OPTIMISING HEALTH CARE

# Engaging stakeholders on Price & Reimbursement of Orphan Medicinal Products and Innovative Therapies

## Definition and proof-of-concept application of a conceptual framework

**30 March 2018**

## Executive summary

We have developed and applied a conceptual framework for facilitating multi-stakeholder discussion on price and reimbursement evaluation processes designed to help organize ideas, structure discussion and identify areas where evaluation processes may be strengthened or improved.

Framework design was based on key concepts identified from a structured literature search complemented with a targeted internet and stakeholder search. The search strategy findings were analyzed and organized into 4 conceptual framework topics (value, uncertainty, budget and sustainability) grouped into 2 components (evidence, i.e. value and uncertainty; and context, i.e. budget and sustainability).

To test the framework, a roundtable discussion was organized on 22 February 2016. Participants selected from different stakeholders – including members of academia, evaluators, sickness funds and authorities representatives – were invited to express their personal views, based on their practical expertise. As such, these views were not to be construed as formal positions or to be representative of the position of any instance or institution any participant may be affiliated with.

The roundtable discussion focused on the key concepts of value and uncertainty in terms of their assessment and impact on price and reimbursement procedures taking into account the specific context of OMPs.

To continue to ensure access to innovative therapies in general, and OMPs in particular, while safeguarding sustainability and maximizing value, open and constructive dialogue on the principles underlying price and reimbursement procedures is of paramount importance. Our approach demonstrates the potential to engage different stakeholders on these principles in a structured and constructive manner.

**hict** main office | Ezelstraat 69 | 8000 Brugge | Belgium | t +32 (50) 33 33 40 | f +32 (50) 33 33 39
info@hict.com | www.hict.com

# I Context

Since the introduction of a specific regulatory framework for orphan medicinal products (OMPs) in 2000[1], the number of approved OMPs in Europe has continuously grown. Despite this favorable framework and the successes in terms of newly authorized products, securing patient access to orphan drugs in a sustainable way remains a topic of key importance and concern for many stakeholders. OMP value and affordability are high priority issues for policy makers; and decisions regarding their pricing and funding are highly complex. There is an ongoing debate on how OMP value should be assessed and valued and policy makers in many countries are considering reforms to improve and sustain access to OMPs.

Celgene, as a bio-pharmaceutical company that has invested, and continues to invest, significantly in OMP research and development, seeks to encourage an open debate on ways to ensure access to OMPs. To initiate this debate, Celgene has previously published a paper outlining an industry view on OMP pricing and reimbursement formulated as 10 principles covering value assessment, innovation & price and the sustainability of the OMP model[2]. This paper served as discussion starter for a European roundtable discussion. To extend discussion to the national level, we intend to refine the '10 principles' framework to a conceptual framework suitable to engage national stakeholders. This framework should help organize ideas, structure discussion and identify areas where evaluation processes may be strengthened or improved. Next, we intend to leverage the framework in a proof-of-concept roundtable discussion, engaging individuals with hands-on expertise from different stakeholders.

This document outlines the two-step approach used to develop the conceptual framework and its application to a proof-of-concept roundtable discussion. First, we describe how the framework was developed based on an analysis of the Belgian price and reimbursement landscape. Next, the approach used to engage stakeholders on the platform is detailed and the results of the roundtable discussion are summarized.

# II Developing the conceptual framework

## 1 Belgian landscape analysis

### 1.1 Methodology

The Belgian price & reimbursement landscape analysis for orphan medicinal products data collection consisted of 4 complementary searches: a structured PubMed search, a targeted website and stakeholder search and a supplementary quantitative web search. The raw findings retained from the different search approaches were processed using consolidated data extraction sheets.

[1] REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products

[2] Gutierrez et al. Orphanet Journal of Rare Diseases (2015) 10:53

The data search was performed from different stakeholder perspectives and focused on the Belgian price and reimbursement context for orphan medicinal products:

- Academics;
- Healthcare providers;
- Industry;
- Sickness funds;
- Belgian policy enablers, makers or executors;
- EU policy makers;
- Patient organizations.

A detailed description of the methodology and approach, as well as an overview of sources consulted in performing the landscape analysis are provided as an appendix to this document (Appendix A).

### 1.2 Key findings

Stakeholders recognize the specificity of OMPs. There is a broad agreement on the fact that uncertainty is typically larger for OMPs than for products in more prevalent disease areas. Stakeholders are also largely aligned in recognizing that elements of value other than those traditionally considered may be of importance in assessing OMP value.

This specificity is to some extent taken into account in price and reimbursement evaluations, with more leeway given to uncertainty on clinical efficacy and a relatively higher willingness to pay, expressed as an acceptance of an expected higher per patient cost.

