. A similar MEA was set up for Harvoni.<sup>25</sup>

### 2.3.2 Weaknesses/Challenges of MEAs

#### 2.3.2.1 General challenges of MEAs

For the manufacturer, these include:

- The problem of “**free riding**”, despite the confidential nature of MEAs: some competitors can benefit from the data or information gathered by the manufacturer engaged in the MEA (eg if their data gathering opens the door for reimbursement).<sup>34, 36</sup>
- The introduction of **uncertainty for manufacturers regarding a payoff for the additional research produced**, and the potential impact that the new evidence could have on future prices or revenues<sup>37, 41</sup> could, in turn, dis-incentivise additional data collection<sup>41</sup> after a MEA is in place.

For the regulator and public payer, these include:

- **Challenges linked to their regulation and transferability of results from one country to another**, in particular in the case of CED MEAs.<sup>36, 41</sup> Different standards of practice, resources used, settings, or costs make it difficult to draw clear conclusions for one country based on the additional evidence or information captured in another one via a MEA. The confidential nature of the data captured adds to the difficulty.
- **High transaction and administrative costs.**<sup>4, 33, 34, 62</sup>
- Temporary reimbursement via a MEA could **discourage manufacturers from capturing additional data.**<sup>41</sup>





- **A risk for potential disinvestment in certain disease areas**, for example, those where a very limited target population is likely to be identified in the context of a MEA, which could translate into low volume use for a product.<sup>42</sup>
- If these schemes become very common, there is a risk that **manufacturers may systematically ask for higher departing prices** in expectation of a MEA.<sup>40</sup>
- **Difficulties to de-list a drug from reimbursement, once a MEA is established:**

Once a decision has been made to fund a drug or device under a MEA, regardless of the evidence, it becomes difficult to discontinue funding. However, if de-listing or price reductions do not follow when medicines are found not to be cost-effective, the ability for these schemes to control costs will be put into question. The literature illustrates that once patients and clinicians have access to, and are familiar with, a new technology, de-listing is highly unlikely to occur.<sup>45, 56, 60</sup>

Political pressure can also play a very important role depending on the disease area considered.<sup>45</sup> For example, politicians may find it difficult to de-list a drug if it is already being used by patients with severe chronic illnesses, as well as for products which have already achieved wide use and acceptance.

If high investment in capital equipment or in training had to be incurred, providers may also become more reluctant to stop using a treatment intervention and, consequently, de-listing will become more difficult.<sup>60</sup>

Given the confidentiality of these agreements it is hard to even identify any attempt to withdraw or limit reimbursement.

Information targeted to patients and to the prescribing physician as well as transparency about the “temporary” nature of the funding and its dependency on the additional evidence captured or the new market situation at the end of the MEA may facilitate, to a certain extent, a necessary de-listing.

In the next sections, a description of the most common challenges identified in the literature per type of MEA is provided, although the distinction per type of MEA was not always straightforward.

### 2.3.2.2 *Main challenges identified related to financial-based agreements*

Discount-based financial schemes do nothing to ensure that the right patient is receiving the treatment of interest. In other words, they may provide a cheaper alternative which can help to limit the impact on the budget, but they are not useful at addressing uncertainties surrounding effectiveness (although this is not their objective, it represents a weakness if there are also clinical uncertainties).<sup>49</sup>

Furthermore, the lack of transparency and confidential nature, which represents an advantage from a manufacturer’s perspective, is a challenge for payers. Confidential discounts impede that payers in other countries benefit from the lower “MEA” prices and oblige them to continue relying on the official “list prices”. Furthermore, the confidentiality of these prices impedes to conduct appropriate cost-effectiveness analyses using drugs under MEA as comparator (list prices need to be used).

Finally, although pre-MEA forecasting for therapy use and budget impact is often an important part of this type of MEA, such calculations have proven to be more challenging than expected.



### Box 3 – Example from the Czech Republic: Validity of budget impact analysis estimations pre-MEA.

An example to illustrate this last point is provided by Zizalova et al.<sup>65</sup> In their analysis they looked at differences between the estimated drug costs (by means of budget impact analysis) and real drug costs for drugs under MEAs in the Czech Republic. They found that the estimated costs were exceeded (by 31-332%) in five cases, while in six cases real costs did not reach the pre-MEA estimation (reaching only between 12-91% of estimated costs). Their conclusion was that although budget impact analysis is a formal requirement for MEA submissions in the Czech Republic, the effective contribution of budget impact analyses to decision making remains unclear.

Following a similar line of thought (difficulties in forecasting future use of a new drug), Hren et al.<sup>54</sup> highlighted in a study focusing on discount schemes the importance of, at the very least, considering the length of treatment in discount calculations. The objective would be to ensure there is no incentive for manufacturers to greatly increase market share over what was originally forecasted once the MEA is in place. This should encourage less unpredictability in the models developed for this type of MEA, while still preserving a lower administrative burden than health outcome-based schemes.<sup>62</sup>

#### Key point

- **When there is an uncertainty on the budget impact, the combination with a cost cap per patient (based on an optimal treatment schemes) or with a budget cap should be considered.**

#### 2.3.2.3 *Main challenges identified related to health outcome-based schemes*

Most of the available literature in this regard focused specifically on coverage with evidence development schemes (CED), given the great number of challenges they appear to pose due to their complexity. Thus, the challenges discussed in this section refer to CEDs only, unless otherwise stated.

#### High administrative costs

First, the most obvious weakness is their administrative costs. Since the planning, organization and running of the studies/registries can be very complex.<sup>4, 33, 34</sup>

#### Lack of governance structure

Second, CED lacks a governance structure, or a systematic approach, as a consequence, schemes are thought to be easily manipulable post implementation.<sup>45</sup>

One of the main reasons for the lack of governance comes from an absence of clear criteria to first decide whether a CED is required and then, once this is ongoing, arrive at a positive or negative decision for reimbursement based on the new evidence provided. Furthermore, there is also a lack of standardised criteria on when and how to link decisions to specific additional requirements (e.g. restricted to specified providers or the need to develop a registry).<sup>47</sup>

#### How much evidence is needed?

A further challenge is the decision on how much evidence may be enough and when a CED should be stopped.<sup>45</sup> The period between evidence generation and a final decision varies considerably from one MEA to another and is sometimes thought to be too long,<sup>47</sup> while in other instances it may not be enough (depending on the indication or outcomes needing to be captured). For example in the case of the Netherlands, the authorities decided at one point to move from 3 years to 4 before re-assessment.<sup>52</sup> Now, the Netherlands moved from CED to financial-base agreements (cfr. Infra, source: personal communication of Huib Kooijman, see the appendices).

Often there are doubts throughout the MEA period on what “corrections” may be required, including whether a cancelation of the MEA would be appropriate.<sup>48</sup>

**Box 4 – Example from the Netherlands: MEA duration.**

An example to illustrate this point comes from the Netherlands<sup>59</sup>, where Mohseninejad et al. performed an analysis of a patient registry set up for oxaliplatin in the treatment of stage III colon cancer by applying value of information analysis based on data from the registry. Their results show that, given the assumptions on cohort size, follow-up time, and purpose of the registry, the registry was not efficient. In particular, the authors highlight that the observation period was too long and that a final reimbursement decision could have been made after a maximum of 2 years as opposed to the fixed 4-year period.

**Key point**

- **One fixed period is unlikely to fit all schemes. Possible adaptations and regular revisions are likely to result in less wastage and more efficient decision making.**

**The lack of clarity on the role of different stakeholders**

The lack of clarity on the role of different stakeholders or their leadership position represent a further difficulty.<sup>45</sup>

- Conflict of interest

In particular conflicts of interest (COI) can represent a real problem when industry is responsible for the funding and/or design of a registry or observational study as well as for the analyses of the results and their publication.<sup>40, 53</sup>

Carefully crafted research design, specific choices made in the context of statistical analyses, exclusion of negative findings, over-inclusion of positive findings, and even misrepresentation of results are thought to be common problems.<sup>53</sup> This is closely linked to the lack of transparency that we will cover later on in this chapter.

**Key point**

- **A clear definition of responsibilities and the active participation of external independent experts should help to control or minimise the unavoidable COI.**

- Social pressures

Often, translating research into policy has proven not to be easy, not just due to data limitations, and financial or time constraints, but also due to the role of social pressures in decision making.<sup>47</sup> This is not necessarily bad and it is a reality in any health system, but it should be clearly and openly recognised.

Already decisions to enter into such arrangements are often heavily influenced by direct and indirect pressure from the pharmaceutical industry, patient advocacy groups, physicians, and patients and their families. Establishing one of these schemes may also be a convenient way for politicians to postpone a difficult confrontation with patient advocacy groups over funding decisions.

There is up to date, little scientific research on this aspect, an exception being a recent qualitative analysis of expert interviews.<sup>47</sup> Once more, the confidentiality surrounding these MEAs makes the identification of political weights in decision-making a challenging task. Without access to the confidential information, it is not possible to determine the extent to which decisions were based on evidence or on other grounds.<sup>48, 56</sup>

**Key point**

- **Future CED studies should be prospectively planned to include an exploration of the political dimensions of the environment in which the study is taking place and to also involve an analysis of the interests of the various stakeholders at various stages of the project.**<sup>45</sup>



### Challenges linked to data collection outside of an “ideal” RCT context

To make observational studies worthwhile and valid, their design, conduct, and analysis need to be rigorous and transparent, particularly with regard to minimizing confounding effects and bias.<sup>56</sup>

Because these studies rely on real-world data sources, such as patient registries or administrative databases, and well-matched historical or contemporary comparative cohorts, they also must be supported by funding agencies, sponsoring companies, clinicians, administrators, and insurers. These studies should complement, rather than replace, the evidence captured by RCTs during the drug development process.<sup>56</sup>

Specific challenges are linked to outcome measurements. Outcomes need to be objective, clearly defined and measurable within the time frame of MEAs, which is usually limited.<sup>62</sup> Some of these MEAs make use of intermediate clinical outcomes and do not foresee a long-enough follow-up to truly assess the relevant final outcomes.<sup>48</sup> Under such circumstances, the intermediate outcomes should be validated in order to ensure the financial and time consumption efforts incurred in are not wasted.

Specifically for orphan drugs, delays in data collection and dissemination due to the small treatment population of a MEA are a crucial challenge that can have a detrimental effect on the effectiveness of CED schemes.<sup>42</sup>

There are also important hurdles directly linked to the development of effective registries, with general agreement that, in order to successfully undertake CEDs, it is necessary to have better access to data and to be able to link databases. Standardizing data elements across registries would also be important. Registries are identified as one of the most commonly used tools to collect data under MEAs. However, finding a sustainable funding model for registries, verifying their accuracy, reliability and completeness of their information, as well as, ensuring the confidentiality of the information they include is respected, are some of the issues linked to the development of registries that should not be overlooked.<sup>45</sup> Investment in high quality information systems is therefore thought to be needed in order to improve the current situation.<sup>62</sup>

### Box 5 – Example from France: Incentives for successful completion of real-world studies.

If a pharmaceutical company does not fulfil its commitment to undertake a real-world study, the CEPS is allowed to pronounce a fine (Paragraph 5 of Article L.162-17-4 of the French Social Security Code). Further, in order to guarantee the successful completion of the studies requested to the pharmaceutical companies, the CEPS set up a committee in 2013 for monitoring real-world studies on medicines in partnership with the “Haute Autorité de Santé” (HAS). This committee meets twice a month.

#### Key point

##### Careful planning data collection:

- **Registries/observational studies linked to CED MEAs should not replace RCTs.**
- **When using intermediate outcomes, these should be validated by independent experts.**
- **High quality information systems are necessary to ensure effective data capturing.**

#### Lack of transparency

Although the lack of transparency is a general problem linked to all types of MEAs, it is particularly problematic in the case of CEDs because of their high costs and very limited information on the status of the evidence during the MEA and even at its completion.<sup>47, 57</sup> There is a need for increasing transparency in general and encouraging publication of study results/registries to facilitate a more efficient decision making.<sup>53</sup>



### Box 6 – Example from Switzerland: Financial incentives to ensure comprehensive data reporting in registries.

Brugger et al.<sup>47</sup> gave an example of a successful model with comprehensive reporting and proof of outcome improvements: The introduction of a Swiss law on transplantation, made reporting of all transplants to the Swiss registry and adherence to a specific quality management system (i.e. JACIE) mandatory in Switzerland in order to be reimbursed. Reporting was paid for as well.

Although this example does not refer to pharmaceutical agents, using financial incentives to encourage reporting is likely to result in better quality and less missing data points also in the case of medicines.

#### Key point

- **Study results / registries should become public after the MEA has come to an end. For registries, a financing to encourage reporting would improve the quality of registries.**

#### Ethical challenges

The ethical aspects of these schemes are often ignored. The question has been raised, for example, about the types of CED programs which count as research (e.g., whether participation in registries counts as research) and what, if any, consent and approval by ethics committee are needed. The authors conclude that registries linked to MEAs are interesting, but raise issues of their own and, if not implemented with care, may ultimately undermine evidence-based medicine and systems for controlling health budgets.<sup>56</sup>

#### Challenges linked to obtaining claw-backs

Finally, for performance-linked agreements, difficulties in obtaining refunds from manufacturers have been reported in the literature. These appear to be primarily linked to late requests or disagreements with pharmaceutical companies.<sup>51</sup>

#### Key point

**Simplifying claw-backs - Simpler systems that favor payments by the health system only for respondents, as opposed to claiming back payments for patients who do not benefit from a treatment should encourage data registration and limit wastage.**

### Box 7 – Examples of challenges linked to health outcome-based MEAs

The best example for illustrating not only the high costs, but also some of the other challenges linked to CEDs previously discussed (e.g. difficulties in stopping MEAs, political pressures and COIs), is that of the UK risk-sharing multiple sclerosis (MS) scheme on disease modifying therapies (interferon-beta 1a; interferon-beta 1b and glatiramer). This scheme was set up in 2002 in view of NICE conclusions, which judged these drugs not to be cost effective. A registry was set up in order to capture long-term data (over a 10-year period) on over 5000 MS patients. At the end of 2009 the first report from the scheme appeared, documenting the status of patients over the period 2005–2007. In this report, patients on therapy appear to do worse than those on placebo. Although this should have resulted in a price reduction or de-listing for the drugs under evaluation, the 2009 report stated that “the scientific advisory group considered that it was premature at this stage to reach any decision about re-pricing the drugs without further follow-up and analyses”. The manufacturers of the drugs were part of the advisory board. As of June 2010 there have been no further annual reports published on this scheme. Although the final results were expected to be published by 2015, at the time of this review no update on the outcomes of this MEA was identified. The annual cost was reported to be around £50 million, making it “the most expensive publicly funded health related study in the UK”.<sup>53</sup>

Another example for the Netherlands was offered by Gaultney et al.<sup>52</sup> Policymakers in the Netherlands instituted a CED scheme for bortezomib in advanced Myeloma in 2006. A review of daily practice data gathering showed that, although outcomes research of bortezomib in this field was useful for generating some real-world evidence for a re-assessment, this was not useful for all types of evidence. It was useful for addressing who received bortezomib and how bortezomib was administered in daily practice.



However, the value of outcomes research was limited in generating robust evidence on real-world effectiveness, with low quality data, mostly due to missing data in patient charts, treatment variations between different sites or professionals, and the dynamics in care during the novel drug's initial market uptake period (often initial rapid uptake followed by a period of stabilization). Important points for payers to consider include: First, a need for patient charts to capture data on important prognostic markers and the date a patient reaches a clinically significant milestone to allow for robust analyses of effectiveness stratified by prognosis. Second, explicit consensus is needed on the frequency of follow-up and the criteria and methods used to evaluate response or progression in daily practice. Third, reasons for treatment decisions and adverse events encountered should be reported as well captured in patient charts. To achieve this, it is crucial to first reach a consensus on the minimal data points that should be made available in patient charts, and to assess the need for explicit treatment guidelines.

