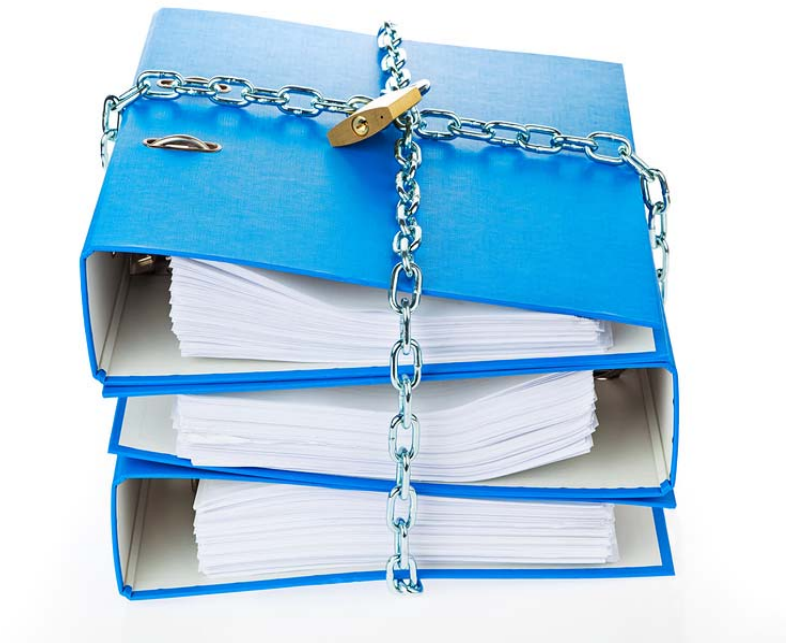


## SHORT REPORT

# HOW TO IMPROVE THE BELGIAN PROCESS FOR MANAGED ENTRY AGREEMENTS?





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SOPHIE GERKENS, MATTIAS NEYT, LORENA SAN MIGUEL, IRM VINCK, NANCY THIRY, IRINA CLEEMPUT





# ■ SHORT REPORT

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## 1. INTRODUCTION

How to use this document?

This short report gives an overview of the key messages resulting from the scientific report and includes additional discussion elements as well as the conclusions and recommendations.

### 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, managed entry agreements (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 e.g. effectiveness and use. These data should then allow to make a final reimbursement decision at the end of the MEA.

Confidential MEAs are also used to negotiate a lower price for very expensive pharmaceutical products. 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: the so called 'art. 81' (bis) conventions. The procedure to obtain such a convention can be introduced by the company if there is no proposal for reimbursement by the Commission for the Reimbursement of Pharmaceuticals (Commissie Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments, CTG-CRM) in the classic reimbursement procedure (art. 81) or, since July 2014, if the CTG-CRM directly proposes a convention (art. 81bis). The possibility to conclude a convention in case of a negative reimbursement proposal by the CTG-CRM is no longer possible since July 2014. Conventions can only be closed for pharmaceuticals described in Box 1.

A more detailed description of the Belgian system can be found in the scientific report.

#### Art 81 conventions can be negotiated for:

- Orphan drugs;
- Pharmaceuticals for which a class 1 was requested (i.e. the company claims an added therapeutic value);
- Pharmaceuticals already included in the list of reimbursed pharmaceuticals or not for which reimbursement of a new indication is requested and for which a therapeutic or social need exists; and
- Pharmaceuticals (class 1 or 2) for which the reference specialty is already under convention.

#### Art 81 bis conventions can be negotiated for:

- Orphan drugs;
- Pharmaceuticals for which a class 1 was requested;
- Pharmaceuticals included in the list of reimbursed pharmaceuticals for which reimbursement of a new indication is requested and for which a therapeutic or social need exists.



About 6 years after the introduction of the MEA procedure in Belgium and under the proposal of 'Test-Santé' and 'kom op tegen Kanker', KCE was asked to assess its strengths and weaknesses and to identify the areas with room for improvement within the entire process leading to conventions, starting with the standard CTG-CRM procedure up to the end of the convention and the possible renewal.

However, the analysis was hampered 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). Only public information could be used. Details on the compensation mechanisms available in the appendices of these conventions could not be used (neither directly, nor indirectly).

Notwithstanding these limitations, we believe that the analyses of all available non-confidential information and the information from a selection of other countries allowed us to come up with an interesting set of observations and recommendations.

### Recommendation

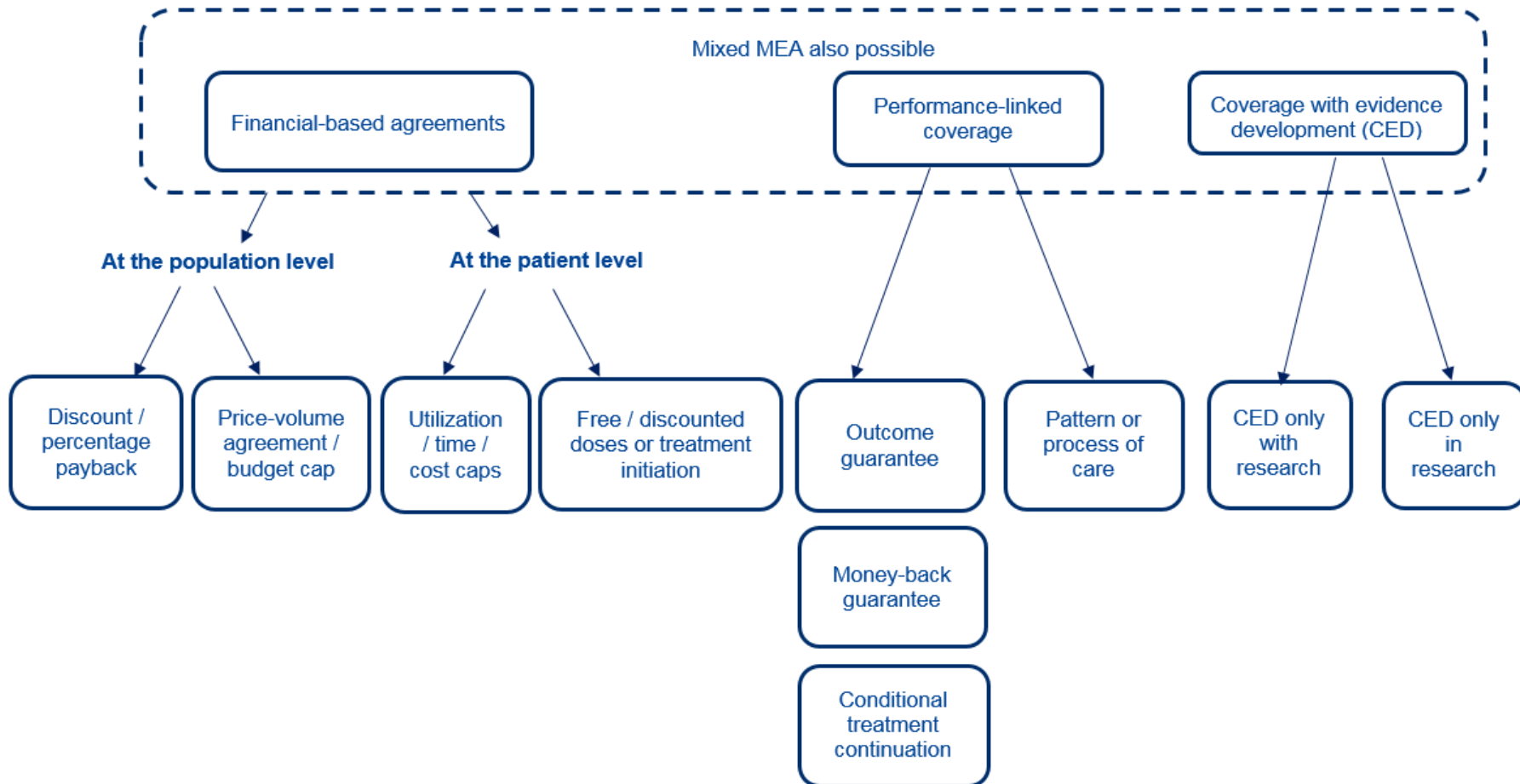
- **Performing an evaluation by an independent body should be possible to be able to steer and improve the current policy. Access to the contractual details under strict conditions should not be hindered. The publication of the results of these analyzes should be possible, for example in an aggregated form, in respect with the confidential and anonymous nature of these data.**

## 1.2. A rapid look at the existing taxonomy

A variety of terms have been used to describe these formal agreements, such as managed entry agreements (MEA), risk-sharing agreements, patient access schemes (PAS), 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 in the literature research (see details in the scientific report) and is presented in Figure 1 and Table 1. It should be noted that MEAs can be a mix of various schemes, e.g. a performance-linked agreement combined with a financial component.



Figure 1 – MEA taxonomy used in this short report



MEA: managed entry agreements. Source: adapted from the literature<sup>2-5</sup>



**Table 1 – Definition of MEA schemes**

Financial-based agreements	Performance-linked coverage:	Coverage with evidence development:
<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 / refund of a percentage of the real turnover.</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. pre-set budget(s)). A compensation mechanism is given once a threshold is exceeded (payback/refund, discount). A variant of this MEA is the budget cap, i.e. no (or &lt;100%) refund until a predefined level of turnover and 100% of refund beyond that level.</li> </ul> <p><b>At the patient level:</b></p> <ul style="list-style-type: none"> <li>Utilisation-, time- or cost-capping schemes: maximum doses, time, or cumulative cost of treatment per patient after which the manufacturer pays / refunds (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>The payment or reimbursement is linked to the performance of the product, to specific outcomes:</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 meets 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.</li> <li>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, or the prescribing is limited to specialized health care centres.</li> </ul>	<p><b>The coverage decision is conditioned upon the collection of evidence.</b> The use must therefore be done under controlled circumstances (i.e. through an RCT or evidence-providing registries).</p> <ul style="list-style-type: none"> <li>CED 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>CED only in research: evidence collection for all patients, i. e. only patients participating in the study are covered.</li> </ul>

Source: adapted from the literature<sup>2-5</sup>



## 2. (SUGGESTIONS TO IMPROVE) THE DIFFERENT STAGES OF THE PROCESS

### 2.1. Horizon scanning

In order to better capture the near future and evaluate whether a drug is really unique in terms of therapeutic added value or whether other similar medicines will emerge in a near future, the outputs of a horizon scanning system should be incorporated in the process. Initiatives are currently taken by the BeNeLuxA collaboration to set up a joint horizon scanning system that can help to improve the national reimbursement processes. The horizon scanning system identifies the new and emerging products and collects all the information available on the international level. For products with a potential high financial, organisational or clinical impact, more in-depth information is collected. In the evaluation of a new product for reimbursement, information collected on this product and on other products for the same indication by the horizon scanning system, can be taken into account. For example, we observed that in a series of cases, multiple products were under convention for the same indication. Some of these products claimed a class 1 compared to an older alternative on the market without clear added value versus the other existing alternatives. A better knowledge of not only current but also possible treatment alternatives coming on the market in the near future could rebalance the negotiation power between decision makers and pharmaceutical companies and would allow them to more easily refuse a product with a price not in relation with its therapeutic value. A possibility for the future is that a public procurement is set up including all products of the same indication, to obtain a better price per treatment. The horizon scanning database would also allow to identify the indications on which research is being performed but for which no reimbursement was asked (yet) by the manufacturer.