Due to the often limited knowledge and scattered expertise in rare diseases, involvement of external experts – patients or healthcare professionals – is required to capture the full disease context and to evaluate value. According to the landscape analysis, there is no clear consensus or support on the degree of involvement of patient and healthcare practitioner expertise in the process of a product's price and reimbursement assessment. Current procedure allows to include external expert advice. However, there is less practical support for the inclusion of patient expertise in the reimbursement procedure. This lack of external involvement has been criticized by some stakeholders, feeling unease with the perceived "technocratic" approach employed in evaluating price & reimbursement submissions.

No specific tools for integration of value elements other than simple cost-effectiveness analyses are routinely used in price and reimbursement evaluations. The submission of a cost-effectiveness analysis is not mandatory for OMPs. This reflects recognition that selecting a suitable comparator is often not straightforward; and that clinical data required for the development of cost-effectiveness models are often lacking.

Some stakeholders find that cost-effectiveness analyses, being the current tool of choice for evaluating value for money and benchmarking willingness to pay should be routinely submitted for OMPs. There is some agreement that traditional ICER values may be insufficiently sensitive to OMP value, resulting in necessarily larger than average ICERs. Alternative approaches, using weighted quality adjusted life years (QALY) or modified ICER thresholds have been proposed to mitigate these issues.

OMP specific elements of value are most often implicitly taken into account, rather than explicitly. The lack of quantification through objective measures can render it difficult to balance these elements in price and reimbursement procedures.

Inclusion of patient-metrics (Quality of Life, Patient Testimonials, Patient Satisfaction) is not always perceived positively, due to the lack of standardized tools and limited feasibility of a quantitative analysis, reinforced by the rarity of OMP conditions.

Formal multi-criteria decision analysis (MCDA) frameworks may offer a more comprehensive approach to integrating disparate value elements. These have thus far not been used in practice and proper theoretical and practical frameworks have not yet fully been established.

Uncertainty discussions are often restricted to budgetary uncertainty, rather than value uncertainty. The estimation of budgetary impact is deemed to be extremely important in the context of OMP price and reimbursement evaluations. The added uncertainty on cost-effectiveness in the context of typically higher per patient prices presents a challenge potentially impeding or slowing access to OMPs.

Real-world data can be used to reduce uncertainty on the value or budgetary impact of a drug. Real-world data can be used to collect additional evidence supporting the effectiveness claims made at reimbursement. Real-world data can help monitoring outcome measures that are the basis of a risk-sharing agreement. Value-of-information techniques can be used to decide whether the benefits of collecting more data exceed the costs of further data collection.

## 2 A conceptual framework

The landscape analysis suggests that the major hurdles faced by OMPs in current price and reimbursement evaluations are linked to “value” and “uncertainty”. The combined impact of the limitations of current evaluation approaches in accounting for OMP specificities and the higher levels of uncertainty typically associated with limited clinical experience, lack of suitable comparator treatments and restricted evidence put considerable pressure on the objective evaluation of OMPs.

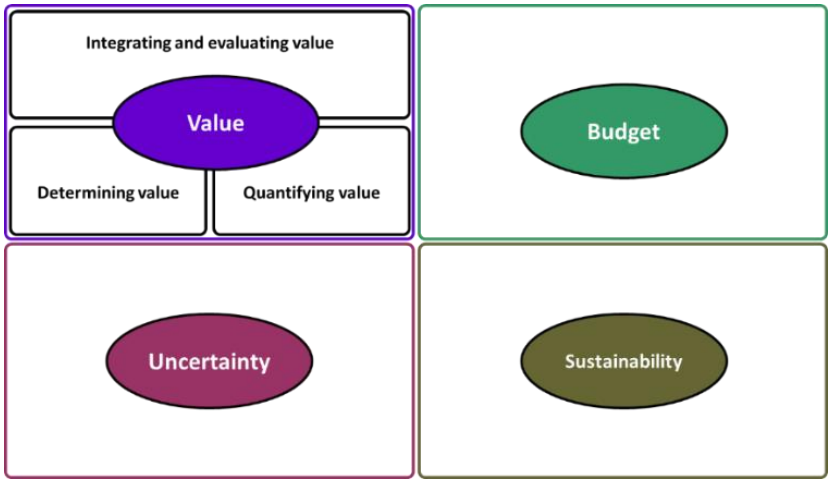


Figure 1: Proposed conceptual framework

In particular, the analysis suggests that separating value assessment and uncertainty management, as well as distinguishing between budgetary and value uncertainty, is key in OMP price and reimbursement evaluations. Therefore, there is a need for a conceptual framework that would allow to have a more structured and articulated approach to these overlapping, yet different concepts. Distinguishing the evidence driven "value" and "uncertainty" concepts from the "budgetary reality" and "societal sustainability context" in which evaluations are performed, may aid in separating "value" from "uncertainty". In this view, the task of the CRM consists of assessing a product's value and uncertainty, established from the available evidence, on the product's intended use in the context of current budgetary reality and future societal sustainability.