The failure of these schemes and in particular of the multiple sclerosis scheme may have contributed to a current trend (specially marked in the UK) which indicates a move away from CED schemes to simpler discount-type of schemes.<sup>49</sup> Thus, as many as 97% (32/33) MEAs agreed in the UK since the end of 2011 have been discounts, while this type of MEA accounted for just 31% (5/16) of the schemes agreed before that date.<sup>67</sup>

It is clear that CEDs increase the complexity of the decision-making process significantly. Consequently, the potential benefit linked to capturing more information that could improve the cost-effectiveness and use pattern of a product, should always be confronted with their complexity and the high costs often linked to following such a route (administrative and others). The necessary resources need to be set in place to ensure an appropriate follow-up and periodic evaluation to avoid insufficient or late reporting of results.<sup>48</sup>

### 2.3.3 What products should be the target of MEAs

A further important general reflection found in the literature is that not all drugs will be right for MEAs.

According to Campillo-Artero et al.<sup>48</sup> MEAs should not be accepted as a way to surpass a poor R&D programme or the usual pricing and reimbursement or cost containment systems/policies. They should neither be considered under any of the following circumstances:<sup>48</sup>

- If there are alternatives which proved to be as (or more) cost-effective;
- If the objectives of the MEA are not clear;
- If no guarantee exists that the different variables of the MEA can be measurable by validated or reliable means;
- If the adherence to the treatment is generally low;
- If the administrative charge to carry out the MEA is not acceptable;
- If the MEA would result in an acceptance from the part of the payer to fund an important proportion of the costs of development of the drug;
- If there are any doubts about the transparency and/or compliance with the MEA.

### 2.3.4 Evaluation process for MEAs

There is at present a lack of a clear evaluation process in itself for MEAs in general, which explains the scarce attempts found in the literature for measuring their impact. This remains to a certain extent unknown, as we will see in the next section of this chapter.



### 2.3.4.1 Financial impact of MEAs

#### The Netherlands

Since 2016, solely financial-based MEAs are negotiated by the “Buro Financiële Arrangementen Geneesmiddelen” of the Ministry of Public Health (VWS). For each pharmaceutical entering the market, the National Health Care Institute makes a prognosis of the expected costs during the first years after marketing authorisation, based on several parameters such as the number of eligible patients, the duration of treatment, duration till a new (better) therapy may appear, the estimated cost per patient, etc. If the maximal prognosis of expenses, i.e. in the hypothesis that the highest estimated number of patients would be treated with the respective pharmaceutical, predicts very high expenses, a financial-based agreement can be considered by the VWS. These agreements are often combined with “appropriate use” conditions (conditions to start/stop treatment, centralisation of treatment in specific centres, registry of outcome data, etc.). In the process, payers (zorgverzekeraars), physicians and patient organisations involved are consulted for advice. In the assessment for the eligibility for a MEA, indicative parameters are used. The financial risk is balanced against the therapeutic added value and cost-effectiveness and research- and development costs of the pharmaceutical.

The Minister of Health, Wellbeing and Sports (VWS) yearly reports on the savings to the second Chamber. For 2014, a total of €13.9 million of savings were realised for 8 agreements, with €336 000 realised via (public) decrease of the list price.

Table 4 gives a global overview of the potential savings due to ongoing financial-based agreements in 2015-2018, in the hypothesis that for all products the highest estimated number of patients would be treated with the respective pharmaceutical. In this scenario, in 2018 the MEA could reduce the expenses for these pharmaceuticals from €459 million to €256 million, i.e. a saving of €203 million (56%). In 2016, new agreements will be concluded which will impact on the prognosis and the possible savings from 2016 onwards. The realised savings for 2015 are expected in 2017.<sup>29</sup>

We remark that these ‘savings’ should be interpreted with caution. It is possible that products where reimbursed without showing any added value versus a relevant comparator. In such cases, it is difficult to talk about savings when the discounted price is still higher than this alternative.

**Table 4 – potential “savings” due to financial-based agreements 2015-2018 (in million euro)**

	2015	2016	2017	2018
<b>Number of ongoing agreements</b>	16	14	10	10
<b>Maximal prognosis of expenses</b>	371	340	355	459
<b>Potential savings (based on maximal prognosis of expenses)</b>	122	114	150	203

Source: Ministerie van Volksgezondheid, Welzijn en Sport<sup>29</sup>

#### Italy

A review by Garattini et al.<sup>51</sup> critically assessed the available data on MEAs in Italy to question the system in place and its effectiveness. At the time of the publication of their review, there were 29 MEAs (on 25 drugs) in place in Italy in October 2012: 11 financial-based MEAs (discounts) and 18 health outcome-based schemes.

The author reported the revenues of MEAs published by the Italian Medicines Agency (Agenzia Italiana del Farmaco - AIFA) in 2013: a total pay-back of €46.3 million for 2012. However, they highlight that only €31.3 million was collected, representing 5% of the total expenditure for the drugs involved (limited to the indications under MEA). Disputes with pharmaceutical companies as well as late requests by hospitals were identified as the main causes for the incomplete claw-back collection. Complete information by drug and/or by region was lacking. Most of the theoretical pay-back (over 80%) for 2012 was linked to just 9 active substances, while the remaining 17 accounted for less than 1 million euros each.



Price discount agreements were presented as financially more efficient schemes than health outcome-based MEAs primarily due to their simplicity which makes them much cheaper to manage.

To further assess the efficiency of MEAs, the authors highlight the importance of taking into consideration their management costs. AIFA awarded a 3-year tender for €8.7 million to a private company to manage the existing registries. Prior to that, they were managed by a consortium of non-for profit institutions (primarily universities), but the system was thought to lack transparency.

A further cost item that should be included in the overall cost calculations should be the hospital consultants' and pharmacists' time for completing the forms, thought to be considerable, although hard to estimate due to the lack of information.

The authors went through the forms referring to the patients' clinical status, which confirmed the use of the products only on the approved indications but concluded that the information captured was unlikely to contribute to the existing "effectiveness" evidence for the drugs. The authors conclude that AIFA's effort to become a "registry factory" may not be worthwhile.

A further review conducted for the same country<sup>61</sup> and also based on data from the Italian national report 2012, showed that these schemes have poorly contributed to fulfil their overall purpose. The overall refund collected by the national health system for all drugs subject to one of these schemes since their initiation in 2006 (22 overall), was estimated to be €121 million out of an overall €3696 million paid, representing merely 3.3% of the overall drug costs to the health system. Looking purely at data for the year 2012, the overall costs covered by the system for the treatment of patients with drugs subject to MEAs was estimated to be €823 million, 95.4% of which were not eligible for reimbursement.

Moreover, as already highlighted by Garattini et al.<sup>51</sup>, only two-thirds of the costs theoretically eligible for reimbursement were finally recovered by the authorities. To the inefficiencies already described by Garattini<sup>51</sup> the authors of this study add the heterogeneity of the mechanisms used by regions, companies or hospitals for the refunds, which were thought to add unnecessary complexities to the system.

In 2016, Garattini et al. again published a short evaluation of MEA in Italy. They reported that in 2015, there were 52 health outcome-based agreements and 27 financial-based agreements and highlighted the fact that no relevant clinical outcomes have been published by the Italian Agency for pharmaceuticals (AIFA) on drugs under health outcome-based agreements since their introduction, i.e. based on a 10-year experience.<sup>28</sup>

### France

As shown in Table 5, the total amount of refunds received in 2015 in France was 1 015 million euros. They nevertheless not mentioned the total amount on which these refunds were based (in order to assess a percentage of refunds).<sup>26</sup> Again, the same remark on the interpretation of 'savings' should be made.



Table 5 – Refunds in France in 2015<sup>26</sup>

Type of MEA	2015 refunds (in million euros)	Repartition
<b>Price-volume agreement</b> <i>'Clause de volume'</i>	573	56%
<b>Budget cap (for orphan drugs)</b> <i>'Clause de chiffre d'affaires annuel hors taxe (CAHT) capé (clauses orphelins)'</i>	139	14%
<b>Health outcome-based agreements (including both performance-linked coverage agreements and coverage with evidence development)</b> <i>'Clause de performance: contrats conditionnels (payer pour voir) et contrats paiement au résultat (satisfait ou remboursé)'</i>	98	10%
<b>Discount</b> <i>'Clause de remise à la 1<sup>ère</sup> boîte'</i>	94	9%
<b>Cost cap per patient (based on a defined treatment scheme or an average daily cost)</b> <i>'Clause de coût de traitement (basé sur le respect de la posologie figurant dans l'AMM ou du coût du traitement journalier moyen)'</i>	82	8%
<b>Others (not specified)</b> <i>'Autre – Accès encadré: périmètre de prise en charge restreint'</i>	29	3%
<b>Total</b>	1 015	100%



### 2.3.4.2 Impact of CED on decision making

#### Switzerland

Brugger et al.<sup>47</sup> completed an analysis on coverage with evidence development (CED) decisions for both pharmaceuticals and devices from 1996 to 2013 in Switzerland.

Their methodology included both a quantitative analysis of data and stakeholder interviews. Factors associated with the incidence of new evaluations or the final decision were identified by means of regression analysis.

Overall, over the period studied there were 46 evaluations out of 234, (20%) that became CED. The number of initial decisions on new services to proceed with 'yes, in evaluation' ranged from 0 to 6, with an average of 2.6 per year<sup>a</sup>. A decision was made for 37 out of 46 'yes, in evaluation' cases (80%) by the end of 2013. Final reimbursement was granted in 59.4% of all decisions. The mean duration of the evaluation was 5.36 years (4.3 years initial and +1.07 years extension) for the 37 'yes, in evaluation' cases that were already decided, but a high variation was present (0.5–11 years).

For a total of 14 (30.4%) cases classified as 'yes, in evaluation' the setup of a registry was required. No criteria were specified on how or by whom the registry had to be established or how the registry should be financed. No public data of any of the registries was available. Impact on patients' outcomes or costs could not be drawn from the available evidence and thus, remains unknown.

They concluded that CED recommendations should be made with care and should be integrated into clear and structured processes that could deliver consistent decisions.

#### France

In France, a one-year observational study was requested for a long-acting injectable formulation of oral risperidone (Risperdal Consta®) to compare hospitalisation rates among 2 092 patients suffering from schizophrenia treated with different antipsychotic drugs. Among the 2 092 patients, 550 patients were being treated with Risperdal Consta®. A total of 1659 were monitored for up to 12 months. The study showed a reduction in the risk of hospitalisation (relative risk of hospitalisation 0.66 (0.46-0.96)). Nevertheless, even if the design had been validated by the French National Authority for Health (HAS) and the Directorate-General for Health, they then considered that as it was an observational study, there were by essence multiple confounding factors making the interpretation of the study very difficult. The HAS did not change their benefit scoring and maintained it as minor.<sup>31</sup>

#### The Netherlands

An overview of experiences (2006-2012) in the Netherlands with evaluations of expensive drugs and re-evaluations after 4 years under CED schemes was identified via our search, although published only in the form of an abstract.<sup>64</sup> The authors looked at the overall consistency of the conclusions at the initial evaluation (year 0) versus those at the completion of the scheme (year 4), and the weight of the outcomes, for which data was developed during the MEA, on the final pricing or reimbursement decisions. Over the 6 years studied, 36 assessments were approved for CED and 10 declined. At the time of their analysis, reassessment after completion of the scheme (year 4) was available only on 4 drugs: omalizumab and ranibizumab for treatment of patients with severe asthma and macular degeneration respectively; and alglucosidase alfa and agalsidase (orphan drugs for Pompe's and Fabry's diseases respectively).

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<sup>a</sup> Other possibilities are "direct yes", "direct no reimbursement decisions", or "no in evaluation" (not reimbursed but the drug or medical device could be used in research studies/programmes)



Based on this limited evidence, conclusions regarding effectiveness appeared to be the most consistent between the initial evaluation and the re-assessment at completion of the MEA. Despite great quality variations on the outcomes captured over the MEA period, most were useful to evaluate costs and appropriate use. Cost data were commonly used as inputs in economic evaluations, while inputs for “clinical effectiveness” were generally derived from the clinical studies, already available prior to the initiation of the schemes. The overall conclusion was that outcomes research as part of a CED in the Netherlands has produced helpful information regarding costs and appropriate use of expensive drugs, but has shown to offer limited value for filling in clinical effectiveness evidence gaps.

Our search identified a further evaluation on **orphan drugs** in the Netherlands.<sup>46</sup> The authors evaluated the first 6 years of their conditional reimbursement system (re-evaluation after 4 years of orphan drugs), from 2006 to 2012 in the Netherlands, and compared it to the situation in France. Their analysis showed that during the implementation of the scheme the Dutch actors involved went through a learning process about regulation. Previous collaborations or already existing organisational structures, preferably including medical specialists and patient organisations, led to faster production of the required data on (cost)-effectiveness.

In France, drugs are re-assessed every 5 years (all products) but for performance-based MEAs, an evaluation is performed earlier (usually a period inferior to 3 years). In the Netherlands the re-evaluation of listed orphan drugs is scheduled only after four years. However, the authors claim that having more time to acquire more data (e.g. on cost-effectiveness), does not necessarily lead to less problematic and well-supported decision making.

Furthermore, the quality of the cost-effectiveness findings was put into question. This was primarily due to the fact that four years in the case of the Netherlands might still be too short to produce good-quality data. The small number of patients (in particular in the case of orphan drugs), small-scale set-up and the ethical complexity of randomising patients to a placebo while the drug has already been approved, call for alternative study designs, including analysis of pooled international data (registries) of sufficient

quality. Nevertheless, some cost-effectiveness thinking did enter the decision making: findings were discussed and even led to narrowing down the criteria for effective use, including, for example, clear stopping rules. The Netherlands might learn from the French system in which these criteria are established in a ‘rolling review’, as opposed to a strict attachment to a four-year reassessment.

None of the analysed drugs were delisted as a result of a reimbursement review. For the Netherlands the final decision of whether it reimbursed a drug or not did not reflect the cost-effectiveness evidence gathered which was generally poor. CVZ gave a negative advice for 3 of the reassessed drugs, which showed costs per QALY above € 200 000, but none of them were eventually delisted. However, the cost-effectiveness findings resulted into further research on narrowing down the criteria for effective use (e.g. stop and start criteria or precise patient subpopulations). For France, of the 46 studied orphan drugs, six (~13% of total) had an assessment resulting in a downgrade. These downgrades did not result in delisting but the price and/or rate of reimbursement may have changed.

For the 14 conditionally reimbursed orphan drugs in the Netherlands only 4 reassessments were completed at the time of the analysis (with an average delay of 563 days over the originally estimated time), the rest were still pending (with some having a delay of at least 3 years). Overall, the comparison with France indicated that the Dutch conditional reimbursement scheme resulted in comparable access to orphan drugs. The extent to which these findings also reflect the reality of non-orphan drugs is to this date unclear.

Based on a personal communication, it should also be noted that in the Netherlands, CED were abandoned since 2016. The following reasons were given by the Zorginstituut Nederland:<sup>b</sup>

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<sup>b</sup> Personal communication: Hedi Schelleman



- Usually there was already sufficient evidence at the moment of market authorisation to conclude that the pharmaceutical was not cost-effective or there was no necessity to collect additional data for 4 years to prove cost-effectiveness.
- It is not legally required to deliver evidence on cost-effectiveness for reimbursement decisions.

### Sweden

A review of results obtained from CED MEAs in Sweden from 2005-2012, was published in the form of an abstract in 2013.<sup>55</sup> Its objective was to assess whether they provide an effective way of managing uncertainty.

The authors identified 38 CEDs overall. Ten of them were not yet completed at the time of their analysis. A further 12, had reached the evaluation time, but no final decision had been taken and the products continued to be reimbursed according to the temporary MEA conditions. For the remaining 16 products reimbursement (full or limited) was granted and no product was rejected. The authors conclude that based on the limited data available it is unclear whether CEDs do contribute to manage uncertainty in Sweden.