Pending the existence of such a database, experts in the field and/or clinical trials databases can be consulted to identify relevant (future) alternatives. The European Medicines Agency as well as the Belgian Federal Agency for Medicines and Health Products (FAMHP – FAGG – AFMPS) already disposes of some of this information. However, due to legal restrictions, they are not allowed to share this information with other agencies.

The FAGG-AFMPS is moreover a member of the European Innovation offices network, which aims to identify promising innovative medicines for unmet needs (e.g. in hospital units, small and medium enterprises and in start-ups) in a timely manner and support and facilitate market access of these medicines.

### 2.2. The CTG-CRM procedure

#### 2.2.1. CTG-CRM submission files

##### **A comprehensive list of studies and their modalities**

A request for reimbursement of a pharmaceutical most often starts with the introduction by the manufacturer of a dossier containing several elements that will be evaluated by the CTG-CRM. It was observed that data is often delivered as a big pile of information in which different types of research are mixed. Although this is probably due to a wish to provide all available information about the product, it complicates analysis by the RIZIV – INAMI experts preparing the assessment report for the CTG-CRM who are bound by strict time limits. The procedure would benefit from some stricter requirements about the way information is presented. In some cases, it was reported that the submitted evidence was not complete. To facilitate the work of the CTG-CRM, an improved submission template could be defined to ensure that the file submitted will contain a comprehensive list of all registered studies with the product under evaluation in the relevant population. The studies should be classified according to the study design (meta-analysis, RCT, review, observational study, etc.) and the status of the study should be mentioned (finished, recruiting, stopped recruitment but still in progress, prematurely stopped and reason for discontinuation, etc.). Reimbursement request not respecting this transparent reporting per study type should not be declared admissible. The completeness of this information by e.g. consulting clinical trials databases (such as the ClinicalTrials.gov database of the U.S. National Institutes of Health, <https://clinicaltrials.gov/> or the International Clinical Trials Registry Platform of the World Health Organization, <http://www.who.int/ictrp/en/>) could be checked by the RIZIV–INAMI experts.



### *2.2.2. The evaluation reports of the CTG-CRM*

#### **Uncertainties and problems highlighted in CTG-CRM reports**

The final assessment report or if not available the evaluation report (day 60 – day 90) of the CTG-CRM are the documents that should serve as a basis for the assessment by the working group in case of an art.81/art.81bis procedure. Therefore, it is of utmost importance that crucial uncertainties or issues identified during the CTG-CRM appraisal process are made very explicit in all CTG-CRM reports. The preparation should start already at day 60, when an evaluation report (day-60 report) is presented to the CTG-CRM by the RIZIV – INAMI experts. Already in the day 60 report a specific section should be dedicated to issues and uncertainties regarding the product. These should be taken forward in subsequent reports (provisional proposal and final proposal). A template should be used for this (see Table 2 for a proposal). The issues or uncertainties mentioned in the CTG-CRM documents should form the basis of the discussion during the convention negotiations. 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.

It is important to make a clear distinction between what is to be considered as a problem or issue and what is to be considered as an uncertainty, as the choice for the type of convention will depend on this distinction. Also the level of importance of these problems / uncertainties (major or minor) should be mentioned. If there is an uncertainty that is considered to be of major importance (e.g. related to the added therapeutic value) the convention should include evidence generation for at least these major issues.


**Table 2 – Template for the identification of problems and uncertainties**

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 a 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 e.g. 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 uncertainties and 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>• This evaluation criterion can support the more selective use of conventions. For example, a high unmet medical need could be an argument in favor of a convention. In case of no unmet need, this might be more questionable.</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>



### Definition of the appropriate comparator(s)

For economic analyses, comparisons must be made with the most appropriate comparator(s), i.e. the most cost-effective alternative(s) available on the market. For budget impact analyses, the comparator is the current situation that would change if the intervention under consideration is introduced in the healthcare system.<sup>6</sup> We noticed that for some economic evaluations RIZIV – INAMI experts indicated that relevant alternatives were not taken into account in the economic evaluation, even after they explicitly requested to do this. Placebo-comparisons and inappropriately excluding relevant alternatives can lead to wrong conclusions and should not be accepted.

The identification of the appropriate comparator includes the selection of all relevant treatments for the targeted indication and population, the removal of dominated or extendedly dominated interventions from the list of relevant comparators, and the calculation of the ICERs of all interventions compared to the next best alternative. The comparator(s) can be medical-pharmaceutical and/or non-medical. Generics should also be included. “Off-label” used products or services should not be used as a comparator in the reference case analysis, unless there is evidence about their clinical safety and efficacy. The choice of the comparator(s) should always be justified in the CTG-CRM reports. Indirect comparisons should only be allowed under specific conditions (see KCE report 183C).<sup>6</sup> The choice for an indirect rather than a direct head-to-head comparison between the study treatment and the comparator should be explained, together with the limitations of the indirect comparison (see also KCE report 183C).<sup>6</sup>

A convention can be a way to eliminate uncertainty about a product’s added value if (direct) comparative evidence versus the most relevant (cost-effective) alternative is not available (see further part 2.4.2).

### Specifications on the added value if the company claims for a class 1, as well as a clear distinction between real innovations and minor changes

The classification of a pharmaceutical is key for its price setting. Class 1 concerns drugs with a therapeutic added value compared to existing therapeutic alternatives, class 2 drugs are those with comparable therapeutic value and class 3 drugs are mainly generics. The therapeutic added value is a broad concept and is determined by an assessment of the efficacy, effectiveness, side effects, but also the applicability and user-friendliness of the product. These elements are used to determine the position of the specialty within the therapy in comparison with other available treatment options.<sup>7</sup>

For class 1 requests, the working group that negotiates conventions should be able to clearly identify whether the CTG-CRM has recognized the added value or whether they considered that uncertainties remained. Depending on the conclusions of the CTG-CRM, the conditions and type of convention will differ. The arguments that are used to recognize an added value should also be clearly stated so that the working group can judge the level of added value (major or minor). In other countries, the level of added therapeutic value is assessed and Sweden for example use a scale to judge the added value and link it directly to the price.

Since July 2014, there is a possibility to opt directly for a convention in the provisional or final proposal (art. 81bis). We observed, however, that the supporting arguments are lost during the process. For example, in a case it was clearly stated in the evaluation report that there was no added therapeutic value, while a later report recommended a convention without mentioning anymore that no added value was recognized. A clear identification of the problems and uncertainties (as mentioned above) and a clear statement on the pharmaceutical’s classification and the arguments used to justify the class will inform the working group in a better way.



### Assessment of cost-effectiveness for extension of indications and for orphan drugs

The reimbursement decision is based on an assessment of the following five criteria (art. 4 and art. 6 of the December 2001 Royal Decree):

- The therapeutic value, taking into account the efficacy, effectiveness, side effects, applicability and user-friendliness of the product,
- The market price of the drug,
- The clinical effectiveness and likely impact of the product, taking into account therapeutic and social needs,
- The budgetary impact for the National Health Insurance,
- The cost-effectiveness of the product from the perspective of the National Health Insurance.

Class 1 pharmaceuticals are products with an added value for which a price premium can be requested. For such products, all of the above criteria are assessed. For class 2 pharmaceuticals, the first four criteria are taken into account. For class 3 pharmaceuticals (generics) only the second and fourth criteria are assessed. It makes sense that the cost-effectiveness criterion is not taken into account for class 2 and 3 pharmaceuticals since for products without a clear added value, any additional cost would be associated with an inefficient use of limited resources.

Nevertheless, it appeared from our analysis that if an extension of indication was requested, the cost-effectiveness of the product for that new indication was not assessed. Yet, safety, efficacy, price of alternative interventions, and thus cost-effectiveness of the product in this new indications can be very different from that of the indications that are already reimbursed. Therefore, if there is a request for reimbursement of a new indication (i.e. through a modification of reimbursement), all of the above five evaluation criteria should be taken into account. For orphan drugs, cost-effectiveness analysis are also not required. However, even though the uncertainty about this estimate is usually higher for orphan drugs, information on the cost-effectiveness would provide relevant information for the decision-making process.