Building on the European '10 principles' value framework[3], integrating the results of the Belgian landscape analysis, we propose a conceptual price and reimbursement framework consisting of 2 "evidence" and 2 "context" driven elements (Figure 1): value, uncertainty, budgetary reality and societal sustainability.

*Value* refers to a product's value elements, in the broadest possible sense, reflecting some aspect of desirability, be it from the perspective of the patient, the payer, or the society as a whole. A value framework should cover three immediate needs: (1) establish a reference of what value elements could and should be included in the presentation of a product's value; (2) provide a means for objective, inter-product comparable quantification of these value elements; and (3) provide a means for integration of these quantified value elements allowing for benchmarking different products, taking into account their expected cost and budgetary impact.

*Uncertainty* is caused by a paucity of evidence, introducing uncertainty on the product's value elements or its projected budgetary impact.

*Budgetary reality* reflects the evaluation of the estimated budgetary impact against currently available budgets.

*Societal sustainability*, finally, reflects a societies' capacity to support a product's reimbursement in the future by considering its impact on society as a whole.

## III Engaging stakeholders on the conceptual framework

Based on the landscape analysis finding that the major hurdles faced by OMPs in current price and reimbursement evaluations are linked to "value" and "uncertainty", these concepts were used to drive a proof-of-concept roundtable discussion with experts with relevant experience representing various stakeholders involved in price & reimbursement procedures. Participants were provided with an overview of the landscape analysis approach and outcomes and a 'discussion starter' text drawn from the landscape analysis, outlined below. They were then asked to complete an electronic survey which was discussed during a 1-on-1 phone interview with each participant. The interviews were organized in November – December 2015 and followed up by the roundtable discussion on February 22, 2016.

[3] Gutierrez et al. Orphanet Journal of Rare Diseases (2015) 10:53

# 1 Background – Discussion starter text

## 1.1 Establishing OMP value

The landscape analysis demonstrates a need for an objective value framework, which can be used for comprehensive, balanced evaluation of OMP value in the context of price and reimbursement evaluations. OMPs have specific elements of value, which in some cases are more difficult to quantify and which do not fall in the scope of current tools used in the price and reimbursement value assessment chains, such as budget impact and cost-effectiveness analyses. As a result, elements such as disease rarity, disease severity, the lack of suitable alternatives to treatment, or even ethical considerations the rule of rescue or the broader societal impact, though essential to OMP value, are difficult to objectively consider in price and reimbursement assessments.

The issue of developing value assessment frameworks integrating differing elements of value has previously been addressed in different countries and in literature. Multi-criteria decision analysis frameworks, both specifically for orphan drugs as well as in non-orphan indications have been proposed. Different frameworks integrate different value drivers, including elements linked to disease impact, target population characteristics, impact of the drug or technology and other decision factors. An overview of published MCDA frameworks and a summary of criteria used in these frameworks is included as an appendix to this document (Appendix B). Despite the efforts in developing MCDA frameworks, there is of yet no consensus on the most appropriate tool, nor the value elements to be included and the use of MCDA frameworks in the context of price and reimbursement submissions remains a subject of ongoing debate.

## 1.2 Dealing with uncertainty in the context of OMPs

Uncertainty on value should be distinguished from value uncertainty. Value uncertainty for OMPs is mainly due to the smaller target populations for OMP indications, typically resulting in less available data to accurately assess effectiveness and efficacy. Budgetary uncertainty is mainly caused by elements outside of a product's value, such as a lack of data on the actual size of the target population.

Without appropriate risk management approaches, uncertainty may disproportionately impact price and reimbursement evaluations. Conceptually, uncertainty can be managed in one of two ways: statically or dynamically.

In static risk management approaches, a pre-defined set of rules is applied at predetermined time points, regardless of the outcome in real life. For instance, a pay-back mechanism to be applied upon reaching a certain budget impact. More clinically driven and pay-for-performance schemes can also be implemented, for instance with predetermined paybacks for non-responders. Pay-back mechanisms are often favored due to their perceived predictability.

Dynamic risk management approaches employ a different philosophy, in which a product's real life performance is continually evaluated against criteria which can be adapted over time. Dynamic risk management approaches are aligned with ongoing discussions on adaptive licensing, in which a product's price and reimbursement conditions can be revised more than once after the initial reimbursement. As such, it offers the possibility of a more long-term product life-cycle management.