#### 2.3.4.3 Impact of performance-linked MEAs

### Spain

Simon et al.<sup>63</sup> analysed the first performance-linked MEA signed in Catalonia for the introduction of gefitinib in the treatment of EGFR-mutation positive advanced non-small cell lung cancer. The analysis looked at the differential cost between two scenarios: one including the total cost of treatment and the other one following the conditions of the MEA by which AstraZeneca reimbursed the costs of patients for whom the treatment failed.

Forty one patients were followed and their response to treatment was assessed at week 8 (responses, stabilisation and progression) and week 16 (stabilisation). The authors reported savings of 6.17% at week 8, 11.18% at week 16, and 4.15% for overall treatment when implementing the MEA. The MEA resulted in an overall saving of around €1000 per patient. However, the authors highlighted the importance of having an adequate information

system to measure outcomes and monitor accountability. They also described as crucial the involvement of health care professionals.

### Italy

The performance-linked MEA (“success fee”) performed in Italy for pirfenidone (see Box 1 in section 2.3.1.2) was ended in October 2015. At the time of re-negotiation of the MEA, new data from phase III trials and clinical practice were available to support a more definitive payers’ decision on the reimbursement of the product.<sup>50</sup> In terms of data collection, by December 2016 (personal communication of the Italian expert contacted, i.e. Pr. Filippo Drago) only regional (Sicilian) data about drug prescriptions and treatment failures were available. From the date of activation of the registry of pirfenidone in 2013 until July 2016, 219 patients were enrolled from the two Sicilian prescribing centres. The treatment was interrupted in almost 40% of all patients. These interruptions were caused by death or progression in 30% of cases and by adverse drug reactions in 45% of cases. Patients that met the criteria for non-responders at the time of assessment set by the agreement were 2.

#### 2.3.5 Checklists for evaluating the need for a MEA or the impact of an already established MEA

##### 2.3.5.1 Checklists for evaluating the need for a MEA

### United Kingdom

*The 2014 Pharmaceutical Price Regulation Scheme (PPRS) of the Department of Health*

The PPRS is a voluntary agreement negotiated between the department of health and the branded pharmaceutical industry to control the prices of branded drugs sold to the NHS.



In this PPRS, a number of principles have been developed concerning MEA (named Patient Access Scheme (PAS)), including a.o. the following:

- “Arrangements must respect the role of NICE in providing the NHS with an independent assessment and appraisal of the evidence on an intervention.
  - PAS proposals are to be discussed first and agreed in principle by the Department and the company. NICE’s principal role is to assess the impact of such proposals on cost-effectiveness taking into account the details of the proposed PAS.
  - The full costs to the NHS of any such arrangements should be included in the costs considered by the Appraisal Committee.
  - PAS should be clinically robust, clinically plausible, appropriate and monitorable (e.g. if it is a responder scheme, there must be a relatively straightforward way to measure a patient’s clinical response).
  - Any PAS should be operationally manageable for the NHS without unduly complex monitoring, disproportionate additional costs and bureaucracy. Any burden for the NHS should be proportionate to the benefits of the PAS for the NHS and patients. Clarity is also required on the exact duration of any agreement and the circumstances in which it might be terminated.
  - It is important that the cumulative administrative burden of PAS remains manageable for all parties involved in their operation, including front-line NHS staff. It is reasonable for the Department to take this issue into account when considering the viability of individual PAS proposals. Priority is likely to be given to PAS proposals that deliver the greatest benefits to patients, for example in enabling the NHS to address a previously unmet need.
  - PAS should be consistent with existing financial flows in the NHS and with commissioning arrangements (e.g. payers must be able to calculate the effective price for their patient population, so the costs and savings accrue to those services making commissioning and treatment decisions.)
- The NHS in England and Wales must be consulted on PAS proposals, in particular where these involve additional data collection beyond that associated with the conventional purchase of medicines – for example in relation to patient numbers, or the monitoring and recording of patient’s condition over and above that for the normal management of a patient. The Patient Access Scheme Liaison Unit (PASLU) at NICE has been established to advise the Department on the feasibility of Patient Access Scheme proposals, and the PASLU process includes arrangements for consultation with the NHS.”<sup>27</sup>

To ensure that these schemes remain manageable they also insisted that these agreements should remain the exception rather than the rule. They also stated that no more than one MEA can be concluded per product, meaning that one agreement should be designed to be applied to all relevant indications and for each enlargement of indications, a new submission will need to be made to the department of health.<sup>27</sup> They currently have 105 MEA, including 83 simple discount scheme or fixed price and 22 more complex schemes (they classified as ‘rebates’, ‘stock supplied at zero cost’, ‘dose capping’, or ‘outcome-based schemes’).<sup>30</sup>

#### *Checklist of McKenna et al.*

McKenna et al.<sup>58</sup> published in 2015 a seven point checklist aimed at standardising reimbursement decisions in the UK and facilitating a common ground for determining if a MEA would be of any value. The seven points/questions read as follows:

- Is the technology cost-effective?
- Are there significant irrecoverable costs?
- Does more research seem worthwhile?
- Is the research possible with approval?
- Will other sources of uncertainty resolve over time?
- Are the benefits of research greater than the costs?
- Are the benefits of approval greater than the costs?



This list gives a general view of the sort of questions McKenna et al. considered in their study. Depending on the answers to all questions, different guidance was provided. For more details the reader can consult the original reference.

The authors applied this checklist to two examples: a non-pharmacological intervention and clopidogrel for patients with non-ST segment elevation acute coronary syndrome. The results highlighted the importance of considering: 1. The expected cost-effectiveness and population net health effects; 2. The need for evidence and whether the type of research required can be conducted once a technology is approved for wide spread use; 3. Whether there are sources of uncertainty that cannot be resolved by research but will resolve over time; and 4. Whether there are significant (opportunity) costs that once committed by approval cannot be recovered.

### France

In appendix 4 of its 2014/2015 annual report, the French “Comité économique des produits de santé” (CEPS) defines 4 prerequisites to conclude a health outcome-based MEA:<sup>33</sup>

- The anticipated, yet unproven, benefit could not reasonably have been demonstrated during the clinical trials carried out prior to marketing authorisation; or, for example, it can only be demonstrated in real-life practice.
- If a benefit exists, it must represent a clear advantage, preferably in terms of public health.
- A study must be developed that, by the end of the fixed-term trial period (generally no more than three years), will allow to unequivocally demonstrate that a benefit exists and the extent of this benefit.
- The medicine manufacturer must agree to conclude a MEA at the end of which he will have to bear, at least partly, financial costs in case of product failure.

These “checklists” were designed as practical and useful starting points for deliberation and add to the transparency and accountability of reimbursement decisions.

### ‘Checklist’ of Bail et al.

Bail et al. in 2013<sup>44</sup> argued that a number of conditions should be fulfilled before a health outcome-based MEA, and more specifically a CED, could be set up. Such conditions included:

- Doubts over the transferability of the clinical trial results to real life practice, (e.g. need for better defining the most appropriate target population to optimise the efficiency of the product).
- Incomplete clinical data in a context of unmet/important therapeutic needs.
- Absence of a comparative study, due to either a lack of an appropriate comparator for a specific indication, or in the context of clinical trials designed at a time when treatment alternatives were not available.
- Need to reduce uncertainties over the medical and economic value of a product, (particularly important in case of an expected large budget impact).

### ISPOR guidelines

In a similar line, a 2013 report by the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force,<sup>6</sup> also drafted recommendations for the development and application of state-of-the-art methods to be used when considering CEDs.

Thus, the ISPOR taskforce recommends that before engaging in expensive and complex CEDs, payers and manufacturers should carefully discuss four crucial aspects:

- The desirability of the scheme (as opposed to some other form of reimbursement or research arrangement),
- The choice of research design,
- The approach to implementation,
- The evaluation method to be used.



### 2.3.5.2 *Evaluating the impact of an already established MEAs*

#### **ISPOR guidelines**

The authors of the ISPOR guidelines go a step further and suggest to also address a number of questions once a MEA ends, in order to be able to evaluate its effectiveness. These include:

- Were the intended outcome measures collected?
- Was uncertainty in associated parameter estimation reduced for the outcomes that were the focus of the scheme?
- Did the scheme run to budget and time?
- Was the integrity of the design/estimation maintained?
- Did the governance arrangements work well?
- Did the process to underpin a decision with further evidence prove successful?

## 2.4 Limitations

Our review is not exempt of limitations. First, our search strategy was not designed to be exhaustive or systematic given the broad nature of the topic, its novelty and the non-standardised terminology linked to MEAs. The purpose of this review was to identify the most common strengths and weaknesses captured in the literature and offer a comprehensive overview of their potential impact, as well as any suggestions on how to overcome the challenges they present.

Given the scarcity of impact evaluations, the authors of this review made a decision to be as inclusive as possible on this regard and to add examples from which lessons could be drawn in order to enrich the informative value of this chapter. This meant that most of the evidence found was mainly descriptive and not usually well backed-up with evidence or examples and when examples were given, not much detail was provided.

Most of the studies found, looked at the strengths and weaknesses of CEDs, given their higher costs but even for these MEAs there was little evidence supporting the facts stated. The main reason for this general lack of detail is likely to be the confidential nature of these schemes, which make it difficult to publish figures on specific MEAs. In addition to this, outcome or usage data captured over a MEA period is hardly ever published and thus, the link between the data obtained in the context of the MEA and the final reimbursement decision is often impossible to make.

The exception to this is the Italian agency AIFA which published costs and revenues obtained via the MEAs they have completed up to date and who also offer data accessibility to the different registries set up in the context of CEDs, encouraging transparency and visibility of financial impact. Nevertheless, accessing and understanding the data is not straightforward and the level of detail offered is not enough for an external researcher to draw clear conclusions.



## 3 DESCRIPTION OF THE LEGISLATION

### 3.1 Introduction

This chapter provides the prerequisites necessary for the proper understanding of the next sections. The aim of this chapter is not to fully describe and analyse the complete process of price settings and reimbursement of pharmaceuticals in Belgium and elsewhere but rather to provide key elements that are needed to be able to evaluate the MEA process.

### 3.2 Method

This section was performed by one researcher (SG) on the basis of previous KCE reports on this topics, completed and updated by exploring legal documents and the website of the National Institute for Health and Disability Insurance (*Rijksinstituut voor Ziekte en Invaliditeitsverzekering (RIZIV) - Institut National d'Assurance Maladie-Invalidité (INAMI)*).

It should be noted that this chapter only describes the process for (i) original (ii) reimbursed pharmaceuticals (iii) for human use. It is also important to mention that this description concerns both outpatient and inpatient pharmaceuticals.

### 3.3 Market authorization, pricing and reimbursement in Belgium (for both outpatients and inpatients pharmaceuticals)

#### 3.3.1 Market authorization

Market authorization can be granted by the European Commission following an opinion by the European Medicines Agency (EMA) via the centralised procedure or by the Federal Agency for Medicines and Health Products (*Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) - Agence fédérale des médicaments et des produits de santé (AFMPS)*) using a national procedure, a decentralized procedure or a mutual recognition procedure.<sup>68</sup>

During the procedure, the quality, safety and efficacy of the product for specific indications is assessed. The EMA publishes a summary of this evaluation via the European public assessment reports (EPAR). It should also be noted that for pharmaceuticals approved via the process of conditional marketing authorization, specific questions and conditions related to data collection are defined.

The centralized procedure is mandatory for:<sup>68</sup>

- Medicines involving biotechnology;
- New medicines for the treatment of cancer, AIDS, neurodegenerative diseases, diabetes, viral diseases, autoimmune diseases and other immune system dysfunctions; and
- Medicines that have been identified as orphan drugs for the treatment of a rare diseases.

For other pharmaceuticals, the manufacturer can choose the procedure. Market authorization of pharmaceuticals in Belgium is under the responsibility of the Minister of Social Affairs and Public Health. In his/her decision the Minister of Social Affairs and Public Health considers the recommendations of the FAGG-AFMPS.<sup>68</sup>

According to the European Directive 2001/83/EC, the procedure cannot take more than 210 days after the submission of a valid application.<sup>69</sup>

#### 3.3.2 Price setting

The maximum ex-factory price of a drug is determined by the Minister of Economic Affairs. Applications for price setting or price increase must be introduced individually by the pharmaceutical company and are mandatory for each package that will be placed on the Belgian market. To take the decision, the Minister of Economic Affairs is advised by the Committee of Pricing for Pharmaceutical Specialties (Commission des Prix des Spécialités Pharmaceutiques (CPSP) –Prijzencommissie voor de Farmaceutische Specialiteiten (PFS)).<sup>70</sup>





For each application, the pharmaceutical company must provide different information, including a justification of the price based on the following cost elements: production, import, analysis, transfer, research and development costs (called the part KP1) and labour, advertising and information, and selling and general costs (called the part KP2).<sup>71</sup> The Federal Public Service (FPS) Economy has nevertheless not enough tools to verify cost elements given by the manufacturer and discussions are currently in progress to improve this.

The decision of the maximum ex-factory price must be based on objective and verifiable criteria. The company may challenge the Minister's decision and in this case must bring new quantitative economic elements to better justify its request. The Minister may reconsider the decision in the light of these new elements.<sup>70</sup>

The pricing decision should in principle depend on the added therapeutic value of a drug and, from a societal point of view, an adequate return on investment. However, a previous KCE report mentioned the following problems:<sup>71</sup>

- The maximum pricing decision is made before the added therapeutic value has been discussed at the CTG-CRM. As a consequence, the maximum price is usually based on the prices of other products in the same therapeutic cluster as the new product (internal reference pricing) and on the prices in other countries (external reference pricing).
- The ministry does not dispose of an estimate of the return on investment. According to the companies, it is impossible to grant more transparency in the pricing. Therefore, the ministry uses prices in other European countries as a reference. A similar process is applied in other European countries. The fact that all countries are looking at each other's prices is not very helpful, as this practice will only lead to companies starting off with asking a high price in the first country they submit their reimbursement request to and to negotiate with the government to keep the high facial price. As companies know that the

only direction in which the price decision goes is downwards, they are actually given an incentive to ask a high price.

In accordance with the EU Transparency Directive, the price decision must be communicated to the applicant within 90 days following the application.<sup>70</sup> The Minister also fixes the maximum distribution margins for the wholesaler and the pharmacist, as well as the maximum public price including T.V.A. (6%). The maximum prices or margins set by the Minister are imperative: they cannot be exceeded. On the other hand, it is always possible for a company to apply prices lower than these maximums.<sup>70</sup>

For class 1 and orphan drugs, it should also be noted that pharmaceutical companies are now authorized to initiate the price-setting procedure as soon as a positive opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) is available and so before that the definitive market authorization is issued. This allows pharmaceutical companies to gain up to 67 days in the price setting process.<sup>70</sup>

### 3.3.3 *The reimbursement procedure*

At the same time, the reimbursement request file is examined by the CTG-CRM, which formulates proposals to the Minister of Social Affairs.

The CTG-CRM is composed of 28 representatives of the sickness funds (8), pharmacists (3), physicians (4), academics (7), pharmaceutical companies (2), the government<sup>c</sup> (3) and the RIZIV – INAMI<sup>d</sup> (1).<sup>72</sup>

The assessment is done by the CTG-CRM board and a group of experts of the RIZIV – INAMI. The assessment slightly varies with the class claim introduced:<sup>71, 73</sup>

- Class 1: the pharmaceutical company claims an added therapeutic value;
- Class 2: concerns claim for pharmaceuticals with similar or analogous therapeutic value;

<sup>c</sup> Representatives of the Ministers of Public Health, Social Affairs, and Economic Affairs.

<sup>d</sup> Representative of the Service for Evaluation and Medical Control of the RIZIV – INAMI.



- Class 3: concerns generics and copies.