### Summary of recommendations on the CTG-CRM process

- **A register including molecules in the pipeline could be helpful for the evaluation process. This should be based on a horizon scan, preferably set up at the European level.**
- **Stricter requirements for the submission file should be defined. The template for submission should be improved for this purpose. The applicant should provide a comprehensive list of finished, abandoned and ongoing studies. The overview of these studies should be classified according to the study design (meta-analysis, RCTs, review, observational study, etc.) and should mention the study status (finished, prematurely stopped, recruiting, etc.).**
- **A submission file that does not respect these requirements should not be declared admissible.**
- **Reports of the CTG-CRM (evaluation reports day 60 and day 90; provisional proposal; final proposal) should include specific sections on:\***
  - **A description of uncertainties and problems highlighted in the CTG-CRM reports, as well as a statement on their importance (minor to major). We recommend to develop a template for this (for example based on Table 2).**
  - **An overview of the conclusions with respect to the benefit-risks from the EPAR;**
  - **An overview of the questions posed by EMA with regard to additional evidence in case of conditional marketing authorization;**
  - **An overview of the appropriate comparators, including generic alternatives and evidence-based off-label use.**
  - **A clear statement on the recognized added value should be mentioned in the provisional and/or final proposal. E.g. for class 1 requests, arguments used to refuse or accept this class should be clearly mentioned.**





- **For an extension of indications and for orphan drugs, the five evaluation criteria should be taken into account, including an assessment of the intervention's cost-effectiveness.**

*\*This list of recommended elements does not mean that they were not already available in some reports. Indeed, a real improvement in the identification of these elements was observed throughout the years, especially for conventions under the art. 81 bis procedure.*

## 2.3. The convention process

### 2.3.1. Composition of the working group

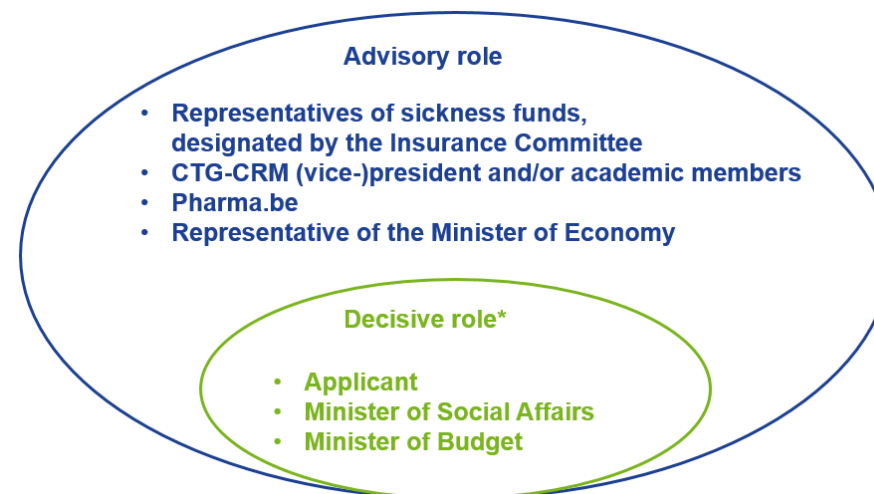
During the convention negotiation process, different interests need to be balanced: the interests of patients who would like to have access to safe innovative and promising therapies, the interests of physicians who would like to provide these innovative and promising therapies, the interests of the industry who wants to sell its products, and the interest of payers who wish to take the right decisions in view of the sustainability, equity and quality of the healthcare system. Yet, according to the law, not all parties are currently involved in the negotiation process. While representatives of pharmacists and physicians are part of the CTG-CRM, they are not involved in the working group (see the composition of the working group in Figure 2).

Some stakeholders consider that implying other people such as representatives of the umbrella organizations of patients associations or medical specialists (without conflict of interest) in the negotiations could be useful in some situations but only as advisors, only when desired by the working group (not for all demands), only on the clinical part, i.e. not for the compensation mechanisms, and only if they have sufficient expertise in the pricing and reimbursement decision process. Representatives of the umbrella organizations of patients associations also expressed their wish to be able to give their opinion for some specific cases (not for all cases) but rather at the moment of the CTG-CRM procedure. A discussion on their implication in the reimbursement decision process is currently ongoing at the European level.

Furthermore, in contrast with the CTG-CRM procedure, there is no voting process. The applicant can decide on whether or not to agree with a convention as negotiated and proposed by the working group and the final decision to conclude this convention is made between the applicant and the Minister of Social Affairs and Public Health, with the agreement of the Minister of Budget (see Figure 2).

The limited composition of this working group and the less formal framework around these negotiations is considered important by the stakeholders interviewed to facilitate the discussions. Moreover, due to the stable composition of the working group, some arguments become implicit and do not have to be re-discussed, which has both advantages (e.g. working faster) and disadvantages (no new views). However, in case of international negotiations with new partners around the table, arguments will have to be discussed with these new partners and will have to be made explicit.

**Figure 2 – Current composition working group**



*\*We use the term "decisive" because the final decision is taken by the applicant and the ministers. Pharma.be= umbrella association of the innovative pharmaceutical industry in Belgium.*



### 2.3.2. *Criteria to qualify for a convention procedure*

The procedures, time limits, and conditions for conventions are outlined in the article 81 and following of the Royal Decree of 21 December 2001. As stated in the introduction, the negotiation of conventions is only allowed for some categories of pharmaceuticals, i.e. those where a class 1 reimbursement is requested by the applicant (but not especially granted by the CTG-CRM), orphan drugs, drugs for which reimbursement of a new indication is claimed and for which a therapeutic or social need exists, and pharmaceuticals (class 1 or 2) for which the reference specialty is already under convention (Article 81 of the RD of 21 December 2001).<sup>7</sup>

However, we observed cases for which a match with one of these eligibility criteria was not straightforward. Moreover, policy makers should be aware of the potential (undesirable) long-term consequences of closing conventions because comparators are under convention.

#### **Exclude conventions for specialties for which the applicant submits a class 1 request but the CTG-CRM considers there is evidence of insufficient added value (and no alternatives under convention)**

It appeared from our evaluation that some conventions were concluded for more expensive pharmaceuticals for which a class 1 had been refused by the CTG-CRM and where no alternative was under convention.

Two situations were observed: one where there is evidence of insufficient added value (problem) and another where there is insufficient evidence about the added value (uncertainty).

- **Problem:** If there is good evidence or there are good indications that a pharmaceutical provides not much added value in comparison with existing alternatives, no convention should be concluded and a transparent price setting should be based on the price of the cheapest equivalent alternative. As such, it could be avoided to have a non-transparent system with too many conventions for products with no major added value. According to the Royal Decree of 21 December 2001, 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). If the applicant refuses to lower the public price, policy makers should (strongly

consider to) refuse reimbursement. From a healthcare payer's perspective, this is justified if policy makers want to make efficient use of their limited resources while trying to do the best for the whole population.

- **Uncertainty:** If class 1 is refused because the CTG-CRM considers there is too much uncertainty (e.g. on the target population or on the optimal treatment schemes) the CTG-CRM should clearly mention the areas of uncertainty as well as their importance (major or minor) in its proposal. The working group should then assess if a convention could resolve these uncertainties or not.

As it was also observed during the analysis of convention procedures, it is also possible that the CTG-CRM does not recognize an added therapeutic value for the whole target population, but only for a subgroup of this population. In this case, reducing the target population is a solution. However, the reliability of results from (post-hoc) subgroup analyses and the importance of confirmatory trials should be kept in mind. In such cases, it is recommended to reflect this uncertainty in the convention.

#### **Not automatically closing a convention because the alternative is also under convention**

A convention is possible for class 2 specialties when the alternative is under convention. The duration and content of the first convention is in most cases not influenced by the introduction of new alternatives. Instead of putting the new class 2 pharmaceutical automatically under convention (with the same end date), it might be an option to review the first convention. If there are no big uncertainties related to the new alternative, a transparent price setting should be preferred above the continuation of non-transparent conventions. Putting products under convention because the alternative is under convention makes the system completely opaque and might give the wrong incentives to industry (see section 2.4.2.1).

Anticipating the entry on the market of new interventions is preferable (see above). A horizon scanning during the CTG-CRM evaluation process could also help the working group to better capture the future during the negotiation process, and incorporate certain expectations in the convention conditions.





### **Therapeutic and societal need**

For new indications, a convention can be closed for a pharmaceutical when a therapeutic or societal need is recognized. The CTG-CRM has not applied an explicit definition of these concepts. It is recommended to use the definition as applied by the “commission for advice in case of temporary compensation for the use of a pharmaceutical” (CATT-CAIT) in the context of the unmet medical needs programme.<sup>8</sup> For the appraisal of the therapeutic and societal need, the CTG-CRM could use the same approach as the CATT-CAIT, being the application of a multi-criteria decision approach (see the KCE report 272 for more details).<sup>8</sup> This is not time consuming or cumbersome, and gives a clear indication of the societal and therapeutic need.

### **Orphan drug status**

Also for orphan drugs, conventions can be closed. However, it is possible that the drug loses its status of orphan drug after an extension of indications. If the orphan status of the pharmaceutical is not appropriate anymore, the convention should be revised or stopped because arguments for granting reimbursement can change. A new evaluation should be done by the CTG-CRM, including a cost-effectiveness evaluation. For example, while it may be justified to grant reimbursement for the first indication despite an unfavourable cost-effectiveness because of a high unmet need, this might not hold for the new indications and hence the cost-effectiveness should be reconsidered. If the new indication is more frequent or other treatment options are available, the reimbursement request should re-consider the cost-effectiveness of the product, and also the budget impact including both indications.

### *2.3.3. Identification of products under convention*

The list of products under convention is not easy to find and can only be identified by looking at which pharmaceuticals have a T code on 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>). The reason for the convention is not available while such information could be interesting both for the patient and the physician. For example, a product can be reimbursed under convention because there is uncertainty about the added value versus other interventions or even versus a placebo. The publication of the reasons of the convention could inform the physician/patient and avoid that, for example, physicians wrongly associate reimbursement (even under convention) with a demonstrated added value of the product. Such a clear communication should also facilitate possible withdrawals or modifications once the convention is expired.

In general, if the reimbursed indications are reduced, this should usually not impact patients already under treatment. The new situation should only apply for new patients.