The optimal risk management approach may be different for managing value or budgetary risk and a combination of approaches may represent the most adequate solution for simultaneously managing budgetary and value uncertainty.

One key differentiator in static versus dynamic risk management approaches is that the latter typically require longer time horizons and may introduce additional uncertainty at initial reimbursement for both payer and provider. A disadvantage of short-term static risk management approaches is that the limited time horizon they offer may not lead to a more defined view of the value of the product.

In considering the collection of real-life data, there should be a general reflection on the most efficient data collection solutions. Objectivity and efficiency gains may be obtained from organizing data collection from a disease point of view rather than a product point of view (i.e. disease registries as opposed to product registries). This may require a more general approach to data collection, management and exploitation than those which can be established in the context of a specific reimbursement evaluation.

Finally, in considering the benefits of acquiring real-life data in the context of specific reimbursement submissions, the cost or complexity of generating these additional data should be balanced against the additional value they contribute. Value-of-information techniques can be used to decide whether the benefits of collecting more data exceed the costs of further data collection.

### 2 Survey questions

A copy of the survey provided to participants is listed in appendix C.

## IV Roundtable discussion

### 1 Meeting participants

Roundtable participants were selected based on their interest or involvement in price & reimbursement evaluations of innovative therapies in Belgium, including members of academia, evaluators, sickness funds and authorities representatives. Participants were invited to express their personal views, based on their practical expertise in price and reimbursement of innovative therapies in Belgium. As such, these views should not be construed as formal positions or to be representative of the position of any instance or institution any participant may be affiliated with.

Additional participants included representatives from **hict**, facilitating the meeting, and Celgene. Celgene provided the logistics for the meeting. Their representatives attended the meeting as observers and did not participate in discussions.

# 2 Roundtable discussion summary

## 2.1 Establishing value

### *2.1.1 Value elements*

**Summary statements**

| Question | Agreement |
|---|---|
| OMPs have specific elements of value in comparison with drugs in more prevalent indications | + |
| Some value elements, notably for OMPs, are not formally considered or valued by current pricing and value assessment tools | - |
| There is a need for an objective value framework for OMPs, covering three immediate needs: (i) establish a reference of what value elements could and should be included in the presentation of a product's value; (ii) provide a means for integration of these value elements; and (3) provide a means for integration of these quantified value elements allowing for benchmarking different products, taking into account their expected cost and budgetary impact | ++ |
| Multi-criteria decision analysis frameworks should be considered for OMP value assessment | +++ |

**Legend:** **Agreement** (**+++**: unanimous; **++**: significant (≥80%); **+**: moderate (≥60%)); **Disagreement** (**---**: unanimous, **--**: significant (≥80%); **-**: moderate (≥60%); No majority agrees or disagrees (**0**)

**Discussion**

In the context of the evaluation of a price & reimbursement submission, by Royal Decree, "value" is determined based on three elements::

- (Impact on) mortality;
- (Impact on) morbidity;
- (Impact on) quality of life.

The main challenge in dealing with all innovative therapies (including, but not limited to OMPs) lies in evaluating these three criteria consistently and thoroughly. For instance, currently, there are no weights assigned to each of them. Hence, in some files mortality may be considered as more important whereas in others morbidity or quality of life will be assigned more importance.

An additional element is that in the consideration of these 3 elements there is a *disease related aspect* and a *treatment related aspect*. The current impact of the *disease* on patients (in terms of mortality, morbidity and quality of life) is an indicator of therapeutic need. Indeed, the higher this current impact (or, more accurately, the lower the remaining medical need not covered by actual treatment alternatives), the higher the need for a new and better treatment. The impact of the *treatment* on each of these elements is an indicator of the size of the benefit that can be achieved, i.e. to which extent can the therapeutic need be fulfilled. The value of a new medicine is driven by both the impact of the disease (unmet need) and the treatment (reduction in medical need through treatment).

Though the three value elements included in the royal decree, taking into account these disease and treatment related aspects, offer a basis for a framework for evaluations,

practical issues remain, hampering actual evaluations. For one thing, it is often not straightforward to provide a sufficiently sensitive and specific quantification of the impact of the disease and/or treatment on the three criteria. Evaluations of new therapies can be further complicated due to the increased use of combination therapies, in which a new drug is used in combination with existing therapies and evaluation may need to take into account the combined impact of the combination therapy.

To increase the sensitivity of value evaluations, other value elements could be considered, such as specific (vulnerable) target populations (e.g. pregnant women, children, ...), disease rarity, age, savings in other areas of healthcare (other than drug expenditure) or areas beyond healthcare and innovation.

An example of a concrete policy to take vulnerable target populations into account is reflected by the fast track procedure for pediatric indications for drugs with existing adult indications. The policy includes shorter procedure timelines and an exemption to the usual price reductions for increased sales volumes. In essence, this is a practical example of target group preference.