For class 1, the assessment covers the scientific analysis of the added therapeutic value. Added therapeutic value is recognised if the pharmaceutical demonstrates an impact on mortality, morbidity and/or quality of life compared to the alternative for the requested indication. If the added therapeutic value is not recognized, a class 2 is assigned. Class 1 pharmaceuticals are allowed a price premium (paragraph 1 of the art. 8 chapter 1 of the Royal Decree of 21 December 2001), i.e. the reimbursement basis is set above those of the comparators based on the added therapeutic value. For Class 2 drugs, the reimbursement basis cannot exceed the reimbursement basis of the comparator with same or analogous therapeutic value (paragraph 2 of the art. 8 chapter 1 of the Royal Decree of 21 December 2001). If there is no reference drug suggested by the applicant, the CTG-CRM fixes one.<sup>71, 73</sup>

Criteria used in the assessment of the reimbursement request are described in Table 6 and as already mentioned, differs according to the class claim. Specific procedures also exist for “orphan” drugs and parallel imported drugs.

**Table 6 – Assessment criteria according to the Class claim<sup>71, 73</sup>**

Criteria	Class 1	Class 2	Class 3
Therapeutic value	X	X	
Drug price and reimbursement basis	X	X	X
Clinical effectiveness and the likely impact of the product, taking into account therapeutic and social needs	X	X	X
Budget impact for the RIZIV – INAMI	X	X	X
Cost-effectiveness	X		

For the evaluation of the therapeutic value, the following five criteria are considered:<sup>71, 73</sup>

- Efficacy: a drug is efficacious if clinical trials demonstrates a better efficacy;
- Safety: the extent to which a drug is free from undesirable side-effects as defined by the Law of 3 July 1969;
- Effectiveness: a drug is effective if it achieves the desired results when provided under usual circumstances of health care practice;
- Applicability: the extent to which the drug characteristics, e.g. contraindications, limit the drug use for certain groups of patients and/or require special precautions;
- Convenience of use: the extent to which the use of the drug by the provider and/or the patient improves administration comfort and/or prevents errors related to drug use.

The evaluation process is limited in time. Since January 2010, the maximum delay has been limited from 90 days to 60 days after the start of the procedure (=day of reception at the secretariat of the CTG-CRM) (see Figure 3).<sup>74</sup> The evaluation report is sent to the applicant, who is invited to express potential remarks and/or objections within a delay of 20 days or longer on specific request of the applicant. In the latter case the remarks need to be sent to the Commission within 90 days following the applicant’s request to suspend the delay. The evaluation of the remarks related correspondence between the CTG-CRM and the applicant takes place at day 120 of the procedure and a preliminary report is then voted on. The applicant can react on this report within 10 days or demand extra time to send remarks and/or objections.

Within 150 days the CTG-CRM votes on the final appraisal report. This report summarizes the results of the appraisal process: e.g. approval or rejection of the Class 1 claim, the reimbursement modalities and time frame and the elements required for the individual reimbursement revision. The reimbursement modalities are defined according to the following four elements:<sup>71, 73</sup>

- The public (or ‘facial’ price) and reimbursement basis (as mentioned in the list of reimbursed pharmaceuticals), i.e. the key variable for calculating the cost-sharing. The reimbursement basis usually equals the public price (except original product in the reference reimbursement



system, for which a reference supplement can be asked). The public price correspond to what we called the ex-factory price + the legally defined wholesaler margin + the legally defined pharmacist margin (no pharmacist margin for inpatient reimbursed pharmaceuticals), increased by value added taxes of 6%.

- The reimbursement conditions, i.e. the conditions restricting the access to reimbursement, e.g. age range, preliminary diagnostic examinations, maximum dosage, etc. Some pharmaceuticals necessitate authorisation of the advisory physician of the sickness funds, i.e. pharmaceuticals in the chapter IV.
- The category of reimbursement, which determines the cost-sharing mechanism. There are five categories (A, B, C, Cx and Cs, Fa, Fb) determining the percentage of reimbursement by the national health insurance.
- The group of reimbursement, i.e. the group of specialties for which similar conditions of reimbursement are applied, based on the therapeutic chemical classification. There are 23 groups in total (see <https://www.inami.fgov.be/webprd/appl/pssp/ssp/rem2/pages/RefundinqGroupList.asp> for more details).

A two-third majority voting rule on approval and rejection is applied, which may result in no proposal at all. Rejection of a proposal implies that a negative advice is sent to the Minister.

In case of no proposition, and only for some pharmaceuticals (see section 3.4 for more details), the applicant can ask for a convention (art. 81). It should also be noted that since July 2014, the CTG-CRM can also directly propose to start a convention procedure “art. 81bis” for some pharmaceuticals (see section 3.4 for more details), if approved by the applicant. The CTG-CRM proposal includes their point of view related to the class, the reimbursement modalities and a description of the uncertainties and the questions they would like to have answers on at the end of the convention.

The motivated positive or negative reimbursement proposal is transferred to Minister of Social Affairs within this limit of 150 days. Then the Minister is responsible for the final decision, which is to be taken before 180 days

following the reimbursement request. It is important to note the following points:<sup>71, 73</sup>

- The Minister is allowed to deviate from the CTG-CRM reimbursement proposal for budgetary or social reasons.
- If the pharmaceutical company does not receive a decision within 180 days, its application for reimbursement is automatically accepted.

The reimbursement decision is valid for the whole country and is implemented after the drug is added on the list of reimbursed pharmaceuticals in the first appendix of Royal Decree of 21 December 2001, by means of a Ministerial Decree in the Official Journal (Belgische Staatsblad - Moniteur belge). The decision comes into force the first day of the month that follows a ten day period after the publication in the Official Journal.<sup>71, 73</sup>

Once inscribed on the list of reimbursed pharmaceuticals, conditions of reimbursements of pharmaceuticals can either be modified or reviewed:<sup>71, 73</sup>

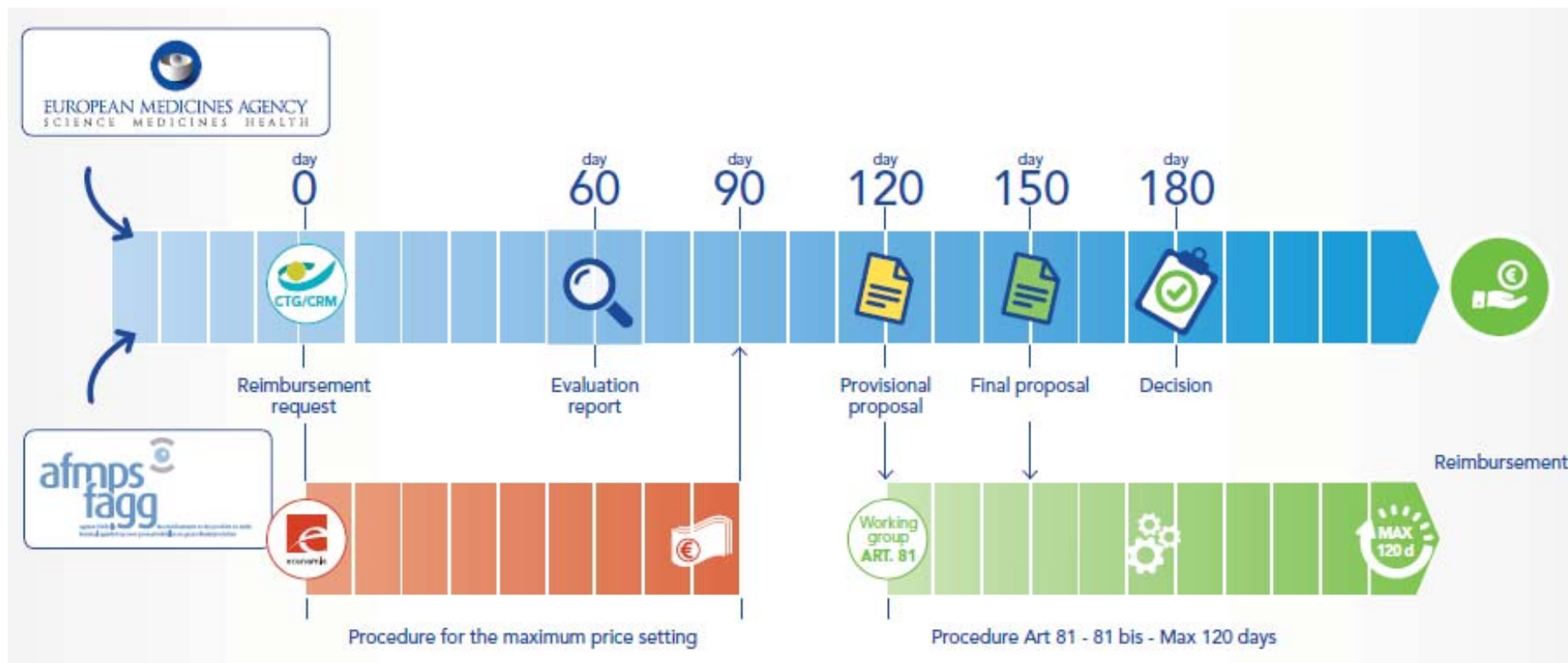
- Modifications concern changes of the reimbursement conditions at the request of the responsible pharmaceutical company, the CTG-CRM or the Minister of Social Affairs. This always concerns an individual file. Proposal of modification must be justified and accompanied by the clinical studies and eventually epidemiologic studies or economic evaluations, published or not published, as well as the scientific reasons that have led to this proposal.
- A revision of reimbursement conditions is done at the request of the CTG-CRM or the Minister of Social Affairs. A revision can either concern a particular pharmaceutical (single revision) or a group of pharmaceuticals for an identical or similar indication (group revision). Drugs in class 1 or orphan drugs must be revised between 18 months and 3 years after their inclusion in the list of reimbursed pharmaceuticals or after modifications of the reimbursement modalities.

Following a revision or modification process, the reimbursement conditions may be changed or remain unchanged. The specialty may also be deleted from the list of reimbursable pharmaceuticals.

The whole process is summarized in Figure 3.



Figure 3 – The reimbursement process





### 3.3.4 Specificities of orphan drugs

To be qualified as orphan drug, a medicine must meet the following criteria:

- “It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- The prevalence of the condition in the EU must not be more than 5 in 10 000 **or** it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.”<sup>75</sup>

Orphan drugs in Belgium are included in Chapter IV of the list of reimbursed pharmaceuticals, meaning that their reimbursement is conditional upon the approval of the advisory physician of the sickness funds.<sup>76</sup>

Because the related pathologies are usually poorly known, a college of physicians for orphan drugs can be established to support the advisory physician. The possibility to ask for an advice of this college is specified in the drug reimbursement modalities and the college is specific to the pharmaceutical. There is, however, not systematically a college for every orphan drug. The decision to establish a college for an orphan drug is taken by the CTG-CRM. It should also be noted that for drugs used in the same pathology, the college is composed of the same people to ensure consistency of advices.<sup>76</sup>

The main tasks of the Colleges are to provide advice to the advisory physicians on individual claims for an orphan drug, to write advice and recommendations on scientific or legal matters for the CTG-CRM or the Special Solidarity Fund, and to propose modifications of the reimbursement modalities.

The colleges are composed of medical experts in the concerned pathology, advisory physicians specialized in regulatory and budgetary aspects mandated by the CTG-CRM, and are headed by a medical specialist and supported by members of the RIZIV – INAMI.<sup>76</sup>

#### Key points<sup>e71, 73</sup>

- **The Minister of Social Affairs is advised by the CTG-CRM for reimbursement decisions. CTG-CRM members include representatives from academics (7), physicians (4), pharmacists (3) and sickness funds (8) (voting members) and representatives from the ministries (3), pharmaceutical industry (2), and RIZIV – INAMI (1) (consultative members). The CTG-CRM is assisted by RIZIV – INAMI and external experts.**
- **Criteria for the evaluation of the reimbursement requests are (added) therapeutic value, drug price and reimbursement basis, clinical effectiveness and likely impact of the product given the therapeutic and social needs, budget impact (and cost-effectiveness).**
- **Economic evaluations (cost-effectiveness) are only required for class 1 drugs. For other classes, orphan drugs or modifications of reimbursement modalities, they are not mandatory.**
- **A two-third majority is required to approve or reject a proposal. This procedure sometimes leads to no proposal at all. In that case and only for some pharmaceuticals (see section 3.4), the applicant can ask for a convention (art. 81).**
- **Since July 2014, the CTG-CRM can also directly initiate a convention for some pharmaceuticals (see section 3.4), if approved by the applicant (art. 81bis).**

<sup>e</sup> Key points mentioned in this report can either be a summary of the section or an attention point that will need to be taken into account in the discussion (performed in the short report).



- In case of a proposal, the Minister may deviate from the proposal for budgetary and social reasons.
- Reimbursement decision must be made within 180 days. Otherwise, the applicant's reimbursement request is automatically enforced.
- Only Class 1 drugs can benefit from a premium that sets the reimbursement basis above those of the comparators based on the added therapeutic value. For Class 2 drugs, the reimbursement basis cannot exceed the reimbursement basis of the comparator with same or analogous therapeutic value. If there is no reference drug suggested by the applicant, the CTG-CRM fixes one.
- Orphan drugs require the approval of the advisory physicians (as other drugs in chapter IV), which can be supported by a college of physicians specific to the orphan drug / disease (if decided by the CTG-CRM).

### 3.4 Evolution of the legislation on MEA in Belgium

In Belgium, MEAs are possible since February 2010 and have the form of 'conventions' (term used in the legislation) concluded between the pharmaceutical companies and the Minister of Social Affairs and Public Health (see Box 8). The procedures, time limits, and conditions of these conventions are outlined in the article 81 and following of the Royal Decree of 21 December 2001. These conventions are national (no differences between regions) and aim to guarantee specific reimbursement and patient's access to the pharmaceuticals until sufficient evidence is available to justify the requested reimbursement basis.

#### Box 8 – Law of July 7, 1994 on Compulsory Health Insurance.<sup>77</sup>

The legal basis for the conventions system can be found in art. 35bis § 7 that has been executed by art. 81 and following of the Royal Decree of 21 December 2001.

Art 35bis § 7 - If the Commission for Reimbursement of Medicines (CTG-CRM) considers the proposed basis for reimbursement disproportionate to the assessment of the criteria mentioned in § 2 or if the CTG-CRM is of the opinion that including the medicine in the list of reimbursable medicines is linked with uncertainties on a budgetary level, the Commission, or the applicant can propose to the Minister to establish a convention with the Institute [...], providing with compensation rules for the compulsory health and disability insurance.

As specified in the public health policy note of October 2008 (see Box 9), the initial objective of these conventions was mainly to reach acceptable ICER for very expensive pharmaceuticals.<sup>78</sup> In the policy note of November 2009, these objectives were also enlarged to all pharmaceuticals with uncertainties (without defining the type of uncertainty).<sup>79</sup>

#### Box 9 – Extract of the public health policy note of October 2008.<sup>78, 79</sup>

2008: ...A new legal basis will be developed to allow individual conventions between the applicant and RIZIV – INAMI for very expensive specialties for which the cost / benefit ratio is not acceptable...

2009: ... The commitment made last year to develop a tool to reimburse innovations even in case where they raise questions in terms of price or uncertainty of some elements of the dossier will be completed in 2010...



### 3.4.1 *Situation from January 2010 until July 2014*

During the procedure for reimbursement requests of pharmaceuticals, applicants could express their wish to the Minister to negotiate a convention with RIZIV – INAMI if the CTG-CRM has not been able to formulate a final proposal within 150 days (no 2/3 in the votes) or if a negative advice was formulated (2/3 voted no). At the request of the applicant, the Minister of Social Affairs and Public Health could allow the negotiation of conventions for the following pharmaceuticals (Article 81 of the RD of 21 December 2001):<sup>73</sup>

- Specialties for which a Class 1 was requested (even if the Class 1 was not approved by the CTG-CRM);
- Orphan pharmaceuticals;
- Specialties (listed or not) for a new indication for which there exists a therapeutic or societal need;
- Specialties for which the reference product (as determined by the commission) is under convention.