### Summary of recommendations on the convention procedure

- If the applicant asks for a class 1 and the CTG-CRM considers there is evidence of insufficient added therapeutic value, no convention should be concluded if the alternative is not under convention. For these situations, either the price setting should be based on a cost match with the cheapest equivalent alternative (including generics) or the reimbursement should be refused.
  - The fact that the alternative is under convention should not be a reason to automatically conclude a convention (see also section 2.4.2.1). A horizon scanning exercise could help to foresee the arrival of new molecules and to take this into account during the negotiations of a convention (for example by including a statement that the convention can be reviewed when a competitor arrives on the market). Otherwise, the duration of the new convention should be limited to the duration of the convention of the first product (even if this period is less than 1 year).
  - If a class 1 was not granted because of remaining uncertainties, the working group should assess if these uncertainties could be resolved by/during a convention or not.
  - If the CTG-CRM does not recognize an added therapeutic value for the whole targeted population but only for a subgroup of patients, a reduction of the target population should be considered and a study allowing to confirm the impact of the pharmaceutical in this subgroup of patients could be asked in the convention.
  - For the definition and appraisal of “therapeutic or societal needs”, the approach used by the CAIT-CATT for the unmet medical needs programme is recommended.
  - If the orphan status requirements are no longer fulfilled, the convention could be revised or stopped. A new evaluation should be done by the CTG-CRM, including a cost-effectiveness evaluation.
- Patients and physicians should be aware that a product they are taking or prescribing is under convention, and should be informed about the reason (i.e. the problems / uncertainties as identified by the CTG-CRM) and the end of the convention.
    - It should be clearly mentioned in the RIZIV – INAMI’s pharmaceutical specialty database that a product is reimbursed under convention. This should also be mentioned in frequently used databases such as the BCFI-CBIP.
    - Both industry, physicians and patients should also be aware that the reimbursement of the pharmaceutical is temporary and could be stopped, especially in case of uncertainties around the clinical value.
  - In cases where the reimbursed indications are reduced, this should not impact patients already under treatment.

## 2.4. The conventions characteristics

### 2.4.1. The type of convention

According to the European report on MEAs (EMI-net project), Belgium mostly concludes financial-based agreements.<sup>1</sup>

If we look at the uncertainties and problems highlighted in Table 2, financial-based agreements on a population level intuitively does not always seem to be the most appropriate type of convention. Even if the collection of appropriate data linked to these Belgian conventions or 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, such as health outcome-based agreements, including both performance-linked agreements and coverage with evidence development (CED) (see Figure 2).



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 and it is for example possible that the percentage of refunds was based on the percentage of non-responders. It can therefore be expected that not all financial-based agreements are thus purely financial based.

Moreover, 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>9</sup>

According to several stakeholders, it should nevertheless not be underestimated how difficult it is to agree on health outcome-based agreements. They imply a much higher administrative burden than purely financial agreements. An approach could be to strive for fewer conventions and focus on those that are really able to resolve uncertainties. Even in this case, it will often remain a problem to determine for example what an acceptable outcome is or which research with sufficient standards can be requested (e.g. an RCT to determine the treatment effect). This might lead to very difficult negotiations. In fact, some stakeholders even assume it probable that pharmaceutical companies will not be willing to step into a convention if only Belgium makes specific requests (like asking for a confirmative RCT). The negotiating power of a government of a relatively small market is rather limited in comparison to bigger markets. Asking for further evidence would be more successful if requested by several countries together and if included explicitly in the reimbursement conditions of several countries. International collaboration is therefore highly recommended.

Also the review of the literature indicates that the positive impact of such kind of convention is not straightforward. The challenges related to health outcome-based schemes, and especially to CED schemes, have contributed to a current trend to simpler financial-based schemes.<sup>10</sup> Performance-linked coverage schemes using reasonable proxies for clinical outcomes and utilizing existing administration systems (e.g. routine data from patient files) is nevertheless perceived by some experts as an "ideal" compromise between financially driven discount schemes and CED

schemes, since they are not as expensive as CEDs but still take into consideration patients' response (unlike financial schemes).<sup>10</sup>

Some stakeholders also criticized purely financial-based agreements: they create a non-transparent system, they do not allow to evaluate whether public sources are well spent, and they support a system of high facial prices (see further).

The option of a convention might also have an influence on the outcome of the CTG-CRM procedure. In cases with insufficient evidence or minor added value, it is possible that the reimbursement request would have been refused in the past, while now the possibility to conclude a convention can be left open by the CTG-CRM if they decide to make no reimbursement proposal.

The analysis of current conventions that have already expired (n = 16) also showed the importance to tune the type of conventions to the uncertainty of the problem that needs to be addressed (as determined by the CTG-CRM). A template could be used to facilitate this stage (see the next section and proposition in Table 4). Indeed, we noticed that in most of the cases, the 'new' submission files looked almost the same as 3-4 years earlier and that usually, concerning clinical uncertainties raised in the first submission process, no appropriate information was gathered to be able to provide an answer. Although this observation is based on a small number of conventions, the mismatch between the type of uncertainty and type of convention does not bode well.

#### Recommendations on the type of conventions

- **The type of convention (financial-based agreement, performance-linked agreement, and coverage with evidence development) should be tuned to the uncertainty or the problem that needs to be addressed (as determined by the CTG-CRM). The guidance provided in Table 4**
- **(see infra) could be used to facilitate this stage, and should be adapted / improved based on experience.**



#### 2.4.2. *A link with the uncertainty / problem identified by the CTG-CRM*

It should be noted that without access to the appendices of the conventions, it was difficult to judge the appropriateness of the current conventions and their compensation mechanisms. We therefore do the exercise based on which type of conventions and compensation mechanisms we judge appropriate according to the uncertainty / problem. This is therefore only a theoretical exercise and this does not mean that the working group not already applies some of these propositions. It should also be noted, though, that these propositions were discussed with and improved by the interviewed stakeholders. These propositions are summarized in Table 4. The main theoretical arguments on which these proposals are based are described in the following sections.

##### 2.4.2.1. *In case of clinical uncertainty*

#### **Not all clinical uncertainties should lead to a convention**

Performing clinical trials is in the first place the companies' responsibility. In a standard reimbursement request, industry should come up with reliable evidence on e.g. the treatment effect. Policy makers can encourage research by an early conditional reimbursement under convention but we recommend to do this in the first place for well-considered cases, based a.o. on the importance of the specialty in the medical practice. We think about e.g.

- unmet medical needs
- interventions where there are good indications that it might improve the efficient use of limited resources (i.e. having a good cost-effectiveness), or
- when for-profit stakeholders have no financial interest to perform the necessary studies.

As such, access to interventions that are really needed and improve the efficiency of our health care system could be stimulated. For other drugs with clinical uncertainties, we recommend to follow the standard CTG-CRM procedure with no possibility to close a convention.

Criteria used abroad to determine cases where an agreement should be concluded can be found in the scientific report (see section 2.3.5.1 on checklists used for evaluating the need for a MEA)

#### **Be aware of the possibility of providing the wrong incentives**

The possibility to have a convention in case of uncertainty on the added therapeutic value can induce wrong incentives for applicants, who may introduce new specialties to the market (at a relatively high facial price) without too much efforts to provide appropriate studies to demonstrate added value. Under the argument of 'providing early access to innovative products', an incentive to provide good studies before receiving reimbursement could be lacking since this would be costly, time consuming, and might provide unfavourable results. Stakeholders might mention that this is not a problem since such evidence might be provided under the convention. Unfortunately, once a product is under convention, the applicant might have no incentive to conduct additional research on safety, efficacy and cost-effectiveness if this is not made explicit in the convention. This wrong incentive might be enforced if he is aware that withdrawing a product from reimbursement seems to be difficult for policy makers. To avoid such an improper use of conventions, requirements to perform the necessary research should be part of the convention. If insufficient efforts are made to perform this research, the convention should be terminated.

#### **Linking the requirements on evidence generation to the uncertainty**

If a convention is judged appropriate, the evidence generation conditions should be related to the uncertainty. Many pharmaceuticals are reimbursed under conventions because there is uncertainty about their added value compared to other alternatives. Nevertheless, based on the public information in art.4-5 of the conventions and subsequent re-assessments by the CTG-CRM, it seems that the conventions often do not explicitly ask to provide further evidence with a specific research design to solve this uncertainty. However, access to the appendices is needed to confirm this. Nevertheless, if only an observational study is asked in the convention while an RCT would have been more appropriate, policy makers should be aware that the same uncertainties will remain at the end of the convention (if no other initiatives were taken by the manufacturer outside of the convention). At that moment, the policy makers run the risk of having difficulties to



withdraw reimbursement of a product that has been reimbursed under convention for several years.

Ideally, to avoid such missed opportunities of gathering the necessary information and allow for good policy decisions, the link between the open research questions and the research design required to resolve these questions should be very clear and should explicitly be required in the convention. For example, if there is uncertainty about the efficacy of a drug in comparison with relevant alternatives, a convention should only be possible if it is associated with data collection (coverage with evidence development) through clinical studies. For other type of uncertainty (e.g. uncertainty on compliance), other instruments could be considered such as registries.

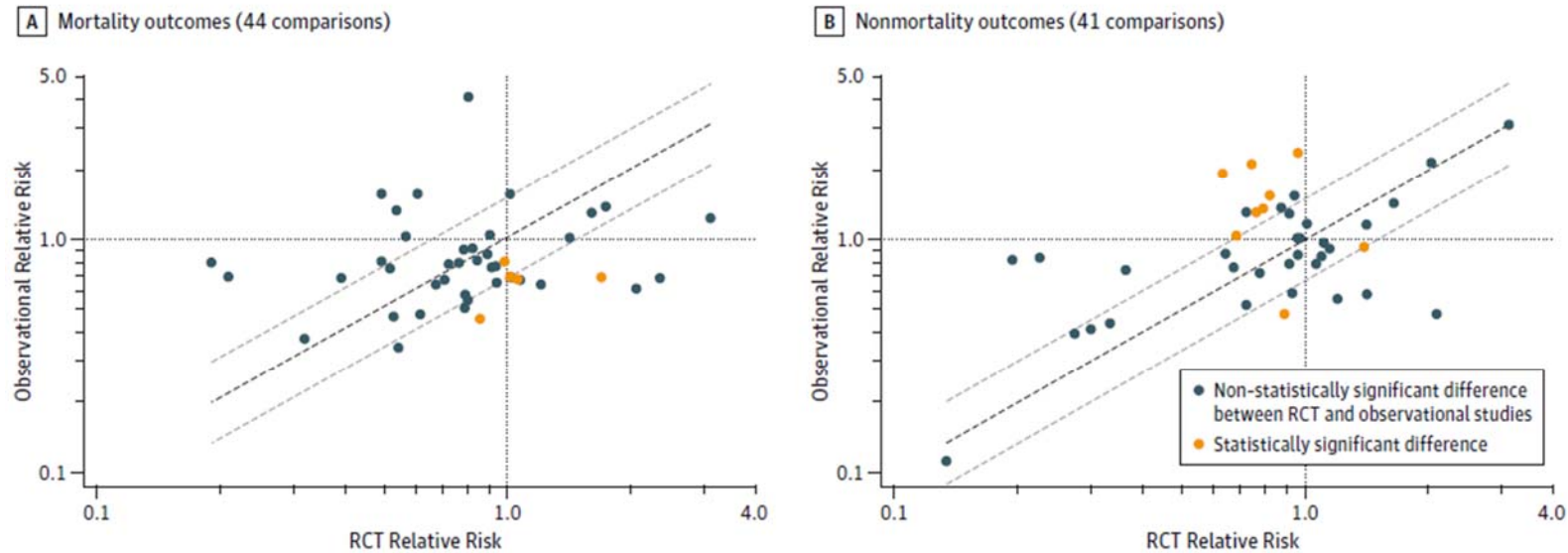
Before closing a convention to solve a clinical uncertainty, trial registries should be searched to find out whether there are already studies ongoing that are able to provide the necessary answers. If this is the case, it should be evaluated whether joining this study or waiting for its results is a good option. Otherwise, we recommend that the applicants explicitly explain in their convention proposal how they will respond to the clinical uncertainties. This proposal should discuss the appropriate research design, including the relevant comparator, appropriate endpoints, etc. RIZIV – INAMI has the possibility to review this proposal with support of independent experts. However, the companies remain accountable for performing good research.