Disease rarity as such may not be a value element to consider above and beyond traditional value elements. However, disease rarity may impose particular challenges in expressing or quantifying traditional value elements, both from a disease and treatment context.

Taking into account age may have important consequences for disease areas. For instance, in those areas which are of particular importance in the elderly, like oncology, the evaluation of 'value' may be influenced by the high age of the target population (hence assigning less value). There is disagreement as to whether this may play a role at all.

Demonstrating savings in other areas of healthcare, and even more so in areas beyond healthcare, requires particular evidence, which is in practice often difficult to generate. Furthermore, savings generated (or predicted to be generated) should likely not directly and entirely translate into proportionally higher medicine prices, but rather be shared between manufacturer and payer. Nevertheless, a study performed by Els Schotte[4] demonstrated, based on published evaluations of reimbursed drugs, that there is an observed preference for reimbursing drugs realizing savings in the healthcare budget, including in areas other than the pure drug budget.

"True" innovation may present a value of interest and there is general agreement that this should be rewarded. Nevertheless, in some cases, repurposed existing therapies are relaunched as "new" drugs in specific indications. In those cases, typical value protecting mechanisms and rewarding, notably for OMPs, may need to be limited. A more refined definition of "innovation" may help identifying those medicines whereby innovation as such deserves to be rewarded.

[4] Els Schotte, Een onderzoek naar mogelijke factoren die een impact kunnen hebben op de terugbetalingsbeslissing van geneesmiddelen. Master thesis, UGent, 2009.

### 2.1.2 *Quantification of value elements*

**Summary statements**

| Question | Agreement |
|---|---|
| Cost-effectiveness analyses should be mandatory for OMPs | ++ |
| Cost-effectiveness analyses should apply to OMPs, but with modified thresholds | + |
| Some value elements, relevant for OMPs, are more difficult to quantify using current tools in price and reimbursement, such as cost-effectiveness, budget impact or patient-reported outcomes | +++ |

**Legend:** **Agreement** (**+++**: unanimous; **++**: significant (≥80%); **+**: moderate (≥60%)); **Disagreement** (**---**: unanimous, **--**: significant (≥80%); **-**: moderate (≥60%); No majority agrees or disagrees (**0**)

**Discussion - Quantifying value**

The appreciation and quantification of value is a particular challenge for OMPs and especially for medicines for ultra-rare diseases, due to the difficulties to obtain solid evidence by the time of submission for reimbursement. Value of OMPs should typically be considered from an individual patient perspective; i.e. in terms of what the current disease burden is for patients and what the expected benefit is of the new treatment in addressing this burden.

In order to better understand how the different elements of value play a role at the disease level, an exercise was performed within the INAMI in the context of the Art. 25 "unmet medical need" program. The exercise was designed to establish a ranking of the unmet need for a set of disease areas. The framework consisted of a sort of MCDA in which multiple criteria were included and weighted to obtain the final ranking. The ranking was found to be fairly robust to changes in weighting. However, comparing acute and chronic diseases in one effort and with one instrument was found to be more difficult.

The KCE has been working[5] on validating the methodology used. Though the current exercise was demand-driven (i.e. driven by products seeking reimbursement under the "unmet medical need" program), it could also be performed outside of a product context. A possible critique on the exercise is that it was solely focusing on disease aspects and not on the effects of the potential treatments of these diseases. Ideally, a ranking exercise should focus on the net effect of disease impact and treatment availability: i.e. prioritizing those treatment areas where unmet need is high while existing treatment set is low.

The quantification of the (impact of a drug on) quality of life presents a clear challenge. Basing quantification on expert advice (be it patient or healthcare practitioner) remains a subjective appreciation rather than an objective quantification. The typically used EQ-5D tool is a rather generic and non-specific tool, often lacking sensitivity and specificity. It is often criticized for not capturing all the elements that really matter to patients.

Improving quality of life measurements requires further development or refinement of existing tools. Whether the most appropriate approach consists of developing a range of

[5] KCE Report 272A

disease-specific or more context-aware generic tools remains a subject of debate. Disease specific tools are more adapted for detecting relative differences in quality of life relevant in a specific disease context, but typically yield results which are difficult to compare across disease areas and disease-specific tools. Generic tools allow cross-domain comparison, but typically lack sufficient sensitivity to disease-specific relevant improvements. Developing generic tools with sufficient sensitivity across disease areas and which can be validated in different disease areas represents a clear challenge.