### 3.4.2 *Situation from July 2014*

Since July 2014, the CTG-CRM can, with a 2/3 majority vote, directly propose to conclude a convention in the provisional or final proposal (Article 81 bis of the RD of 21 December 2001). From July 2014, a distinction is thus made between art 81 conventions and art 81 bis convention.

#### **Conventions Art. 81**

During the procedure for reimbursement requests of pharmaceuticals, applicants may always express their wish to the Minister to negotiate a convention with RIZIV – INAMI if the CTG-CRM has not been able to formulate a final proposal within 150 days (art. 36 of the RD of 3 June 2014<sup>80</sup>). This is nevertheless not possible anymore in case of negative advice.

Moreover, class 2 requests for which the reference product is under convention were added in the list of authorized pharmaceuticals for art 81 conventions:

- Specialties for which Class 1 was requested (even if the Class 1 was not approved by the CTG-CRM);
- Orphan pharmaceuticals;
- Specialties (listed or not) for a new indication for which there exists a therapeutic or societal need;
- Specialties for which enrollment to the list is requested and the reference product (as determined by the commission) is under convention.
- Specialties for which the therapeutic value is expressed in Class 2 and for which the reference product with a similar therapeutic effect is under convention.

#### **Conventions Art. 81 bis**

As stated above, since July 2014, the CTG-CRM can, with a 2/3 majority vote, directly propose to conclude a convention in the final or the provisional proposal (Article 81 bis of the RD of 21 December 2001). This may be the case if the CTG-CRM judges that the reimbursement proposal is excessive in relation to the criteria of the Art.4 of RD 21 December 2001 (looking at efficacy, safety, effectiveness, applicability, and convenience of use; the price of the specialty and the proposed reimbursement level; the position of the pharmaceutical in medical practice (therapeutic and societal needs); the budgetary impact for the health insurance; and cost-effectiveness) or that including the specialty on the list is accompanied by budgetary uncertainties, often relating to the volume (number of patients that can be treated with the pharmaceutical). Nevertheless, even in this case, the final decision to request a convention to the Minister remains in the hands of the applicant.

It should also be noted that for art. 81 bis conventions, the list of authorized pharmaceuticals slightly differs. The CTG-CRM cannot propose a convention for class 2 pharmaceuticals where the reference specialty is under contract or for new indications for which there exists a therapeutic or societal need if the specialty was not listed. If in such cases a convention is desirable, the only solution is an art. 81 convention, meaning that the CTG-CRM must omit to give an advice.



Art 81 bis conventions is therefore only possible for:

- Specialties for which Class 1 was requested (even if the Class 1 was not approved by the CTG-CRM);
- Orphan pharmaceuticals;
- Listed specialties for a new indication for which there exists a therapeutic or societal need.

### 3.4.3 *The negotiation process*

The applicant has the possibility to address a request to negotiate a convention to the Minister, with a copy sent to the secretariat of the CTG-CRM, within seven days after being informed by the CTG-CRM's secretariat that there is no timely motivated proposal<sup>f</sup> of the CTG-CRM (art 81) or that the conclusion of a convention is proposed (art 81 bis). This request includes elements that justify the appropriateness of negotiating such a convention and a request to suspend the 180-day procedure. This suspension must take no longer than 120 days. If a convention was proposed by the CTG-CRM in the provisional or final proposal (art 81 bis), the applicant must join propositions of budgetary compensations in the request.

The Minister has seven days to judge the admissibility of this request. If the Minister does not take a decision the request is automatically admissible. The 180-day period is then suspended until the day a convention is agreed on or that the Minister notifies the applicant it is not possible to make such an agreement.

RIZIV – INAMI organises working group meetings to discuss the possibility and the modalities to set up a convention. This group is composed of:

- a representative of the Minister of Social Affairs,
- a representative of the Minister of Budget,
- a representative of the Minister of Economics;

- three representatives of the sickness funds and three alternate representatives; appointed by the insurance committee of the RIZIV – INAMI
- two representatives of the applicant;
- a representative of the professionals associations of the pharmaceutical industry; appointed by the applicant
- the chairman or one of the two vice-presidents and/or an academic member of the CTG-CRM.

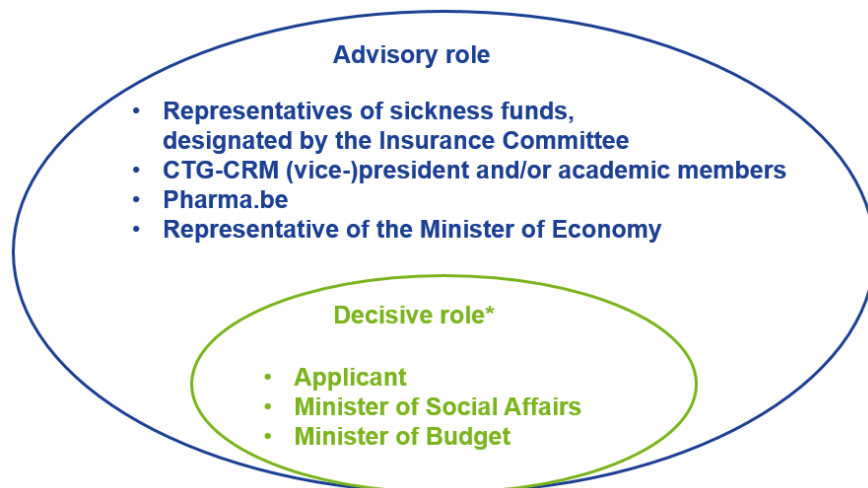
If there was no final proposal of the CTG-CRM, the final assessment report approved by the CTG-CRM serves as a basis for discussions in the working group. The final decision to conclude a convention depends on the agreement of both the Minister of Social Affairs, the Minister of Budget after advice from the Inspector of Finance, and the applicant (see Figure 4). The other members of the working group only have an advisory vote. If no agreement can be closed between the applicant and RIZIV – INAMI, the Administrator General of RIZIV – INAMI informs the Minister and a convention can be concluded between the applicant and the Administrator General. Finally, the Minister takes a motivated decision on the amendment of the list of reimbursable pharmaceuticals. It is mentioned, however, that this inscription is only temporary (T code, see the list of all reimbursed pharmaceuticals published on the RIZIV – INAMI website: <http://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/remboursement/specialites/Pages/specialites-pharmaceutiques-remboursables-listes-fichiers-reference.aspx#.WLa-fk2FOUk>).

<sup>f</sup> or a negative advice before July 2014





Figure 4 – The working group “art 81”



#### 3.4.4 The convention

The convention includes amongst other things the following elements (art. 83):

- the price and reimbursement basis;
- the possible modalities for compensation of the budgetary risks, linked to the proposed reimbursement basis and / or the estimated volume of prescription, i.e.:
  - a refund to RIZIV – INAMI of a percentage of the turnover achieved for this pharmaceutical in Belgium (this rate is modulated in function of the achieved turnover and / or the estimated turnover).
  - a refund to RIZIV – INAMI of an amount corresponding to the whole or part of the difference between the estimated expenditure and the actual expenditure for the pharmaceutical concerned.
  - a reduction of the reimbursement basis of other pharmaceuticals marketed by the applicant, applicable on the date of entry into force of the agreement.

- a refund to RIZIV – INAMI of the difference between the proposed reimbursement basis and the value of the pharmaceutical corresponding to the evaluation criteria of the Article 4 of the Royal Decree of 21 December 2001.

- if appropriate, the terms related to the scientific reporting and evaluation that should be done by the applicant during the period of the convention;
- the modalities regarding the payment of taxes on the turnover and the control by the RIZIV – INAMI;
- the consequences of non-compliance with the convention;
- the reimbursement modalities;
- the modalities concerning the entering into force of the convention, the revision and the possible extension of the convention.

Details of compensation modalities are in the appendices of the convention and are confidential. In July 2016, a new law entered into force to strengthen the confidentiality of these appendices.<sup>81</sup>

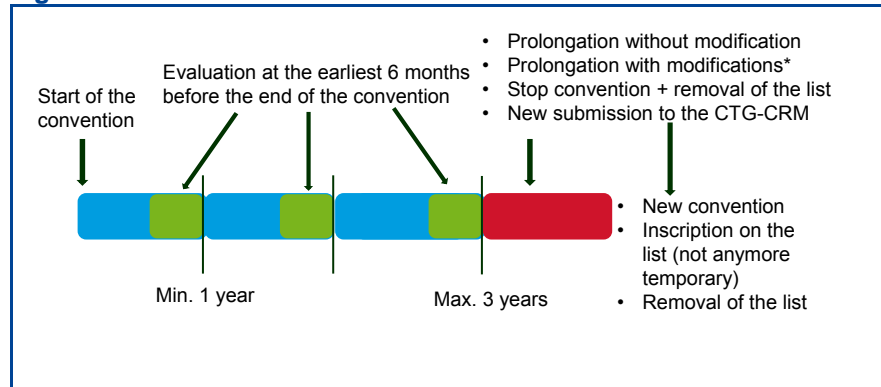
#### 3.4.5 Process at the end of the convention

The conventions are valid for a minimum period of one year and maximum 3 years and may be renewed periodically up to a maximum of three years (see Figure 5). At the earliest six months before the expiration of the convention, RIZIV – INAMI and the working group that prepared the convention evaluate the gathered information and explore the opportunity to prolong the convention with or without modifications, to terminate the convention or to propose the applicant to submit a new application for inclusion on the list. In the latter case, for conventions agreed on before 1 July 2014, a prolongation of max. 1 year (mostly “year 4”) is possible with the possibility to discuss the conditions of the 4th year of convention (e.g. changes in budgetary mechanism as compared to previous year). For conventions concluded after 1 July 2014, prolongation of max. 1 year (mostly “year 4”) is possible without the possibility to discuss the conditions of the 4th year of convention. In this case the conditions valid in “year 4” are identical to the conditions in the last year of the convention (mostly “year 3”). The decision to prolong the convention depends on the agreement of both the Minister of Social Affairs, the Minister of Budget after advice from the



Inspector of Finance, and the applicant. The other members of the working group only have an advisory vote.

**Figure 5 – Process at the end of the convention**



\*For conventions concluded after 1 July 2014, prolongation of max. 1 year (mostly "year 4") is possible without the possibility to discuss the conditions of the 4th year of convention.

### 3.5 No regulation of MEAs in a European context

Although MEAs are implemented at country level, it is important to see them in a European (EU) dimension. The Directive relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems (Transparency Directive) mainly aims to ensure the transparency of measures established by EU countries to control the pricing and reimbursement of medicinal products.<sup>82</sup> It defines a series of procedural requirements designed to verify that national pricing and reimbursement decisions do not create obstacles to the pharmaceutical trade within the EU's Internal Market. Major requirements with respect to individual pricing and reimbursement decisions are the following:

- decisions must be made within a specific timeframe (Rule = 90 days from receipt of application for decisions on prices and 90 days for decisions on reimbursement schemes or 180 days for both pricing and reimbursement decisions altogether);

- decisions must be communicated to the applicant and contain a statement of reasons based on objective and verifiable criteria;
- decisions must be open to judicial appeal at national level.

Currently, no unified regulation on MEAs exists nor is such a regulation anticipated at the European level. In 2012, the Commission proposed a new Directive to replace the longstanding Transparency Directive.<sup>83</sup> The aim was to streamline and reduce the duration of national decisions on pricing and the reimbursement of medicines. Article 1.2 (a) of the European Parliament Legislative Resolution on the proposal for the New Transparency Directive expressly excluded MEAs from its scope.<sup>84</sup> The exclusion reflected the need for a flexible legal framework that can be tailored to the characteristics and specificities of each national system that allows a.o. parties to negotiate MEAs within the time they need to achieve a successful agreement. With regard to transparency of information regarding medicinal products in MEAs, the proposal for a new Transparency Directive stated that "*In accordance with Union and national law regarding business confidentiality, basic information regarding medicinal products included in contractual agreements or public procurement procedures, such as the name of the product and the name of the marketing authorisation holder, shall be made publicly available once agreements or procedures are concluded*" (1.2 (b) of the proposed Directive<sup>83</sup>). There was no mention of the price among the information to be made public. This issue is subject to national regulations on confidentiality. Yet, the proposal for a New Transparency Directive was withdrawn in March 2015.



## 4 ANALYSIS OF THE BELGIAN PROCESS FOR MEA: WHAT LESSONS CAN BE LEARNED FROM THE BELGIAN EXPERIENCE?

### 4.1 Introduction

This chapter aimed at responding to the following research questions:

- Which kind of MEAs were concluded in Belgium up to now and what are the possible practical problems with each type of convention in the Belgian context?
- Which uncertainties and/or problems were addressed, how were they addressed and to what extent were these uncertainties and/or problems resolved?
- Which conditions were imposed in the conventions and to what extent were these conditions respected?
- What were the results of the MEAs already expired? Were the initial objectives reached? What was the impact of these conventions on the reimbursement negotiation process that followed from them?

### 4.2 Method

A list of all convention procedures that started between 2010 and 2015 was provided by the RIZIV – INAMI on November 2015. From this list, only the procedures that led to a convention signed before this date were selected for analysis.

The following analytical method was applied:

- Development of an in-house data extraction sheet: two French-speaking researchers (SG-LS) and two Dutch-speaking researchers (MN-IV) analysed all available information on three French and three

Dutch conventions respectively. The whole process was analysed, i.e. from day 0 (submission date by the applicant) until the current situation. Based on this analysis, a common in-house data extraction sheet and a summary table were developed. The data extraction sheet contained every interesting detail, divided by stage of the reimbursement process: report 60, provisional proposal, final proposal, convention, and new submission process.

- Development of a summary table: from the data extraction tools, each researcher identified all topics of interest for this report. A common summary table highlighting all these topics was developed during a brainstorming meeting with all researchers. These topics were then presented to one president of the working group in charge of the negotiations on MEAs in Belgium and to the head of the directorate of pharmaceutical policy and administrator of the CTG-CRM of the RIZIV – INAMI in order to detect any missing points.
- Analysis of all conventions using these data extraction sheets and summary tables by two researchers (SG-MN), in their mother tongue.
- Presentation of results to stakeholders in face-to-face meetings (see section 5).

It should be recalled that these analyses are only based on public information and that details on compensation mechanisms were confidential. It was therefore not possible to respond to all research questions (see also Table 7).

It should also be noted that most percentages presented in this section come from a manual analysis done by the authors from the reading of CTG-CRM reports. These percentage must therefore be used with caution because it is possible that some important elements were not reported in these documents (only orally discussed or only discussed during the working groups from which notes were not public because of their confidential content) or that the expert missed the information.