### **Real-world effectiveness is not the same as observational data**

The medical pact of the future mentions that “*In line with among others the recommendations of the European Medicines Agency (EMA), we encourage therefore conditional reimbursement agreements (which may be created in the framework of the article 81 procedure) putting less focus on data from clinical trials, but focus more on real-world data*”.<sup>9</sup> Often people refer to observational data. This is true to get information on e.g. real-world compliance or safety risks. However, in some conventions, people refer to observational data to get information on a treatment’s effectiveness, being the treatment effect under real-world conditions. This contrasts with efficacy, which reflects the treatment effect under ideal circumstances. Observational data can be useful to transform efficacy results into potential effectiveness results by making an adjustment for baseline risk.<sup>11</sup>

Unfortunately, without good efficacy results such a transformation is not possible and observational data as such do not provide good estimates of the treatment effect under real-world conditions due to a lack of a comparative arm. Pragmatic RCTs are usually needed to provide reliable information on effectiveness. The pragmatic part refers to the inclusion, follow-up and other elements that reflect real-life conditions. Policy makers should thus not confuse observational data with effectiveness information. The following figure shows how contradictory results of observational studies can be in comparison with RCT information, even after applying sophisticated methods. The figure also shows there is a lack of a clear pattern in this relationship making it difficult to rely on the results of such studies. Purely observational data are usually thus not capable of providing a good estimate of the treatment effect and might provide misinformation.



**Figure 3 – Illustration of contradiction between observational and RCT study results**

Source: Dahabreh, JAMA, 2014

Propensity score methods try to draw causal inferences from observational data. The figures presents “scatter plots of results from empirical comparisons of propensity score analyses (y-axis) and corresponding randomized clinical trial (RCT) results (x-axis). Markers denote comparisons between observational and randomized study estimates for the same research question (similar populations, interventions, and outcomes). ... Markers in the top-right and bottom-left quadrants in each panel indicate agreement between randomized and observational results with respect to the direction of effects. Markers in the top-left and bottom-right quadrants indicate discordant direction of effects between designs. Black dashed diagonal lines indicate the line of identity (perfect agreement) between RCT and observational study results; gray dashed lines demarcate observational study relative risks that are between 0.67 and 1.5 times those produced by the corresponding RCT results.”<sup>12</sup>

### A tool for decision making on evidence generation

In case involved parties would agree to conclude an evidence-generating convention, we listed some points that need to be addressed during the negotiations in Table 3.

**Table 3 – Proposal of a tool for the decision making process on data collection**

For all uncertainties	Specificities for clinical uncertainties
<ul style="list-style-type: none"> <li>• Should a convention be concluded?</li> <li>• What are the uncertainties identified by the CTG-CRM?</li> <li>• Which type of information / data is needed to answer them?</li> <li>• What time is needed to be able to collect these data?</li> <li>• Which instruments should be used:               <ul style="list-style-type: none"> <li>○ Sales and expenditure databases (IMS data),</li> <li>○ Registries</li> <li>○ New clinical studies</li> <li>○ Existing administrative databases (IMA-AIM)</li> <li>○ Online systems for reimbursement approval (via chapter IV)</li> </ul> </li> <li>• What are the methods of review during the convention period, who should do this and when? Which points / criteria should be met?</li> </ul>	<ul style="list-style-type: none"> <li>• Is a new study needed? Which studies are currently in progress and to what extend will they be able to resolve the uncertainties?</li> <li>• What quality of evidence must be obtained and what should be the study design?</li> <li>• In case of comparative studies, which comparator(s) should be included?</li> <li>• What are the relevant endpoints?</li> <li>• Who finances this additional research?</li> <li>• Who supervises and coordinates this additional research?</li> <li>• What are the consequences of not meeting the requirements?</li> <li>• Is the study feasible in Belgium or is an international collaboration needed?</li> </ul>

Beside data collections, performance-linked agreements according to the type of clinical uncertainty could also be considered if appropriate and measurable outcomes can be identified (see Table 4).

#### Recommendations on evidence generation

- **We recommend to keep the responsibility of providing good evidence in the first place with the companies. Conventions with evidence generation should focus on well-considered cases such as e.g. unmet medical needs, interventions with a high potential of being very cost-effective, or interventions for which for-profit stakeholders have no financial interests to perform the study.**
- **Before starting a study, clinical study registries should be searched to find out whether relevant studies are already carried out.**

- **In case no ongoing studies are identified to solve the remaining uncertainties about a product, we recommend that the industry explicitly mention how they will respond to the uncertainties identified by the CTG-CRM (including research design, aspects of the relevant comparator, appropriate endpoints, etc.). This proposal could be reviewed by NIHDI experts with the support of independent experts. The companies should remain accountable for performing good research.**
- **We recommend not to rely on purely observational data for estimates of effectiveness.**
- **Evaluation of the fulfilling with data collection requirements by the working group is an important stage in the convention process. Not respecting these requirement should lead to a revision, or even to the end of the convention.**
- **For evidence generation, international collaboration is highly recommended.**



#### 2.4.2.2. *In case of clinical problem*

##### **No convention if there is sufficient evidence of no added therapeutic value versus the reference product not under convention**

As stated in the section 2.3.2, if the CTG-CRM considers there is sufficient evidence of no added value and if the alternative is not under convention, there is no rationale to accept a convention and a transparent price setting should be based on a cost match with the cheapest equivalent alternative. According to the Royal Decree of 21 December 2001, a higher price versus its comparators is not acceptable.

##### **The fact that the reference product is under convention should not be a reason for a convention**

As stated in section 2.3.2., specialties (even class 2) for which the reference product is under convention can also obtain a convention. 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. Yet, the application of this rule creates a snowball effect and may lead to a system where confidential MEAs in Belgium become the rule rather than the exception. A non-transparent system is difficult for future evaluations of new products. Especially the estimation of the cost-effectiveness is hampered by this lack of transparency. A non-transparent price of many products can also have a negative influence on future price settings. It would also imply the necessity to extend the workforce to be able to properly respond to the increased requests for conventions. In our opinion, conventions should not be automatically given to class 2 products when the alternative is under convention (see also section 2.3.2).

#### 2.4.2.3. *In case of economic uncertainty*

##### **Economic uncertainty linked to medical variables**

Even in case of well performed clinical studies, uncertainty about the cost-effectiveness of an intervention may still exist and may be linked to the measured uncertainty e.g. around the treatment effect or impact on QoL. In such cases, policy makers could support further research by closing a convention with inclusion of an appropriate research design. Partly reimbursing the drug through a convention can be seen as a co-financing of the research. If policy makers wish to support such research without running great financial risks, reimbursement up to the level of the alternatives could be considered. If policy makers would accept to pay a higher price than the comparator, we recommend also in this case to take the uncertainty about the treatment effect into account in the price discounts and to avoid that only (over)optimistic assumptions are taken into account when negotiating prices.

##### **Economic uncertainty linked to the volume**

Uncertainty on the volume is always present but such uncertainty becomes important only when it is linked to a risk of a high budget impact. In those cases, price-volume agreements would be appropriate. Moreover, if there are multiple equivalent products for the same indication, a common agreement allowing to limit the total pharmaceutical budget impact for this indication would be needed (i.e. percentage of refunds according to pre-set level of total budget impact for all pharmaceuticals concerned, with a division of refunds according to the turnover repartitions of the concerned pharmaceuticals).

##### **Economic uncertainty linked to costs related to use**

If there is uncertainty on doses that will be given in practice, on treatment duration or on combined therapies that will be used, financial-based agreements at the patient level could be considered, based on the definition of maximum doses, time, or cumulative cost of treatment per patient (including for example combined therapies) after which the manufacturer(s) pays (at least partly) for any additional doses required.





#### 2.4.2.4. *In case of economic problem*

##### **Confidential price agreements might provide wrong incentives for setting an acceptable public price**

Ideally, economic problems should not be a reason to conclude a convention. A potential side effect of the existence of confidential conventions is that companies might prefer to go for such an agreement in order to try to get a 'better public price' than during a classic CTG-CRM procedure. The main intention of a convention should not be to keep public prices too high.