It is important to consider the perspective of evaluation and to be sufficiently broad in the assessing potential value, e.g. consider (i) patients and caregivers; (ii) healthcare payers; (iii) society. Value from the broad perspective can be of particular importance for some drugs and it should be possible to take this into account. It should, however, be noted that demonstrating value beyond direct patient value (such as saving resources in the health care system) requires sufficient evidence to support this value (which may be difficult to collect) and that realizing this value may itself require investments (e.g. moving from hospital to home care requires sufficient home care infrastructure and support). These additional investments could be included in the drug's budget impact analysis.

**Discussion - Cost-effectiveness**

For OMPs, submission of a cost-effectiveness analysis (calculation of an Incremental Cost-Effectiveness Ratio - ICER) is currently not mandatory. In reality, the CRM appreciates calculation of an ICER. In case an ICER is not presented, experts sometimes approximate a “dummy ICER”, or consult reimbursement applications in other countries where an ICER was presented. There might be value in more formal ICER submissions in the assessment for OMPs.

If current procedures were to change to include mandatory ICER calculation for OMPs, several elements should be factored in.

For instance, when calculated, OMPs can be confronted with high(er) ICER values (in comparison to some drugs in more prevalent indications) in combination with relatively minor budgetary impact (due to smaller target populations). There is, however, debate amongst the roundtable participants whether or not the relatively low budgetary impact or OMP designation should be factored in when appraising calculated ICER values. Some participants feel low budgetary impact or OMP designation should not translate into different ICER appreciation. Other participants feel that some incentive is required for manufacturers to develop drugs in small populations with difficult to demonstrate or less cost-effectiveness. Using modulated ICER thresholds could be a tool to allow for this.

Unmet need could also play a role in higher ICER thresholds as is the case in the U.K.

**A note on pricing**

The meeting participants recognize that given the small target population, drug prices for OMP's are higher, but also agrees that drug pricing suffers from a lack of transparency[6,7]. Using purely value-based pricing, i.e. basing price solely on the willingness to pay for health benefit, is felt to hold the risk of driving manufacturer's prices as high as possible, rather than being justified on required return on investment. Hence, there is need on more transparency of costs, thereby acknowledging that better value should also be rewarded. The FOD Economic Affairs, which is competent for reviewing drug prices, could play a role. Nevertheless, true cost transparency in a cost-plus pricing method may be elusive and other techniques may be of use (such as demand-based modulated ICER pricing).

For future drugs with high prices and/or high ICER values, the horizon scanning performed by KCE can help to initiate an early dialogue between manufacturers and payers. A similar platform initiative exists on the EU level (MOCA).

### *2.1.3 Value assessment*

**Discussion**

The Belgian evaluation procedure first considers the evaluation of value, before the evaluation of the economic implications. The value evaluation procedure consists of a combination of value *assessment* (i.e. quantification of value) and value *appraisal* (i.e. evaluation of the quantified values). Meeting participants found the appraisal part of the reimbursement procedure (i.e. the "subjective" interpretation aspect), to be important – even though they agree strengthening the assessment ("i.e. the "objective" quantification of value) fueling the appraisal is important. A pure assessment based procedure, as in the UK for instance, is found to be less desirable than a procedure in which experts are able to provide an opinion/interpretation of assessment.

Evaluation and appraisal of drug and disease context for price and reimbursement requires an extremely broad set of expertise. In practice, it is not always straightforward for the CRM (commission for the reimbursement of medicines) members to consistently and coherently perform evaluations. Formally, academic CRM members represent the institution they are selected from, and as such are required to inform themselves within their institution with respect to the different areas of expertise required for specific evaluation dossiers. Stimulating coordination meetings between university representatives prior to meetings of the CRM could result in a more coherent and informed academic point of view.

In practice, additional support in performing the evaluations may be of use in the preparation of assessments for CRM appraisal. One possible approach would be to have assessments performed by a committee of (internal or external) experts and the appraisal performed by a committee of stakeholders.

[6] Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet Journal of Rare Diseases 2011, vol. 6, no. 42.
[7] Picavet E., Morel T., Cassiman D., Simoens S. Shining a light in the black box of orphan drug pricing. Orphanet Journal of Rare Diseases 2014, vol. 9, no. 62

The CRM currently already involves an external (disease) expert for Class I and OMP submissions. Involving disease experts may introduce potential conflicts of interest, as disease experts are often involved in clinical trials.

Likewise, involving patients may be of considerable value, but their involvement should be carefully considered as it may create a subjective conflict of interest (e.g. patients will usually deem interventions for their condition to be of value). Finding patients willing and able to contribute to evaluations may be challenging, especially for drugs in less prevalent indications. The role of patients is nevertheless crucial, notably with respect to providing disease experience context (documenting and assessing unmet medical need and drug impact on the unmet need) and input for establishing reimbursement criteria. Hence the meeting participants believe that patients should be heard and consulted but that they should not be directly involved in the actual decision making or prioritizing. Civilians (non-patients) may however be involved in determining priorities.