Table 7 – Research questions and methods

Research question	Parameters	Method and feasibility
<ul style="list-style-type: none"> <li>Which kind of MEAs were concluded in Belgium up to now and what are the possible practical problems with each type of convention in the Belgian context?</li> </ul>	<ul style="list-style-type: none"> <li>Number and type of conventions (see section 4.3.3.3).</li> <li>Discussion on the practical problems (in the short report)</li> </ul>	<ul style="list-style-type: none"> <li>Type of convention: Without access to the appendices of the conventions describing the compensation mechanisms, we were unable to analyse this question in details. Only the number of convention is available.</li> <li>Practical problems: Opinion of the research team + stakeholders interviews</li> </ul>
<ul style="list-style-type: none"> <li>Which uncertainties and/or problems were adressed, how were they adressed and to what extent were these uncertainties and/or problems resolved?</li> </ul>	<ul style="list-style-type: none"> <li>A list of all uncertainties and problems identified by the CRM-CTG (see section 0).</li> <li>An analysis between the type of conventions and the uncertainties and problems identified by the CTG-CRM (not possible).</li> <li>For conventions that already finished (see section 3.4.5): a comparison between the uncertainties and problems identified by the CRM-CTG in the first process and their 'resolution' at the end of the process.</li> </ul>	<ul style="list-style-type: none"> <li>This list was not based on pre-assumed uncertainties and problems. A qualitative analysis was performed by identifying all passages in the CTG-CRM reports that mentionned a problem or an uncertainty. Categories were then define afterwards.</li> <li>Without access to the appendices, it was not possible to determine if the type of convention corresponded to the identified uncertainties / problems. A theoretical exercise can be found in the short report.</li> </ul>
<ul style="list-style-type: none"> <li>Which conditions were imposed in the conventions and to what extent were these conditions respected?</li> </ul>	<ul style="list-style-type: none"> <li>An analysis of the conditions mentioned in the appendices of the conventions.</li> </ul>	<ul style="list-style-type: none"> <li>Without access to the appendices, neither the conditions nor the respect of these conditions could be analysed.</li> </ul>
<ul style="list-style-type: none"> <li>What were the results of the MEAs already expired? Were the initial objectives reached? What was the impact of these conventions on the reimbursement negotiation process that followed from them?</li> </ul>	<ul style="list-style-type: none"> <li>Analysis of the budget impact and 'savings' (see section 4.3.5).</li> <li>Analysis of the 'data collected' (see section 4.3.3.4)</li> <li>Analysis of the new reimbursement process (see section 4.3.4)</li> </ul>	<ul style="list-style-type: none"> <li>The RIZIV – INAMI evaluation report of the convention is not available. Only the new submission file and evaluation report (day 60) could be analysed.</li> <li>Details on refunds are not available per convention (only a total amount is given).</li> </ul>



## 4.3 Results

### 4.3.1 Description of the convention procedure

#### 4.3.1.1 Number of procedures and evolution across the years

From the introduction of conventions until 25 November 2015, a total of 127 procedures were launched (see Table 8). Procedures that were still in negotiation on the 25<sup>th</sup> of November 2015 or that finished with a refusal were excluded from the analysis, resulting in an analysis of 74 procedures.

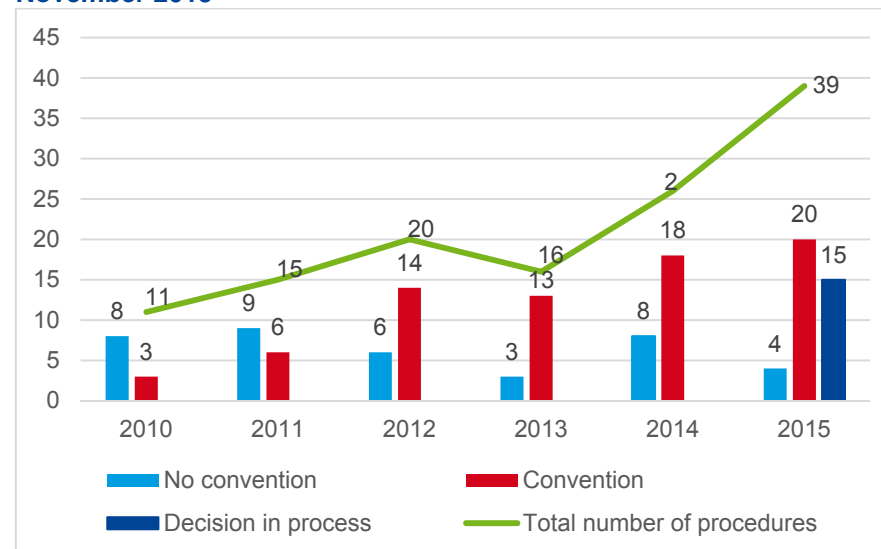
It should be noted that among the 74 approved procedures, in three cases two procedures resulted in one and the same convention, resulting in a total number of 71 conventions.

**Table 8 – Situation on 25 November 2015**

Status of convention procedures	N
<b>Total number of procedures</b>	127
<b>Decision in progress</b>	15
<b>No convention concluded</b>	38
<b>Approved conventions</b>	74
<b>Convention still in progress</b>	63
<b>Closed conventions</b>	11

Figure 6 shows an increase in the number of convention requests throughout the years.

**Figure 6 – Number of convention requests between 2010 and 25 November 2015**

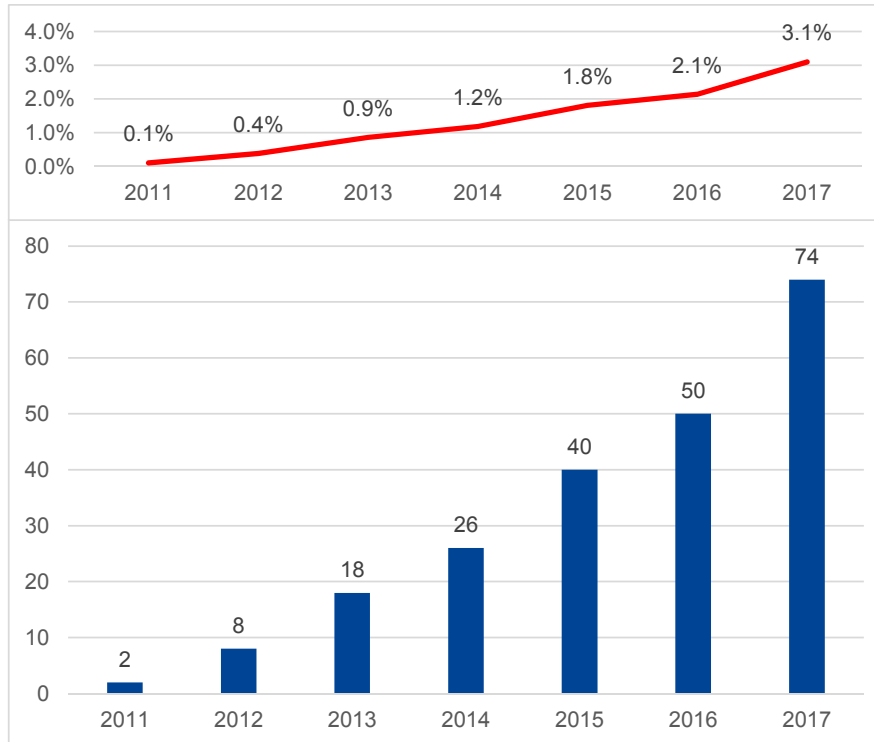


Based on the date from which the normal procedure was suspended and the convention procedure was launched

We also analysed the share of pharmaceuticals (based on the brand name) under convention in the total number of reimbursed pharmaceuticals on the first of January of each year (from 2011 because there was no product under convention on January 1, 2010). As shown in Figure 7, the share of pharmaceuticals under convention in the list of reimbursed pharmaceuticals increased over the years.



**Figure 7 – Number and share of pharmaceuticals (brand name) under ongoing conventions on the list of all reimbursed pharmaceuticals (situation on January 1 of each year)**



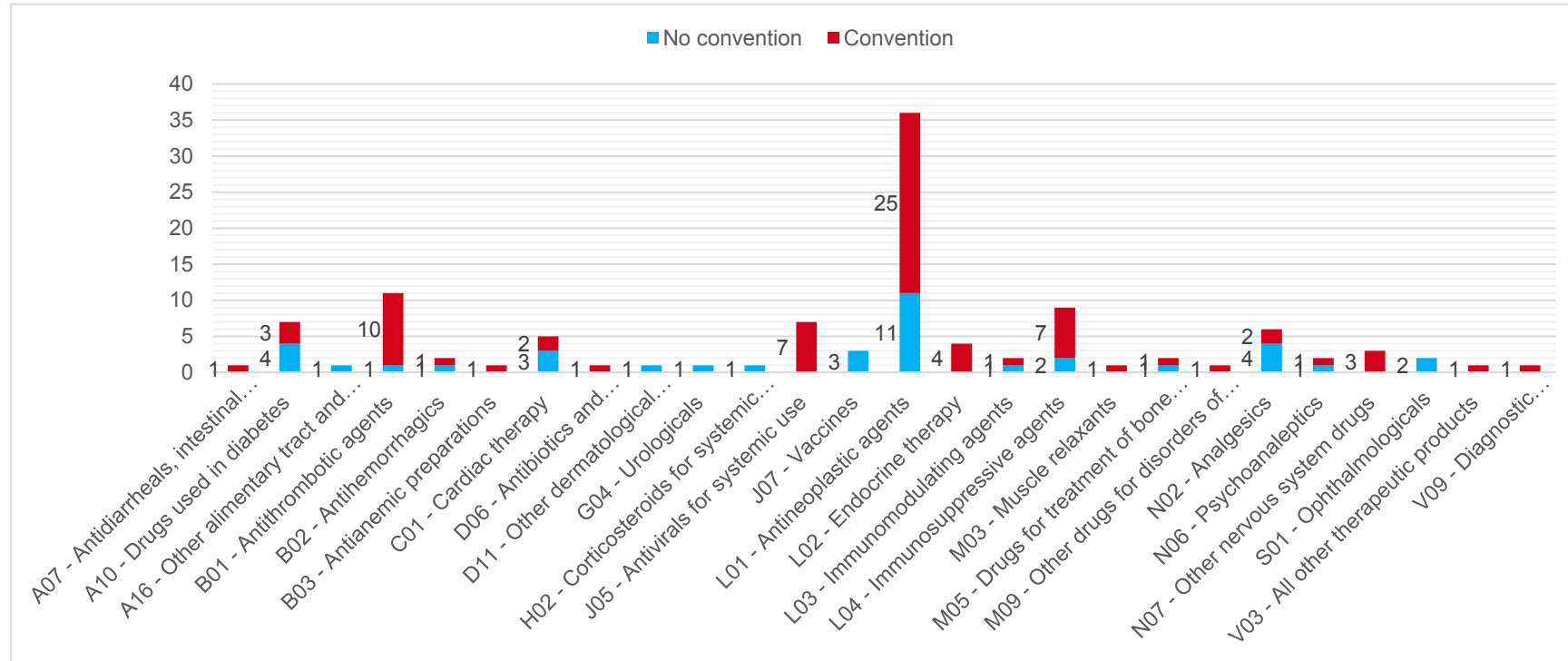
*Analysis based on the brand name (grouping all diverse doses/packaging of the pharmaceutical). This means that if a pharmaceutical had at least one packaging under convention for at least one of its indication(s), the pharmaceutical / brand name was considered as under convention. It should also be noted that a pharmaceutical / brand name may have more than one convention (e.g. for different indications) explaining the differences with the total number of conventions described at the beginning of this section)*

#### 4.3.1.2 Types of therapies

The most approved conventions concerned antineoplastic agents (n = 25), followed by antithrombotic agents (n = 10) antivirals for systemic use (n = 7), and immunosuppressive agents (n = 7, see Table 9). The most refused conventions also concerned antineoplastic agents (n = 11), followed by drugs used in diabetes (n = 4) and analgesics (n = 4). It should also be noted that all of the 3 procedures for vaccines and the 2 procedure for ophthalmological resulted in no convention.



Table 9 – ATC codes



A07 - Antidiarrheals, intestinal antiinflammatory/antiinfective agents; A10 - Drugs used in diabetes; A16 - Other alimentary tract and metabolism products; B01 - Antithrombotic agents; B02 - Antihemorrhagics; B03 - Antianemic preparations; C01 - Cardiac therapy; D06 - Antibiotics and chemotherapeutics for dermatological use; D11 - Other dermatological preparations G04 - Urologicals; H02 - Corticosteroids for systemic use; J05 - Antivirals for systemic use; J07 - Vaccines; L01 - Antineoplastic agents; L02 - Endocrine therapy; L03 - Immunomodulating agents; L04 - Immunosuppressive agents; M03 - Muscle relaxants; M05 - Drugs for treatment of bone diseases; M09 - Other drugs for disorders of the musculo-skeletal system; N02 - Analgesics; N06 - Psychoanaleptics; N07 - Other nervous system drugs; S01 - Ophthalmologicals; V03 - All other therapeutic products; V09 - Diagnostic radiopharmaceuticals



#### 4.3.1.3 Class asked by the manufacturer

Most procedures concerned requests for class 1 pharmaceutical products (48%), followed by modifications of reimbursement (26%), and orphan drugs (19.7%). Requests for class 2 products concerned a minority of demands (6.3%). It can easily be assumed that conventions for class 1 drugs and for orphan drugs respect the initial objective of improving patient access to innovative drugs. This is nevertheless less evident for modifications of reimbursement and for class 2 drugs.

For requests for class 2 drugs, an alternative product was under convention for all of them, justifying the convention as allowed by the law (see section 3.5). Even if this is justified by the fact that it is not possible to align the prices of two products if the actual price of one of them is confidential, this does not meet the core objectives of MEAs (reducing uncertainty about (cost-)effectiveness and budget impact and improving patient access to innovative drugs). This modification of law for class 2 pharmaceuticals has also the unwanted consequence of leading to a system that will essentially be based on conventions in the future, with the risk that MEAs in Belgium become the rule rather than the exception. This may have an impact on the human resources needed for concluding conventions, as the convention system is rather time consuming and resource intensive.

A similar remark can be made for modifications of reimbursement. On the basis of the reports of the CTG-CRM (report 60, provisional / final proposals), it was not always clear if the modification asked showed an added therapeutic value or if there was a therapeutic or societal need. A clear definition on what is a therapeutic or societal need is lacking. The Commission for Advice in case of Temporary Reimbursement of a drug (CATT-CAIT) at the RIZIV – INAMI, which decides on the temporary financial contribution for the use of products for high unmet needs which have not received market authorization yet, already uses operational definitions of therapeutic and societal need. These definitions, with explicit criteria, could be considered also in the context of reimbursement decision making.<sup>85</sup>

Finally, it should also be noted that in 30% of the approved conventions for products for which a class 1 was asked by the applicant, this class was not recognized by the CTG-CRM in the provisional / final proposal. Indeed, the law specifies that conventions can only be made for products for which the applicant has requested a class 1. It does not say, however, that this class must also be granted by the CTG-CRM. The criteria to accept a convention should be based on characteristics recognized by the CTG-CRM and not on what the applicants claim for. It should nevertheless be noted that such percentage is uncertain because the analysis was manually done by the experts based on the reading of CTG-CRM reports. Furthermore, it is not possible to make a distinction between a rejection of a class request because 1) there is good evidence showing there is no added value, versus 2) there is insufficient reliable evidence to determine the added value. It should also be noted that in one case, the class 1 was first in doubt and then accepted with a restriction of the reimbursement criteria on the target population.

**Table 10 – Number of procedures for conventions per class of pharmaceutical products asked by the applicant**

	No convention	Convention	In progress	Total
<b>Class 1</b>	16	41	4	61 (48%)
<b>Class 2</b>	3	3	2	8 (6.3%)
<b>Modifications</b>	10	18	5	33 (26%)
<b>Orphan drugs</b>	9	12	4	25 (19.7%)
<b>Total</b>	38	74	15	127





## Key points

- **Most convention procedures (32%) concerned cancer drugs**
- **In some cases, a convention was approved even if the class 1 claimed by the firm was not approved by the CTG-CRM. The reason for rejecting the class 1 request should be made explicit with e.g. a distinction between 1) having evidence showing there is no sufficient added value, versus 2) there is insufficient reliable evidence to determine the added value. The first case is a 'problem', the second case an 'uncertainty'.**
- **To improve the transparency of the MEA system without neglecting its objective of improving patient's access:**
  - **Criteria to accept a convention should be based on characteristics recognized by the CTG-CRM and not on what the applicant claims for.**
  - **For modifications of reimbursement, clear criteria that would justify a convention should be defined. Objective criteria to identify a therapeutic or societal need should be defined. The criteria used by the unmet needs commission at the RIZIV-INAMI (CATT-CAIT) could be considered for this purpose.**
  - **The possibility of convention for class 2 drugs or for class 1 drugs for which the added therapeutic value was not recognized (evidence of no sufficient added value) should be questioned and alternatives should be examined (see also section 0).**
- **If the system is maintained as today, it can be expected that MEAs in Belgium will become the rule rather than the exception with the following consequences:**
  - **Reduced transparency of the system**
  - **Necessity to enlarge the current structure / workforce to be able to properly respond to these increasing demands**

## 4.3.2 The evaluation by the CTG-CRM

### 4.3.2.1 An increasing role of the CTG-CRM

As stated in section 3.4, before July 2014, a convention could be concluded even if the CTG-CRM had formulated a negative advice. Table 11 shows that among the 61 procedures that followed a negative advice of the CTG-CRM before July 2014, 31 of them obtained a convention (51%).