However, as long as other countries continue to maintain a high facial price and to make confidential agreements to improve the cost-effectiveness of the product, Belgium has no other choice than to do the same. The reduction of the facial price to an acceptable ICER or an acceptable budget impact is only feasible through an international collaboration. A recent European report also stressed the importance of enhancing transparency and of increasing voluntary collaboration among member states concerning pricing and reimbursement of pharmaceuticals.<sup>13</sup>

The current system established in Belgium is therefore not the ideal situation in terms of transparency of the system but is the only solution in the short term to provide patients access to these expensive pharmaceuticals. In the short term, it seems like entering into confidential conventions is positive for our society since it is possible that we pay less than the public price. However, not making the actual price public also has disadvantages, especially in the longer term:

- Negotiating confidential discounts does not provide any incentive to a company to set a reasonable public price. On the contrary, setting a too high price and negotiating confidential discounts provides the company the opportunity to go for a price discrimination in which profits are maximized by obtaining the highest possible price on the various markets. In a monopolistic market for health care interventions, this can result in very high profits. This is enforced by the market conditions in which not only the company wants its products to be reimbursed but where also physicians and patients appreciate to have more treatment options at their disposal while government is paying for this. Allowing a

system of confidential price discounts gives thus a sign to companies to continue to set unacceptable high public prices. When negotiating prices, companies easily use the argument that "the price in Belgium is already the lowest", where reference is made to foreign public prices without discounts. Governments can also be put under pressure because "in other countries, the product is already reimbursed", again without specifying the actual price.

- There is also no incentive to set public prices at an acceptable level for future innovations. Why would a company immediately set a relatively reasonable price instead of starting with a very high price, knowing that it can refer to the very high public prices of other products and being aware that the possibility exists to negotiate confidential discounts? There is no evidence that the public prices are in relation with the actual costs to develop them. It is often stated that prices reflect "what the market can bear". In fact, a system with conventions possibly even ensures that public prices are put at a higher level than "what the market can bear".

From a game theoretic point of view, companies have a high bargaining power because not reimbursing an intervention for cost issues is not popular. It would not be surprising to see comments like "how is it possible that the policy makers don't put the patients' interest in the first place", or "how is it possible that a wealthy country like Belgium is not able to take care of its patients", etc. However, due to the limited resources and the opportunity costs, reaching prices that are in relation to their added value is of utmost importance. Unfortunately, if policy makers in Belgium are willing to negotiate public prices, they are confronted with the problem that Belgium is a relatively small market. This limits their negotiating power since they run the risk that companies might prefer not to enter the market if public prices should decrease. Doing so might influence foreign prices and have a negative influence on their profits.

The pact of the future stipulates that "in case a joint initiative is taken with one or more countries for the reimbursement of a drug, confidentiality cannot be an obstacle, to the extent that the RIZIV – INAMI and foreign reimbursement authorities respect this confidentiality." However, we also recommend policy makers to collaborate not only to get confidential price discounts but to strive for setting acceptable public prices.



### **The price negotiated should be in relation to the added therapeutic value**

We recommend to look at the added value to determine the price of an intervention:

- For class 2 pharmaceuticals, the prices should be set at the level of the cheapest equivalent alternative. Cost-effective generic alternatives should not be excluded from this list of relevant comparators.
- For class 1 pharmaceuticals, we recommend to set prices in relation to the added value of the intervention. When the problem is only a too high ICER, transparent price negotiations should be performed. If companies are not willing to change the public price, refusing reimbursement or seeking collaboration with other countries should be considered.

*Remark: what is an acceptable ICER? - the unknown but implicitly used ICER threshold*

A very important question that is often asked is: what is an acceptable ICER? Belgium has no explicit ICER threshold and it is impossible to exactly determine this value. Nevertheless, although it is no exact science, as mentioned in KCE report 100: *“cost-effectiveness should be a criterion in the decision making process, as ignoring economic efficiency is unethical.”*

Only in the UK, NICE has explicitly mentioned its ICER threshold in their national guidelines with a value between £20 000 and £30 000 per QALY. Under a value of £20 000 per QALY, an intervention will usually be considered as acceptable, unless there is e.g. great uncertainty about the applied treatment effect in the ICER calculations. Above £30 000 per QALY, an intervention is usually considered too expensive in relation to its added value and strong arguments will be needed to obtain reimbursement.

During the stakeholders meetings, there were discussions on the applicability of an ICER threshold value.

In the assessment files of the CTG-CRM, a value around €40 000 is often mentioned, but it is unclear where this value comes from.

According to some experts, a pragmatic approach could be to build up experience with applying an arbitrary implicit ICER threshold. Policy makers

will then experience whether this value is too high or too low, given their limited budgets. If time after time, policy makers find out that “they don’t get there” with a certain threshold, a stricter threshold should be used. Or in other words: *“If displaced services are more cost effective than the threshold, that threshold is too high”<sup>14</sup>*, and vice versa. The challenge will be to identify the displaced services, which has, as of yet, not happened. Deviating from this ICER threshold for specific reasons is acceptable, for example, one could accept a higher ICER for unmet needs. Or vice versa, even a low ICER can be considered unacceptable if the intervention or disease is not considered to be a high priority. Moreover, even if the ICER is acceptable, other criteria, such as the budget impact can lead to a negative decision (see also below).

Alternatively, other experts propose to define the acceptable budget impact per indication ‘a priori’, and then, define the threshold value for each indication accordingly. The reasoning behind this approach is that the limits of the healthcare budget determine the ICER threshold value (as in the original approach) and at the same time takes into account the fact that society defines health care priorities, and subsequently wishes to allocate different budgets to different conditions. For instance, the acceptable budget impact will be higher for diseases with a high unmet need. This approach requires, however, a measure of unmet need (see above) and an estimation of the possible health gains (e.g. very severe diseases with low QALYs have a higher potential to gain QALYs). More research in this field is ongoing, e.g. in the Netherlands with the concept of “ziektelast-gebonden terugbetaling”.

We also remark that it is sometimes stated that the threshold reflects what we are willing to pay for a (quality-adjusted) life year. Some researchers then try to seek this willingness-to-pay value. Unfortunately, this approach is ignoring the fact that budgets are limited. Under fixed budgets, it is in fact our ‘ability to pay’ that is more relevant.

*Remark: transparent public price reduction (as suggested by CTG-CRM) versus confidential price reductions*

As stated above, transparent price reductions require an international collaboration. Without this possibility, a convention might be considered in the short term but the confidential price reductions should at least be sufficient to reach acceptable ICERs.



In cases where a convention is closed because the treatment effect is still uncertain, government is in fact co-financing the research. Also in these cases, taking into account this uncertainty, we recommend the confidential price reductions should at least be sufficient to reach acceptable ICERs.

*Remark: acceptable profitability*

Several stakeholders mentioned that from the perspective of the public decision maker, the discussion could be ameliorated by defining an acceptable level of profitability for the company (e.g. high price accepted until a certain level of profitability that should then be reduced). However, companies have always refused to give information on the profitability of a specific product, which makes it impossible to have a good view of the underlying cost elements and therefore to judge about justified prices. Furthermore, even if all underlying costs are clear, the discussion on what is an acceptable profit will also not be straightforward.

#### **For extension of indications, the price negotiation should also be in relation with the added therapeutic value**

There is also the possibility that a company first asks the reimbursement for their product in an indication with a limited number of patients, requesting a high price, and then to progressively extend the reimbursement to other indications (a technique called salami slicing). Economic evaluations are currently not requested for extension of indications. We recommend to change this by explicitly including cost-effectiveness as one of the evaluation criteria in such cases. This could allow to judge the 'value for money' of extending indications.

Ideally, the re-negotiation of the price of the product in case of extension of indications should be done considering both the budget impact of the product for all indications and the ICER of the different indications. Theoretically, a financial-based agreements with a price per indication, based on an acceptable ICER for each indication, could be considered, but in practice it might be difficult and more costly to implement this.

#### **The price negotiated should also imply an acceptable budget impact, even if the ICER is considered acceptable**

If the cost-effectiveness is considered acceptable, but the budget impact of the pharmaceutical is deemed to be too high, transparent price reductions based on an appropriate budget impact should also ideally be negotiated. If not possible, confidential agreements where the percentage of refunds increases as sales increase can be negotiated. This could be combined with e.g. a budget cap or a percentage in the last block leading to coverage of the production costs.

#### **Recommendations on price negotiations**

- **If the CTG-CRM considers there is sufficient evidence of no added value or for class 2 requests, the prices should be set at the level of the cheapest equivalent alternative. Cost-effective generic alternatives should not be excluded from this list of relevant comparators.**
- **If the CTG-CRM recognize there is sufficient evidence of added value, transparent price negotiations are preferred. For this, joint price negotiations with other countries could be useful.**
- **If the main issue is the budget impact, and negotiated price reductions are not sufficient to ensure an acceptable budget impact, agreements where the percentage of refunds increases as sales increase can be negotiated.**
- **For extension of indications, the re-negotiation of the price of the product should be done considering both the cost-effectiveness for the new indication and the budget impact of the product for all indications.**
- **For price negotiations, international collaborations should be considered. Countries should work together to reach a justified facial price, which would no longer entail the need for confidential agreements with artificially high prices.**



**Table 4 – Proposal of guidance linking the type of problem or uncertainty with the type of convention**

Main addressed uncertainty →	Preferred type of agreement →	Main objective
<b>Clinical uncertainty</b>		
<p><b>All uncertainties on clinical evidence</b></p> <p><b>e.g. on efficacy:</b> More robust clinical evidence on added therapeutic value is needed or more robust clinical evidence on a direct comparison with the appropriate alternative is needed.</p> <p><b>e.g. on safety:</b> More robust clinical evidence on safety is needed.</p> <p><b>e.g. on quality of life:</b> More robust evidence on the quality of life impact is needed.</p>	<p><b>No reimbursement or Coverage with evidence development (CED only in research or with research):</b> the coverage decision should be conditioned upon the collection of evidence (which could necessitate an international collaboration). The use must therefore be done under controlled circumstances (e.g. through RCT or evidence-providing registries).</p> <p>The decision on the possibility to collect data at the Belgian level should be discussed. This type of convention could be linked with performance-linked agreements (see below on the specific uncertainties).</p>	<p>Generate evidence to make a final reimbursement decision based on solid clinical and economic evidence.</p>
<p><b>Specific uncertainties about the target population:</b> Not clear who is likely to benefit most from the treatment or whether there are biomarkers to identify them.</p>	<p><b>No reimbursement or Coverage with evidence development</b> (see above) possibly combined with:</p> <p><b>Performance-linked agreements:</b> link the performance of the product (measure of clinical outcomes) to payment or reimbursement.</p> <p>Outcomes guarantee: e.g. payment / reimbursement for responders only.</p> <p>Money-back guarantee: e.g. refund or discount for non-responders.</p> <p>Financial-based agreements at the population level <b>if no appropriate measurable clinical outcomes are possible:</b></p> <p>Percentage payback: e.g. percentage of the real turnover that must be refunded, based on a pre-estimation of the non-responders.</p>	<p>Generate evidence on the appropriate target population and/or improve (cost-) effectiveness.</p>
<p><b>Specific uncertainties about optimal treatment scheme:</b> Not clear which duration, doses, or drug combinations are optimal.</p>	<p><b>No reimbursement or Coverage with evidence development</b> (see above) possibly combined with:</p> <p>Performance-linked agreements if appropriate clinical outcomes are measurable and can easily be collected and verified:</p> <p>Conditional treatment continuation: e.g. payment / reimbursement for continued use only for patients reaching a pre-defined (intermediate) treatment outcome.</p> <p><b>Financial-based agreement at the patient level:</b></p> <p><b>Utilisation or time or cost capping schemes: e.g. maximum doses, time, or cumulative cost of treatment per patient (including for example combined therapies) after which the manufacturer pays (at least partly) for any additional doses required.</b></p>	<p>Generate evidence on the appropriate treatment scheme and/or improve (cost-) effectiveness.</p>
<p><b>Specific uncertainty about patient adherence and clinical practice:</b> There are doubts about the</p>	<p><b>No reimbursement or</b></p>	<p>Manage, monitor (rational) use and thereby improve (cost-)</p>