In the value assessment process, an increased 'filter' role of the EMA is requested: EMA registration procedures should be more critical in assessing the added value of a new intervention, rather than shifting this responsibility towards the national levels. A possible step forward would be that the EMA provides an appraisal of the size and clinical significance of the added therapeutic value of a new OMP. It should be pointed out that though HTA expertise may be organized on EU level, HTA is a distinct discipline. EMA's primary function is marketing authorization; even if EMA-experts may provide useful insights, HTA expertise is different and requires other experts.

Finally, there should be room for publicly funded trials, adhering to the same standards as industry sponsored research, to fuel new indication applications. This requires a change in legislative context.

## 2.2 Dealing with uncertainty

### *2.2.1 Managed entry agreements*

**Summary statements**

| Question | Agreement |
|---|---|
| Uncertainty on value should be considered while making abstraction of budgetary reality | + |
| Dealing with budgetary and value uncertainty requires different approaches | + |
| There is merit in careful consideration of the nature and typology of uncertainty in considering the need for its management | +++ |
| The cost or complexity of generating additional data should be balanced against the additional value they contribute | ++ |

**Legend:** **Agreement** (**+++**: unanimous; **++**: significant (≥80%); **+**: moderate (≥60%)); **Disagreement** (**---**: unanimous, **--**: significant (≥80%); **-**: moderate (≥60%); No majority agrees or disagrees (**0**)

**Discussion**

In case of insufficient evidence at the time of submission for reimbursement, additional data should be required once a medicine is in the market. Indeed, a lot of data is still lacking at that time and important concerns often remain regarding uncertainty on claimed efficacy or effect.

The collection of real-world data can go hand in hand with outcomes-based market access agreements. The current 'Art. 81 contracts' offer a framework for managing uncertainty, including through integration of real-life data. As such, they lower the threshold to reimbursement through the creation of a "safe" temporary reimbursement. Nevertheless, proper follow-up of data collection, including defining consequences in terms of price & reimbursement should be guaranteed to avoid Art. 81 contracts to offer no more than a false sense of security. If claimed value cannot be demonstrated, authorities should be able or should apply the possibility to de-reimburse products. Furthermore, it is unclear whether temporary reimbursement schemes manage to provide answers to uncertainty at time of initial assessment; other than to provide temporary budget savings (~26%; MORSE report 2014).

### *2.2.2 Real-life data collection & data governance*

**Summary statements**

| Question | Agreement |
|---|---|
| Real-life data collection should be organized from a disease point of view rather than from a product point of view | ++ |
| Real-life data collection should be organized by the manufacturer | + |
| Real-life data collection should be organized by the authorities | +++ |

**Legend:** **Agreement** (**+++**: unanimous; **++**: significant (≥80%); **+**: moderate (≥60%)); **Disagreement** (**---**: unanimous, **--**: significant (≥80%); **-**: moderate (≥60%); No majority agrees or disagrees (**0**)

**Discussion**

In order to guarantee the quality of the collected data, provide meaningful insight and effective grounds for re-evaluation, a well-defined data collection protocol is required, based on the specific questions it needs to address. Such data protocol should minimally include:

- A clear description of the type and nature of uncertainty that the data collection protocol should address;
- A clear description of the specific questions that should be answered in light of the type and nature of uncertainty that is to be managed;
- An indication of the most appropriate form of data collection to support answering the specific questions posed;
- For each parameter to be considered
  - An overview of the main causes of uncertainty related to this parameter;
  - An appreciation of the importance of reducing the uncertainty on this parameter, e.g. a sort of "uncertainty index";
  - An indication of the adequate follow-up time needed to address the uncertainty.

There is a relationship between the data needed in this re-evaluation process and the data needed in respect to pharmacovigilance. This relationship/synergy should be better explored.

Proper data governance is needed to ensure quality of data collection at a reasonable cost as real-life data collection on efficacy and effect requires data collection from healthcare practitioners and may require collecting data from patients. Private practices should not be lost sight of, as not all (rare disease) patients are necessarily routinely seen in the hospital or expert center setting.

To ensure cost-effective data collection and manage data quality, data collection tools should integrate with day to day working tools of the physicians. Furthermore, data collection efforts should be aligned on (i) integration with international data collection efforts; (ii) concentrating expertise in reference centers; (iii) the inclusion of peripheral hospitals (and private practice) through networks.

Data collection on OMPs indeed transcends national boundaries and should ideally be organized on the European level. Nevertheless, in the absence of EU data collection protocols and frameworks, pragmatic, coordinated and concerted national data collection is necessary. Collaboration on registries is included in the BeNeLuxA protocol, in which other countries have expressed an interest.