On the one hand, this could imply an increase in patient access because without the convention the pharmaceutical would not have been on the market. On the other hand, before the existence of the convention system, the applicant sometimes directly negotiated with the Minister in case of a negative decision. It is therefore difficult to analyse the level of improvement in access. Compared to the traditional procedure before 2010 (i.e. before the possibility to have a convention), negotiations now have a more structured framework within a working group with different stakeholder representatives. Another difference is the confidentiality of the negotiated price, which was not possible before the system of convention.

The reasons for a negative reimbursement advice by the CTG-CRM for pharmaceuticals that finally obtained a convention were also analysed and showed that these reasons were mostly financial (the price was not in relation with the therapeutic value or it concerned an extension of indication without reduction of the price). The distinction between refusals for clinical (no efficacy) or financial (price not in relation with the therapeutic value) reasons was, however, often not clear. More precisely, it was not clear whether the CTG-CRM considered that this product should not be reimbursed or whether it could be reimbursed with appropriate compensation mechanisms.

After July 2014, the process was improved:

- Conventions were no longer allowed in case of a negative advice by the CTG-CRM ;
- Conventions are only possible following a no timely proposition of the CTG-CRM or a direct proposal of the CTG-CRM (even if the applicant remains the initiator of the demand, see section 3.4.2). In the latter cases, problems – uncertainties to be covered are usually mentioned.



This means that the CTG-CRM now is more active in the convention decision and tries to assess from the beginning whether a convention will be able to handle the problems and/or uncertainties related to a product. Members of the CTG-CRM (with a voting right) have now more influences if they consider that problems or uncertainties they identified would not be resolved by a convention (by giving a negative reimbursement advice).

Nevertheless, the identification of all uncertainties and problems identified by the CTG-CRM was not always straightforward, especially in cases of no proposition. A specific section in the provisional and final proposals summarizing the identified problems and uncertainties, their importance as well as propositions to resolve them could serve as starting point for the negotiation process and would yet improve the impact of the CTG-CRM on the convention decisions.

Specific attention should also be paid to the conditions relating to evidence collection imposed by the EMA for pharmaceuticals approved via the process of conditional marketing authorization. An evaluation of the extent to which the conditions are met should be made, as well as the remaining issues. The conclusions of the European Public Assessment Report (EPAR) with respect to the benefit-risks of the pharmaceuticals should also be considered carefully (see also section 3.3.1).

**Table 11 – Decision of the CTG-CRM**

	No convention	Convention	Total
<b>Decision of the CTG-CRM (before July 2014)</b>			
• Negative	30	31	61
• No proposal	4	28	32
<b>Decision of the CTG-CRM (After July 2014)</b>			
• No proposal	1	1	2
• Contract (art 81 bis)	3	14	17
<b>Total</b>	<b>38</b>	<b>74</b>	<b>112</b>

#### 4.3.2.2 Arguments used during the price negotiation and the use of an ICER

In the provisional proposal, discussions on the required price reductions were included, based on arguments such as:

- The incremental cost-effectiveness ratio (ICER) and an threshold;
- A sharing of additional budget impact for extension of indications between RIZIV – INAMI and the applicant (rule 1/3 - 2/3: the company pays 1/3 of the additional cost related to this extension of indications, the RIZIV – INAMI pays 2/3);
- A cost match with the comparator (in cases where no added therapeutic value was recognized).

Such discussions, with the use of objective arguments, should also be used as starting point during the negotiation of conventions.

Concerning the use of the ICER, a previous KCE report on threshold values for cost-effectiveness in health care concluded that “*ICER threshold value against which the ICERs of interventions should be compared is unknown and is variable over time*”.<sup>86</sup> Nevertheless, they also added that “*it is not an argument against the use of economic considerations in health care decision making*”.<sup>86</sup> The following recommendations were done in this previous reports:

- “*Cost-effectiveness should be a criterion in the decision making process, as ignoring economic efficiency is unethical. Dossiers submitted to support policy makers should therefore always include an economic evaluation.*”
- “*Economic models should be reported in a transparent way, presenting all information used in the model in a way that allows the policy makers to verify the assumptions, view the uncertainties and weigh the importance of the assumptions and uncertainties for the decision. Transparency and control of economic models is crucial to increase their credibility.*”



- *The results of economic evaluations should be presented in disaggregated form. This includes “unpacking” the ICER but also presenting other economically relevant outcome parameters that can be derived from the economic evaluation but that are not necessarily visible in the ICER estimate.*
- *Alongside the disaggregated presentation of economically important elements, also the ICER should continue to be presented, calculated following standard methodological guidelines.*
- *Scientific research should continue to be used in the decision making processes on the allocation of health care resources. It will allow policy makers to back up arguments in favour of or against a particular decision by scientific evidence.*
- *Decision makers should be more transparent in their decision making criteria and the relative importance of the different criteria in each decision”.*<sup>86</sup>

It should also be noted that for modifications of reimbursement (enlargement of indications) and for orphan drugs, a cost-effectiveness evaluation is not legally required (see also section 3.3) and was usually not done. For enlargement of indications, even if the first indication had an acceptable ICER, it is not necessarily the case for the new indication and this need to be taken into account in the decision. Also for orphan drugs, even if the uncertainty around the input variables might be much higher, the evaluation of the ICER also remains a key parameter.

### Key points

- **The impact of the CTG-CRM on the convention decision has been improved since 2014 (conventions are not possible anymore in case of a negative reimbursement decision). Their role would yet be improved by a clear identification of problems and uncertainties in a specific section.**
- **For orphan drugs and enlargement of indications, an economic evaluation should also be legally required and be used as an evaluation criterion.**

### 4.3.3 Analysis of approved conventions

#### 4.3.3.1 Conventions' duration

The median duration of the approved conventions including prolongations was 36 months (with a maximum of 48 months). At the end of the convention, a prolongation of 1 year is usually given to cover the new submission process (see also section 3.4.5). Most of the conventions (62%) had a duration of at least 3 years.<sup>9</sup> The total duration can be longer than 4 (3+1) years since at the end, a new (similar) convention can be closed for another 3 years.

For approved conventions, the mean duration between the submission by the firm (Day 0) and the day the convention entered into force was 383 days (median time 362)<sup>h</sup>. The average and median time between the day 0 and the day the convention entered into force was slightly shorter after July 2014 (i.e. an average of 392 days and a median of 370 days before July 2014 versus an average of 356 days and a median of 331 days after July 2014).

<sup>9</sup> Based on the situation in November 2015. Additional prolongations after this date are not taken into account.

<sup>h</sup> It should be noted that the Day 0 for the first convention was 2006, resulting in a duration of 1443 days.



#### 4.3.3.2 *Uncertainty and problems identified*

All uncertainties and problems identified in the different reports of the CTG-CRM (report 60, provisional proposal, definitive proposal) are summarized in Table 12 and Figure 8 (multiple uncertainties and problems were possible for each contracts).

As shown in Figure 8, they mainly concerned cost-effectiveness aspects (price not in relation with the therapeutic value - high ICER) or budget uncertainty (uncertainty on the volume or on the total cost related to use).

It should also be noted that, in the period 2010-2015, in around 30% of all conventions (percentage to use with caution<sup>i</sup>), no added therapeutic value was mentioned in the reports while a convention was still concluded. In these cases, the necessity of a convention should be questioned. We analysed these conventions more in detail and found that even if they thought there was no added value, they recognized that there remained uncertainties in 33% of these conventions (no direct comparison, doubts about the target population, about the optimal treatment schemes, or about the impact on quality of life). For other cases, the comparator was under convention (24% of cases) or the CTG-CRM had given a negative reimbursement proposal (43%).

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<sup>i</sup> Percentages presented in this section come from a manual analysis done by the authors from the reading of CTG-CRM reports. These percentage must therefore be used with caution because it is possible that some important elements were not reported in these documents (only orally discussed or only discussed during the working group from which notes were not public because of their confidential content) or that the expert missed the information.

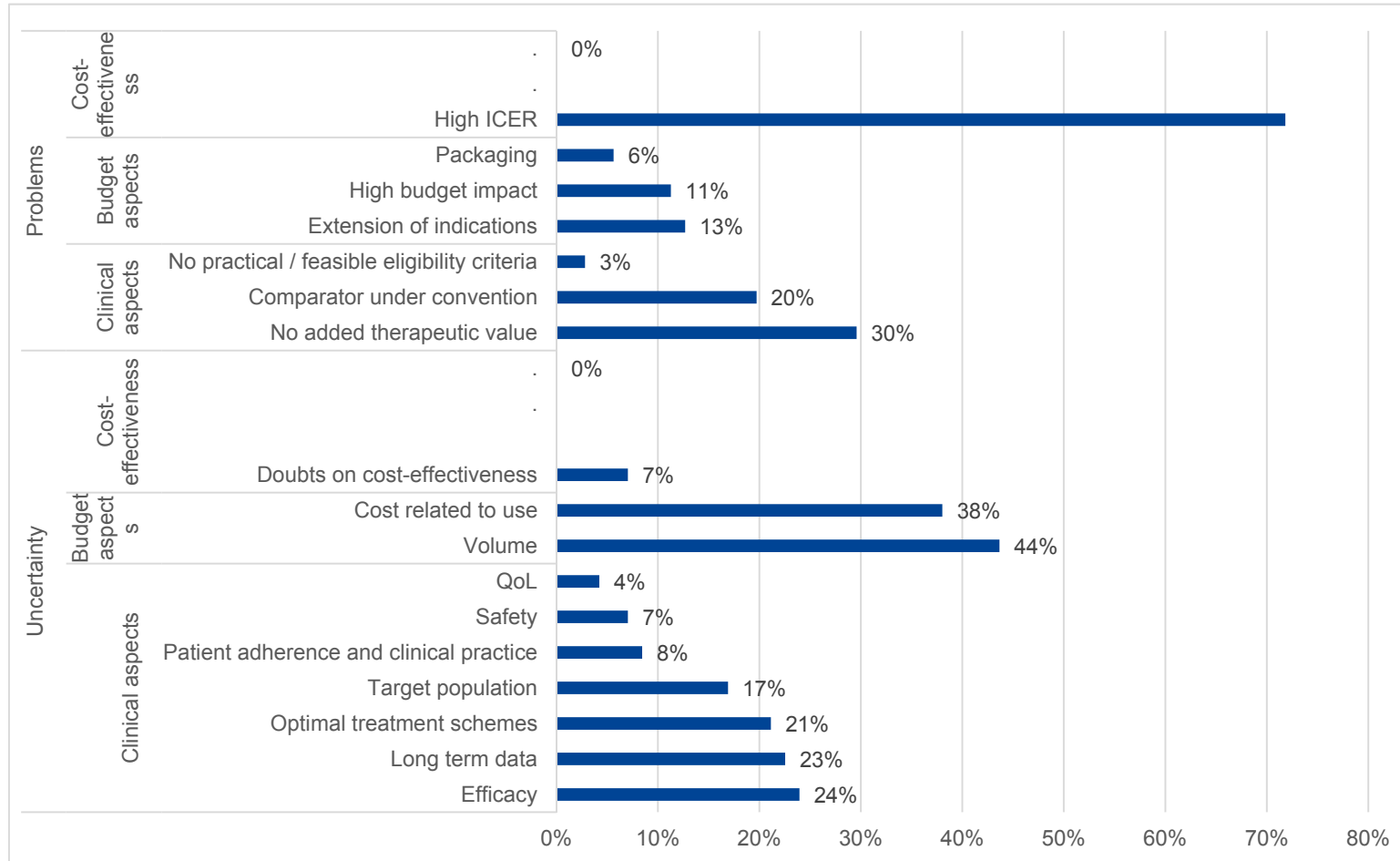


Table 12 – Problems and uncertainties identified

Evaluation criteria	Uncertainty	Problem / issue
<b>Clinical evidence</b>	<ul style="list-style-type: none"> <li>• <b>Efficacy:</b> More robust clinical evidence on the added therapeutic value is needed or more robust clinical evidence on direct comparison with the appropriate alternative is needed.</li> <li>• <b>Safety:</b> More robust clinical evidence on safety is needed.</li> <li>• <b>Long term data:</b> More robust clinical evidence on long term effects is needed.</li> <li>• <b>Patient adherence and clinical practice:</b> There are doubts about the effect in real life because of concerns about wrong use in clinical practice or bad patient adherence.</li> <li>• <b>QoL:</b> More robust evidence on the quality of life impact is needed.</li> <li>• <b>Target population:</b> Not clear who is likely to benefit most from the treatment or if there are biomarkers to identify them.</li> <li>• <b>Optimal treatment schemes:</b> Not clear which duration (e.g. stopping rules), doses, or drug combinations are optimal.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>No added therapeutic value:</b> A class 1 is claimed by the applicant but is not accepted by the CTG-CRM and the product is more expensive than the comparator (while this comparator is not under convention).</li> <li>• <b>Comparator under convention:</b> (i) A class 2 is claimed by the company (i.e. no added therapeutic value) and the comparator is under convention or (ii) a class 1 is refused by the CTG-CRM and the comparator is under convention.</li> <li>• <b>No practical / feasible eligibility criteria:</b> Patients who are likely to benefit most are not (easily) identifiable in practice (e.g. not all hospitals have the capacity to perform the most appropriate test that would allow to identify the appropriate target population).</li> </ul>
<b>Price</b>	<ul style="list-style-type: none"> <li>• For 'price', the problems are already reflected under the criteria 'Budget impact' and 'cost-effectiveness'.</li> </ul>	
<b>Importance of the specialty in the medical practice</b>	<ul style="list-style-type: none"> <li>• For this evaluation criterion, it is not exactly a problem or uncertainty that is identified, but rather an opinion is given on this aspect.</li> </ul>	
<b>Budget impact</b>	<ul style="list-style-type: none"> <li>• <b>Volume:</b> Not clear how many patients will be eligible for the treatment and/or what will be the market share of the product (also influenced by the behavior of the prescribing physicians, which is difficult to predict).</li> <li>• <b>Costs related to use:</b> (i) Treatment duration and doses that will be given in practice are not clear; or (ii) the cost of associated therapies, of potential (avoided) complications or other (avoided) health care costs are not sufficiently known.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>High budget impact:</b> The budget impact is considered too high according to the expected number of patients (high number of patients and/or high costs even if the price is in relation with the added therapeutic value).</li> <li>• <b>Inappropriate packaging:</b> The drug packaging is not adapted to the recommended treatment schedule (waste).</li> <li>• <b>Extension of indication:</b> Indications are extended and no reduction in price is proposed by the company while reductions are asked for by the CTG-CRM.</li> </ul>
<b>Cost-effectiveness</b>	<ul style="list-style-type: none"> <li>• <b>Cost-effectiveness:</b> The "value for money" of the intervention is unclear or there are discussions on the way it was addressed. This uncertainty can be due to a combination of several of the above uncertainties (e.g. related to the size of the (uncertain) treatment effect, impact on QoL, (avoided) costs for complications or other health care costs, etc.).</li> </ul>	<ul style="list-style-type: none"> <li>• <b>High ICER:</b> The ICER is considered as too high by the CTG-CRM or no ICER is calculated and CTG-CRM considers the price not being in relation with the therapeutic value of the product.</li> </ul>



Figure 8 – Uncertainties and problems related to 71 approved conventions (2010-2015 period)



ICER: Incremental cost-effectiveness ratio; QoL: Quality of life. NB: These percentages should be used with caution (see the method description).