effect in the real life because of concerns about wrong use in clinical practice or bad patient adherence.	<p><b>Coverage with evidence development</b> (see above) possibly combined with: Performance-linked agreements: <b>Conditional treatment continuation: e.g. payment / reimbursement for continued use only for patients reaching a pre-defined (intermediate) treatment outcome.</b> <b>Pattern of care: e.g. reimbursement limited to reference centres, with treatment protocols.</b></p>	effectiveness.
<b>Specific uncertainty about long term outcomes:</b> More robust clinical evidence on long term effects is needed.	<b>No reimbursement or convention</b> with, at least, longer follow-up information from existing trials should be requested. The type of the convention will depend on the other types of underlying uncertainties (see above).	Provide long-term evidence to make a final reimbursement decision.

*Remark: The main focus of the convention in case of uncertainty (as a major issue) should be to solve this uncertainty. In most cases, evidence development will be needed. Therefore, CED is most often mentioned in the above table as the most appropriate type of convention. However, this does not mean that the uncertainty cannot be solved by other types of conventions. For example, collecting long-term evidence can also be enforced with a (long-term) outcome guarantee convention. The link between the possibility to solve the identified uncertainty and the type of convention should always be checked.*

Main addressed problem →	Preferred type of agreement →	Main objective
<b>Clinical problem</b>		
<b>No added therapeutic value:</b> A class 1 was claimed by the applicant but was not accepted by the CTG-CRM and the product is more expensive than the comparator (while this comparator is not under convention).	No convention should be concluded if the CTG consider that there is sufficient evidence of insufficient added value and if there are no other uncertainties. In other cases, the working group should assess if the convention will allow to resolve the remaining uncertainties and whether a convention is considered appropriate.	Improve consistency with the CTG-CRM procedure and transparency
<b>Comparator under convention:</b> (i) a class 2 is claimed by the applicant (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.	<p>Different options:</p> <ul style="list-style-type: none"> <li>Revise the first convention. For this, a horizon scanning exercise should be done to foresee the arrival of new molecule and to take them into account during the negotiations of a convention (for example by including a statement the convention can be reviewed when a competitor arrives on the market).</li> <li>Align the end of the following conventions to the end of the first convention.</li> </ul>	Avoid the continuation of conventions that have lost their reason of existence. Improve consistency with the CTG-CRM procedure and transparency.
<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).	<p><b>No reimbursement or Performance-linked agreement:</b></p> <ul style="list-style-type: none"> <li><b>Outcomes guarantee:</b> e.g. payment / reimbursement for responders only.</li> <li><b>Money-back guarantee:</b> e.g. refund or discount for non-responders.</li> <li><b>Pattern or process of care:</b> e.g. the prescribing is limited to specialized health care centres and / or reimbursement is granted only for patients that satisfy eligibility criteria for example as a result of a genetic test.</li> </ul>	More efficient resource use





Main addressed uncertainty →	Preferred type of agreement →	Main objective
<b>Economic uncertainty</b>		
<p><b>Uncertainty about the budget impact due to uncertainty on the volume:</b> It is 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 behaviour of the prescribing physicians, which is difficult to predict), and hence the budget impact is also uncertain.</p>	<p><b>Data collection on use, combined with:</b></p> <ul style="list-style-type: none"> <li>• <b>Financial based agreements at the population level:</b> <ul style="list-style-type: none"> <li>○ Price-volume (budget) agreement (PVA), with an appropriate percentage of refunds for the last block: One or various thresholds of expenditure (volume) can be defined (i.e. pre-set budget(s)). A compensation mechanism is given once a threshold is exceeded (payback/refund, discount). A 100% refund is possible in the last block.</li> <li>○ The determination of refunds might be based on an acceptable budget impact for that indication, given the estimated outcome.</li> </ul> </li> </ul> <p><b>If there are multiple products with an equivalent therapeutic value for a same indication:</b></p> <ul style="list-style-type: none"> <li>• An agreement could be concluded at the level of the indication (budget cap per indication). Appropriate monitoring mechanisms should be in place for this option to be feasible.</li> <li>• This could be combined with a public procurement, including all products of the same indication, to obtain a better price per treatment.</li> </ul>	<p>Control the budget impact</p>
<p><b>Uncertainty on cost 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.</p>	<p><b>Data collection on use, combined with:</b></p> <p><b>Financial-based agreement at the patient level:</b></p> <ul style="list-style-type: none"> <li>• Utilisation or time or cost capping schemes: e.g. maximum doses, time, or cumulative cost of treatment per patient (including for example combined therapies) after which the manufacturer pays (at least partly) for any additional doses required.</li> </ul>	<p>Manage the use and limit the treatment cost per patient.</p>
<p>Uncertainty on the cost-effectiveness: 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.).</p>	<p>This is often linked to the uncertainty about a medical aspect. In such cases, similarly as with clinical uncertainty, the convention should oblige to perform a study with an appropriate research design to be able to resolve these issues and the negotiated prices should strive to reach acceptable levels.</p> <p>For suggested schemes, please see suggestions under “clinical uncertainties”.</p>	

<sup>a</sup> For an indication for which the medical needs are high, the acceptable budget might be relatively higher. However, if the extent to which the treatment resolves the medical need is limited, the acceptable budget might be limited accordingly.



Main addressed problem →	Preferred type of agreement →	Main objective
<b>Economic problems*</b>		
<p><b>High budget impact:</b> the budget impact of the pharmaceutical is considered too high (high number of patients and/or high costs even if the price is in relation with the added therapeutic value)</p>	<p><b>Ideally, transparent (international) price negotiations</b>  <b>Otherwise, financial-based agreements at the population level:</b></p> <ul style="list-style-type: none"> <li>• <b>Price-volume (budget) agreement (PVA), with an appropriate percentage of refunds for the last block:</b> One or various thresholds of expenditure (volume) can be defined (i.e. pre-set budget(s)). A compensation mechanism is given once a threshold is exceeded (payback/refund, discount). The determination of refunds should be <b>based on an acceptable budget impact for the treatment of the disease.</b></li> </ul> <p><b>If there are multiple products with an equivalent therapeutic value for a same indication:</b></p> <ul style="list-style-type: none"> <li>• An agreements could be concluded at the level of the indication (budget cap per indication).</li> <li>• A public procurement could be considered, including all the products for the same indication.</li> </ul>	<p>Control the budget impact (especially with a 100% cap in the last block)</p>
<p><b>High ICER</b></p>	<p><b>Ideally, transparent (international) price negotiations</b>  <b>Otherwise, financial-based agreements at the population level:</b></p> <ul style="list-style-type: none"> <li>• <b>Discount on the price / percentage payback:</b> percentage reduction of the price / percentage of the real turnover that must be refunded. The determination of refunds should be <b>based on an appropriate ICER.</b></li> </ul>	<ul style="list-style-type: none"> <li>• Improve the cost effectiveness</li> </ul>
<p><b>Extension of indications:</b> Indications are enlarged and no reduction in price is proposed by the company while reductions are asked for by the CTG-CRM.</p>	<p><b>Reassessment of the safety, efficacy and cost-effectiveness of the intervention in the new indication.</b>  <b>Financial based agreements at the population level:</b></p> <ul style="list-style-type: none"> <li>• Discount on the price / percentage payback: e.g. percentage reduction of the price / percentage of the real turnover that must be refunded, based on the ICER of this new indication.</li> </ul>	<ul style="list-style-type: none"> <li>• Improve the cost effectiveness</li> </ul>
<p><b>Packaging:</b> The drug packaging is not adapted to the recommended treatment schedule (waste).</p>	<p><b>Ideally, transparent price negotiations based on the estimated waste.</b>  <b>Otherwise, financial-based agreements at the population level:</b></p> <ul style="list-style-type: none"> <li>• <b>Discount on the price / percentage payback:</b> e.g. percentage reduction of the price / percentage of the real turnover that must be refunded, <b>based on the estimated waste.</b></li> </ul>	<ul style="list-style-type: none"> <li>• Improve the efficient use of resources and incentivize companies to adapt packages to treatment schedules.</li> </ul>

\*A combination of economic problem is possible. For example, a high ICER and high budget impact. In such cases, a price-volume agreement would be required, with an appropriate percentage of refunds for both the first (~ICER problem) and the last block (~budget problem).