### Key points

- **No added therapeutic value was recognized for 30% of contracts, putting in question the necessity of a contract in these cases (percentage to be used with caution).**

#### 4.3.3.3 Type of conventions

According to the European report on MEAs performed by the EMI-net group and the LSE, Belgium mostly concludes financial-based agreements.<sup>15</sup> The type of convention as mentioned in the article 3 of the public part of the conventions confirms such a finding, i.e. the focus seems mostly financial and the determination of refunds seems mostly set globally (i.e. not at the patient level; see Table 13). Nevertheless, if we look at the uncertainties and problems highlighted in Table 12

, financial-based agreements on a population level intuitively does not always seem to be the most appropriate type of convention. Even if the way refunds are calculated could allow to resolve partly some uncertainties and problems, the review of the literature shows that other types of conventions could be appropriate (e.g. health outcome-based agreements). These percentages should be interpreted with caution since it is possible that the discount in a financial-based agreement is based on an outcome such as the percentage of non-responders. Not all financial-based agreements are thus purely financial based.

Because we had no access to the appendices of the conventions (including details on the compensation mechanisms), it was not possible to analyse more in detail the type of conventions that were concluded.

It should also be mentioned that in the 'pact for the future' closed between the Minister of Social Affairs and Public Health and the pharmaceutical industry, it is mentioned that the government will implement a supportive policy for conventions where the actual health outcome of the patient is put central (pay-for-performance), at the expense of purely financial agreements.<sup>87</sup>

**Table 13 – Share of the different types of compensation mechanisms used in Belgium**

Type of compensation mechanisms	%
Percentage of the declared turnover	84.6%
Fixed amount per package	10.8%
The whole or part of the difference between the estimated expenditure and the real expenditure for the pharmaceutical concerned	4.6%
A reduction of the reimbursement basis of other pharmaceuticals marketed by the applicant*	3.0%*

*\*This type of compensation could be associated with other compensation mechanisms above. This table was performed by using information provided in the article 3 of the published part of the convention. Without access to the appendices of the convention, we are not able to refine this classification.*

### Key points

- **The type of conventions in Belgium seems mostly financial but the introduction of more health outcome-based conventions seems in discussion. It is also possible that the ways refunds are calculated include outcomes arguments.**
- **The type of convention should be tuned with the uncertainty it is expected to resolve.**

#### 4.3.3.4 Data collection

According to the paragraph 5 of the convention (public part), data collected in the conventions seemed usually more dedicated to the reduction of budgetary uncertainty rather than clinical uncertainty. Data mostly concerned the use in real practice, i.e. the number of patients, the treatment duration / average doses given in practice, or the combined therapy given in practice. In term of process, an improvement is observed over time, with for example the use of data of the intermutualistic agency (IMA – AIM).



### Key points

- **The use of existing databases to collect budgetary and clinical data is something that should be further investigated. The delay to obtain these data is nevertheless also important, which limits the possibilities.**

#### 4.3.3.5 Analysis of specific cases

##### Products with multiple procedures for a contract

In the 2010-2015 period, 15 products had multiple convention procedures, with a median number of two procedures and a maximum number of 5 procedures for the same product (brand name). It should also be noted that for some of them, the new convention was integrated in the old convention. Reasons for the subsequent procedures are described in Table 14.

**Table 14 – Reasons of the subsequent convention procedures for a same product (brand name)**

Reasons	%
Enlargement of indications	68.8%
Similar indication: First refused - Second accepted	25.0%
Similar indication: All refused	12.5%
Similar indication: New convention process after expiration (accepted)	18.8%
Similar indication: New convention process after expiration (refused)	6.3%

*NB: The sum of percentage is not 100% because some products have multiple procedures and therefore multiple reasons*

### Multiple products for a same indication

There were also cases in which multiple products were under convention for the same indication. In these cases, if the conventions are performed per product, the control of the budget impact for the whole indication is more difficult.

#### 4.3.4 Analysis of expired conventions

At the moment of the analysis, a small number of conventions already expired (n=16). From these expired conventions, we selected below a sample of interesting findings:

##### Not much extra information

Unfortunately, in most cases, we observed that the new submission files for the CTG-CRM contain not much extra information. In several new evaluation reports (day 60 of the new submission procedure, see section 3.3.3), RIZIV – INAMI experts indicate e.g. that:

- no new clinical studies were provided,
- the present reimbursement request dossier is largely identical to the initial dossier (of 4 years before),
- the clinical uncertainty on the added therapeutic value of X versus Y still exists,
- there are still insufficient data to judge whether X has a therapeutic added value,
- there are no (long-term) comparative studies between X and Y,
- the convention has not permitted to remove uncertainties,
- the effect on QoL has not been investigated,
- etc.





We also observed that uncertainties related to clinical aspects highlighted in the first submission process were not systematically discussed in the evaluation report of the new submission. This could show that at the end of a convention, once a product is already reimbursed for several years, re-discussing the clinical effectiveness of the product might be a difficult task. This should especially not be the case if clinical uncertainty was a major issue.

The initial experience with resolving uncertainties, based on the resubmitted files, looks thus rather disappointing. However, it is difficult to judge this outcome because we had no access to the discussions of the working groups and it is possible that these conventions did not aim to solve specific uncertainties but rather to only improve the cost-effectiveness or the budget impact. Moreover, we didn't have access to the appendices to see how explicit specific information was requested. Nevertheless, it is recommended to establish a clear link between the uncertainties identified by the CTG-CRM and the required information/conditions included in the convention. It should be possible to monitor whether requirements agreed in the convention are fulfilled and consequences of not fulfilling these requirements should be foreseen.

#### **Publication of clinical data**

The fact that the new evaluation report was almost identical to the first evaluation report could also be explained by the confidentiality of data collected during the convention. This nevertheless impedes the member of the CTG-CRM to correctly assess the product during this new submission. At least clinical data should be made public.

#### **Prolongation of conventions**

In the more recent conventions, it is specified that the costs for RIZIV – INAMI after the convention should not exceed the costs during the last year(s) of the convention. Nevertheless, this does not mean that the facial price (i.e. the price as mentioned in the list of reimbursed pharmaceuticals) should be reduced to this level. Identical levels of refunds are also accepted.

We observed cases where a new convention was again concluded because the company refused to change the facial price of the product. With this possibility, there exists a high incentive to extend indefinitely confidential non-transparent conventions. It should also be noted that the negotiating power of our policy makers is reduced at the time of renegotiations since it is often perceived as being difficult to withdraw products from the market when they are already used for several years. Conditions for (not) renewing conventions should be made clearer from the beginning of entering a convention. A limitation in the number of renewals should also be discussed.

#### **Impact on introduction and pricing of generics**

In Belgium, the price of the generic (i.e. the reference price) is calculated as a percentage reduction on the price of the original specialty, e.g. a decrease of 51.52% of the ex-factory price for pharmaceuticals with a vital importance (category A pharmaceuticals).<sup>81</sup> With the unlimited possibility to be under convention, two potential problems that need to be further investigated have been identified:

- Difficulties in price setting: if the original is always under convention at the arrival of the generic, a decrease of the 'public' ex-factory price without taking into account the confidential refunds could lead to a reference price superior to the 'net' price (after refunds) of the original specialty. Solutions would be to stop automatically the convention of the original speciality and to automatically reduce the facial price of this products according to the refunds or to also conclude a convention with the generics. In these two cases, the generic companies do nevertheless not know in advance which price will be accepted. If the facial price of the original product is considered too high and the price of the generics is based on this public price, the price of the latter will also be too high. In the long term, to avoid too much products (incl. generics) under convention, the problem of too high prices should be tackled by (international) transparent price negotiations.



- A potential barrier for generic companies: if generic companies have no idea in advance about the price that will be accepted in Belgium, this could be a disincentive to introduce the product on the Belgian market. For one of the expired conventions, we for example observed that the generic arrived later than in other countries (about one year after the end of the convention). One case is insufficient to draw conclusions and the underlying reasons deserve further investigation. However, this potential problem for the near future should be monitored.

#### Key points

- **Uncertainties and problems identified by the CTG-CRM should clearly be highlighted in the first submission process so that experts can analyse if sufficient efforts are made to resolve these uncertainties during the convention and to check whether the requested information is provided at the end of the convention.**
- **Consequences of not solving the identified uncertainties should be discussed from the beginning of the first convention.**
- **The renewal of conventions under the same conditions to keep facial prices high should be restricted.**
- **The impact on the introduction and pricing of generics should be monitored and discussed.**
- **At least clinical information collected during the convention procedure should be made public.**

#### 4.3.5 *Impact on the health care budget for pharmaceuticals*

Because we had not access to the compensation mechanisms, it was difficult to analyse the impact of conventions on the health care budget for pharmaceuticals. Nevertheless, the RIZIV – INAMI publishes each year a financial monitoring of reimbursable pharmaceutical expenditures. In their 2015 report, they published a total budgetary compensation of € 54 515 531 perceived by the RIZIV – INAMI for the year 2015, which corresponded to 26.3% of the turnover for all specialties under conventions. Pharmaceuticals with ATC class L (Antineoplastic and immunomodulating agents) and B (Blood and blood forming organs) accounted for most of the budgetary compensation, i.e. 93% of the 2015 compensations.<sup>88</sup>

Because we had not details per pharmaceutical, it was not possible to determine if such a percentage was sufficient.

Furthermore, ‘savings’ should be interpreted with caution. Calculating e.g. an average percentage of all discounts does not say much about the success of conventions. What is a discount of 10%, 20% or 50% if this still results in a much higher price versus alternatives and if the product does not offer much added value? What is the meaning of a discount of 30% if the product is priced 10 times too high? The same counts for the budget impact. What is the meaning of a refund of €10 million on a total budget impact of €30 million if no added value is shown: do you interpret this as €10 million of savings or as an unnecessary expenditure of €20 million? We make some recommendations related to whether the price negotiations are related to an intervention’s added value or whether there is a budget impact issue.

#### Key points

- **In 2015, compensation mechanisms received by the RIZIV – INAMI accounted for 26.3% of the turnover for all specialties under convention. It was nevertheless not possible to analyse if such a percentage was in line with the requested price reduction by the CTG-CRM.**
- **‘Savings’ related to conventions should be interpreted with caution.**



## 5 STAKEHOLDER CONSULTATION

Based on the previous chapters, a short report that offers an overview of the whole scientific report and contains additional elements of discussions as well as our conclusions and policy recommendations was done (see the short report). Several stakeholder consultations were organized to get feedback on and complete this short report. Representatives of all institutions implied in the decision process were contacted.

### Members of the CTG-CRM

To select representatives of the CTG-CRM, we used the list available on the RIZIV – INAMI website, including representatives of:

- Sickness funds;
- Pharmacists;
- Physicians;
- Academics;
- Pharmaceutical companies;
- The government;
- The RIZIV – INAMI. For the RIZIV – INAMI, we both invited people participating in the working groups for the convention negotiation and experts preparing the first evaluation report (day 60, see section 3.3.3).

The full list of representative members of the CTG-CRM can be consulted here: [http://www.riziv.fgov.be/SiteCollectionDocuments/commission-rem\\_boursement-medicaments-liste-membres.pdf](http://www.riziv.fgov.be/SiteCollectionDocuments/commission-rem_boursement-medicaments-liste-membres.pdf). It should be noted that not all those people responded positively to our invitation and only people that participated were mentioned in the colophon of this report.

### Members of the working groups

A selection of people that participate in the working groups to negotiate the conventions were also invited but only members of the RIZIV – INAMI, representatives of the Minister of Budget and representatives of the Minister of Economy accepted the invitation. As mentioned in the beginning of this report, most people implied in the negotiations refused to participate because of a fear to be falsely accused of having shared confidential information. It should also be noted that none of the people who participated gave any information that was either directly or indirectly related to the confidential part of the agreements (neither on the content of the appendices nor on what was discussed within the working groups).

It should also be noted that initially, members of the pharmaceutical industry (the six companies with the highest number of conventions) as well as representatives of the pharmaceutical industry (pharma.be) were invited to participate. Because this resulted in a formal refusal and a legal threat, they were not implied anymore in the further research process.

### Representatives of patients associations and academic experts

To complete our analysis, we also contacted representatives of patients associations and a selection of Belgian academic experts that published on this topic (see the colophon of this report).

### Method

Face-to-face interviews were organized with all stakeholders mentioned in the colophon (stakeholders and experts). Semi-structured interviews were organized on the basis of open-ended questions we included in the short report at their attention.

The aim was not to obtain a consensus but rather to obtain their feedback on our propositions. All their feedbacks are included in the short report.

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Results of this stakeholder consultation, as well as a final discussion and conclusion are integrated in the short report, published as a separate document.

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## ■ APPENDIX

### APPENDIX 1. UPDATE LITERATURE SEARCH FOR MEAS

#### Appendix 1.1. Medline (Ovid) search

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- 1 access with evidence.mp. (9)
- 2 conditional coverage.mp. (12)
- 3 conditional reimbursement.mp. (9)
- 4 cost sharing scheme\*.mp. (14)
- 5 coverage with evidence.mp. (65)
- 6 evidence development.mp. (124)
- 7 money back.mp. (46)
- 8 outcome\* based contracting.mp. (2)
- 9 outcome\* guarantee.mp. (2)
- 10 patient access scheme\*.mp. (22)
- 11 payment by result\*.mp. (140)
- 12 price volume agreement\*.mp. (3)
- 13 risk sharing agreement\*.mp. (31)
- 14 risk sharing deal\*.mp. (3)
- 15 risk sharing scheme\*.mp. (33)
- 16 pharmaceutical risk sharing.mp. (5)
- 17 managed entry agreement\*.mp. (5)
- 18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (429)
- 19 limit 18 to yr="2011 -Current" (176)



## Appendix 1.2. EMBASE search

-----  
(‘access with evidence’:ab,ti and [embase]/lim and [2011-2016]/py) or  
(‘conditional coverage’:ab,ti and [embase]/lim and [2011-2016]/py) or  
(‘conditional reimbursement’:ab,ti and [embase]/lim and [2011-2016]/py) or  
(‘cost sharing scheme\*’:ab,ti and [embase]/lim and [2011-2016]/py) or  
(‘money back’:ab,ti and [embase]/lim and [2011-2016]/py) or (‘outcome\*  
based contract\*’ and [embase]/lim and [2011-2016]/py) or (‘outcome\*  
guarantee’ and [embase]/lim and [2011-2016]/py) or (‘pharmaceutical\* risk  
sharing’ and [embase]/lim and [2011-2016]/py) or (‘price volume  
agreement\*’ and [embase]/lim and [2011-2016]/py) or (‘risk sharing deal\*’  
and [embase]/lim and [2011-2016]/py) or (‘risk sharing scheme\*’:ab,ti and  
[embase]/lim and [2011-2016]/py) or (‘evidence development’:ab,ti and  
[embase]/lim and [2011-2016]/py) or (‘payment by result\*’:ab,ti and  
[embase]/lim and [2011-2016]/py) or (‘patient access scheme\*’:ab,ti and  
[embase]/lim and [2011-2016]/py) or (‘coverage with evidence’:ab,ti and  
[embase]/lim and [2011-2016]/py) or (‘risk sharing agreement\*’:ab,ti and  
[embase]/lim and [2011-2016]/py) or (‘managed entry agreement\*’:ab,ti and  
[embase]/lim and [2011-2016]/py)  
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## Appendix 1.3. International experts contacted

- UK: Alessandra Ferrario (London School of Economics)
- Italy: Livio Garattini (Centro di Economia Sanitaria A. e A. Valenti (CESAV)) and Filippo Drago (BIOMETEC, Dept. of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania)
- The Netherlands: Hedi Schelleman (Zorginstituut Nederland) and Huib Kooijman (Buro Financiële Arrangementen Geneesmiddelen, Ministerie van Volksgezondheid, Welzijn en Sport)
- France: Jean-Philippe Cicurel and Elisabeth Lajnef (Comité économique des produits de santé (CEPS), without response).



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