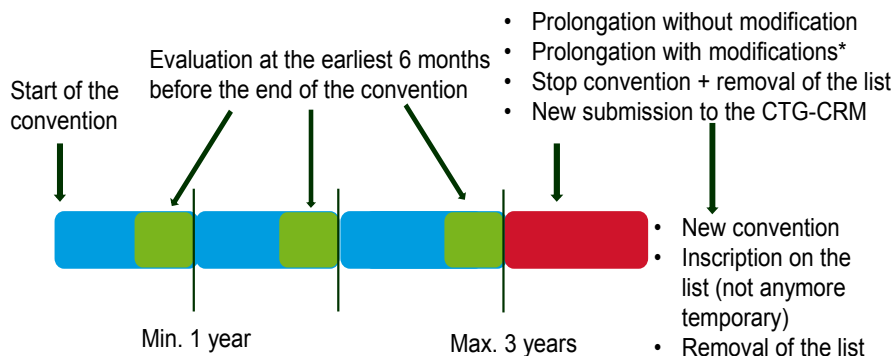


### 2.4.3. The convention duration and the new evaluation process

Currently, the registration of a specialty under convention is valid for a minimum period of one year and maximum of 3 years, and may be renewed periodically up to a maximum of three years (see Figure 4). In the pact of the future it is mentioned that this maximum duration will be extended to a maximum of 5 years. According to some stakeholders, the reason is that it might take more time to gather the relevant information. However, as discussed before, it is possible that the relevant information related to the added value of interventions is not gathered at all. It is problematic to find out about this shortcoming only after 3 or 4 years.

It should also be noted that an evaluation of the convention is done at the earliest six months before the expiration of the convention. For long-term conventions (3 years), this means that the situation is only examined after 2.5 years at the earliest. This is too late. For conventions where information or evidence needs to be gathered, it should be evaluated at an earlier stage whether sufficient efforts are made to comply with the conventions' conditions (e.g. whether the requested study is carried out correctly). A yearly audit could allow to stop a convention if insufficient efforts are made.

Figure 4 – Conventions' duration and evaluation process



We observed that at the end of the convention, it is possible to close a new convention. In the convention, it is stipulated that the company should come up with a proposal to make sure that the costs for the health-care payer are not higher than during the last year of the convention or more (e.g. the whole period) but a simple prolongation of the finished convention is possible. This means that in practice, there is no limitation in the convention duration. A reflection on a maximum duration of conventions (including renewal of conventions) is needed, balancing the need for an appropriate duration for data collection and avoiding the creation of an exponential number of pharmaceuticals under convention creating a system with non-transparent prices.

It should also be noted that in most of the cases, the 'renewed' submission files look almost the same as 3-4 years earlier. This could be due to both the lack of gathering further information, to the fact that data are not yet available, or to the confidentiality of data collected during the convention. The latter also means that the capability of the CTG-CRM to correctly assess the new submission is limited because not all data are available. While e.g. net turnover can be kept confidential, clinical results should at least be made public within an acceptable timeframe.

The analysis of expired conventions also showed that for one of them, a generic was available on the market in other countries during the convention process while in Belgium, the generic was only available one year after the end of the convention. Even if this is not especially directly linked to the fact that the original product was under convention, the confidentiality of these agreements and therefore the uncertainty around the price of the original product could be a barrier for generics to enter the market. Difficulties in setting appropriate prices will also appear as the price of the generic depends of the facial price (without the confidential discounts) of the original product. This should be monitored / investigated in the future.

The analysis also showed that clinical uncertainties observed in the first submission process were not systematically reassessed in the second submission process. This shows the importance of a clear identification of uncertainties and problems by the CTG-CRM to be able to systematically analyse if they are resolved in the second submission.





### Recommendations on the convention duration and the new evaluation process

- **For conventions with evidence generation or where specific information needs to be gathered, we recommend the introduction of an audit, maximum one year after the start of the convention, to check whether the necessary efforts are made to gather the requested information. The convention should be stopped if these efforts are considered insufficient or if inappropriate information is gathered.**
- **The possibility to stop an ongoing convention in case of important market changes should be included. This might be appropriate when an alternative (incl. a generic) is entering the market.**
- **A reflection on a maximum duration of conventions (including all renewals) is needed as well as a monitoring of the impact of these conventions on the arrival and price setting of generics.**
- **Data collected, except sensitive elements such as the net turnover, should not be considered as confidential at the convention expiration and should be made publicly available within an acceptable timeframe. This should be clearly mentioned in the convention conditions.**

### 2.4.4. *Impact on the health care budget for pharmaceuticals*

In 2015, compensation mechanisms received by the RIZIV – INAMI accounted for 26.3% of the turnover for all specialties under convention. Nevertheless, calculating 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 facial price of the product is not based on objective criteria? 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? ‘Savings’ related to conventions should therefore be interpreted with caution. Moreover, an access to the appendices of these conventions is needed to analyse whether the refunds obtained were in line with what should be requested based on appropriate incremental cost-effectiveness ratios and budget impact.



### 3. CONCLUSION

Initially, in Belgium, the main purpose of MEA was to resolve uncertainties linked to an early access to pharmaceuticals and to obtain lower prices.

In case of resolving clinical uncertainties, the initial experience with conventions that are already terminated shows that the expectation of 'evidence generation' has not been fulfilled. For finished conventions, the new reimbursement evaluation reports often show that observed uncertainties were not resolved or that the evidence was 'almost' the same than 3-4 years before. More generally, and also based on our review of the literature, we observed that no evidence information was gathered or that clinical results collected during these MEAs were not published, neither in Belgium nor in other countries. In our opinion, such clinical information should nevertheless not be considered confidential.

In case of tackling high prices, the current application of MEAs provides the short-term advantage that policy makers might succeed in getting a positive reimbursement decision with lower confidential prices, while this would have been a negative decision or a reimbursement at higher prices under a traditional reimbursement. However, the confidential nature of these compensations impede stakeholders outside of the convention working group to analyse if the negotiated prices were in line with e.g. the added value of the intervention. Therefore, it is difficult to judge whether the price reductions are sufficient.

The dangers of the current convention system should not be underestimated:

- Once an intervention is reimbursed there might be *no further incentives to gather additional evidence*, knowing that it is often difficult to turn back a positive reimbursement decision.

- It is possible that *reimbursement requests are submitted earlier without the necessary supportive evidence* and that the manufacturer hopes to be able to close a convention without further evidence generation (see first bullet). The goal should not be just to have an early access but rather to reimburse better and financially acceptable and affordable interventions. This is necessary to have a sound health care system in which quality, accessibility and financial sustainability are central.
- For the pharmaceutical companies, the confidential nature of the conventions is attractive because it implies that public prices are not reduced. In an area where external reference pricing is used to set prices of pharmaceuticals, it is important for them to keep the public price at a high level, as countries are looking at public prices in other countries to determine their national price. For public payers, nevertheless, with those *secret agreements*, the actual price in other countries is unknown and the *system of external reference pricing is becoming obsolete*. This problem was also highlighted in two recent European reports.<sup>13, 15</sup>
- With a system of confidential negotiated prices, which is applied in several European countries, there is *no incentives to set public prices at an acceptable level*. This might also *influence future price setting* of new interventions. In general, in our opinion, a system of confidential prices is not the best approach to tackle the problem of high pharmaceuticals prices.
- More and more pharmaceuticals becomes reimbursed under conventions. For example also pharmaceuticals without any added value when the comparator is under convention. This snowball effect *might make the system completely non-transparent*.
- The possibility of "unlimited" renewals of conventions also makes the *impact on the introduction and price setting of generics* not clear. What if for example the manufacturer does not want to reduce its facial price before the first generic enters the market?



To maximize the potential of the convention system, we suggest an alignment between the content / requirements of the conventions and the identified uncertainties (e.g. added value versus comparator, or budgetary uncertainty). A distinction should also be made between identified problems and uncertainties:

- In cases of problems, it is preferable to tackle this in a transparent way. However, since stakeholders indicate that this is often very difficult at the Belgian level due to a lack of negotiation power, an international collaboration is recommended.
- For uncertainties, in first place, it is the manufacturers' responsibility to provide good evidence. Nevertheless, governments can stimulate research by closing conventions in well selected cases. For example for pharmaceuticals in an area with a high unmet medical need or research with a high importance for the society that otherwise would not be performed by the industry. No such convention should be closed for expensive pharmaceuticals with a questionable added value in broad indications where alternatives are already on the market for many years.

When closing a convention, there should be a clear communication towards physicians, patients and the manufacturer on the identified uncertainties and the temporary character of the conventions. At the end of the convention, the negotiation position of the government should not be undermined, for example, by the difficulty to withdraw a reimbursed pharmaceuticals.

In conclusion, even if MEAs were firstly considered as a win-win situation, it has rather evolved to a system with clear benefits for the pharmaceutical companies while it is actually increasingly unclear whether the public payer is getting such a good deal in the long term. We hope that the described recommendations will support the policy makers when optimizing the current convention system. To tackle the limitations of the current system in the long term, international collaboration is nevertheless needed both for price negotiations as well as for evidence generation.



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## COLOPHON

Title:	How to improve the Belgian process for managed entry agreements? – Short report
Authors:	Sophie Gerkens, Mattias Neyt, Lorena San Miguel, Irm Vinck, Nancy Thiry, Irina Cleemput
Project coordinators:	Nathalie Swartenbroeckx (KCE), Dominique Paulus (KCE)
Reviewers:	Cécile Dubois, Mélanie Lefèvre
External experts:	Lieven Annemans (UGent), Francis Arickx (RIZIV – INAMI), Vinciane Knappenberg (INAMI – RIZIV), Annemie Quanten (RIZIV – INAMI), Ward Rommel (Kom op tegen Kanker), Katrien Van der Veken (RIZIV – INAMI), Inneke Van de Vijver (RIZIV – INAMI), Walter Van Dyck (Vlerick Healthcare Management Centre), Martine Van Hecke (Test-aankoop)
Stakeholders:	Lut De Baere (RaDiOrg, BOKS v.z.w.), Anne Hendrickx (Union Nationale des Mutualités Socialistes), Caroline Lebbe (Landsbond der Christelijke Mutualiteiten), Anneleen Lintermans (Vlaams Patiëntenplatform), Sophie Lorent (Association Belge des Pharmaciens Hospitaliers), Evelyn Macken (Landsbond van de Onafhankelijke Ziekenfondsen), Patrick Robert (BOSA), Françoise Marlier (SPF Economie – FOD Economie), Piet Vancraeynest (RIZIV – INAMI), Nancy Van Helleputte (FOD Economie – SPF Economie), Véronica Zakowski (BOSA)
External validators:	Isabelle Huys (KULeuven), Valérie Paris (OECD), Sabine Vogler (GOEG)
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- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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