Data collection can be organized from a product, disease or broader perspective. The potential disparity of ongoing product-driven efforts results in solutions that may scale poorly, or may be hampered by practical and methodological issues limiting their exploitability in a broader context. Mitigating this risk can be done either by organizing data collection from a broader perspective (disease perspective, or even across diseases, for instance across all OMPs), or by providing a clear framework in which the different bottom-up initiatives can be plugged to increase interchangeability, transparency and quality.

Part of data governance is data ownership/financing. Different models are possible, such as:

- *Public-private partnerships,* e.g. as set-up for biologicals: a database managed/owned by an expert group, providing access with differing levels of transparency, taking into account patient/product confidentiality governed by a data board. Experience shows industry is willing to pay for access to certain types of information.
- *Trusted third parties (TTP)*, e.g. registry in oncology. The TTP should have the legal means to coordinate the study and be able to bring relevant parties together. The IMI-EMIF is working on providing such a platform.
- *Public infrastructure, supported by private funding*: e.g. in Italy pharmaceutical companies fund the development of data registries developed by payers.

With respect to data integration, there is an ongoing effort to standardize EPD (electronic patient dossier) systems to integrate with a central data interchange platform (healthdata.be). This data platform is also designed to form the link with international data sharing initiatives. Standardization is to be gradually stimulated over the course of several years through requirements to meet industry (HIMMS) standards.

### *2.2.3 Re-evaluation*

**Discussion**

The re-evaluation after a period of data collection is similar to the type of evaluation performed at the time of initial reimbursement. Based on an assessment of the data collected a re-appraisal should be performed forming the basis of a potential price & reimbursement revision. Thereby it is important to take into account again the nature and type of uncertainty, and the specific questions that needed to be addressed and the parameters that needed to be collected (as was specified in the protocol). As for the original evaluation performed at the initial reimbursement, the re-assessment can be supported by external expert (groups) providing assessment input for appraisal by the CRM experts.

The impact of the evaluation may be defined on individual patient or population level. In most cases, rather than ending reimbursement of a product, an “optimization” is likely to occur, for instance refining the target population or reimbursement conditions. The implications of data collection for reimbursement warrant further consideration. Revisions in reimbursement conditions can pose ethical problems, for instance in case a drug is found to be effective in only a segment of the initial target population. Better measures should be in place to anticipate on such situations.

Ideally, the assessment process should integrate all relevant stakeholders who are responsible for the uncertainty. These include:

- Manufacturers (responsible for demonstrating the effect of the product);
- Healthcare experts (responsible for the correct prescription and use of the product);
- Patients (e.g. part of the uncertainty could be related to compliance, or to assess real-life impact).

Dealing with uncertainty is a shared responsibility in which industry, payers and healthcare practitioners should work together to combat uncertainty.

# V Conclusions

Our conceptual framework demonstrates the potential to engage different stakeholders for a constructive discussion on the principles of price and reimbursement of innovative therapies in general, and OMPs in particular. Separating evidence from context and structuring discussion on 4 key elements (value, uncertainty, budget and sustainability) allows to focus discussion on each of these elements on their own merit.

At the basis of our framework, the Belgian landscape analysis delineated the existing boundaries and challenges. Stakeholders recognize the specificity of OMPs. This specificity is – to some extent – taken into account in price and reimbursement evaluations. However, no specific tools for integration of value elements other than simple cost-effectiveness analyses are routinely used in price and reimbursement evaluations. The submission of a cost-effectiveness analysis is, at present, not mandatory for OMPS. As such, OMP specific elements of value are most often implicitly taken into account. Explicit inclusion of patient-specific metrics is not straightforward, both from the evaluator's and the submitter's perspective, due to the lack of standardized tools and limited feasibility of a fully quantitative analysis, reinforced by the rarity of OMP conditions. In general, for evaluation of OMP value in its broader context, involvement of external experts is required. There is, however, no clear consensus or support of patient and healthcare practitioner expertise.

Leveraging our 4-element framework, this context was discussed extensively during the roundtable. Differing views on elements of value, their quantification and assessment, and on dealing with uncertainty through managed entry agreements were discussed. These were built on participant responses on a set of statements queried in a preparatory survey and fleshed out through subsequent one-on-one phone interviews.

Though stakeholders were explicitly invited to discuss their personal, rather than their institutional, views, our proof-of-concept suggests that using a similar platform in a more formal context may be feasible and constructive. Ensuring continued access to innovative therapies while safeguarding sustainability and maximizing value, requires the possibility to engage in open and constructive dialogue on the principles underlying price and reimbursement procedures with different stakeholders. Our approach demonstrates how a structured approach may assist in providing a platform to engage on.

# VI Contact

**hict**

| Sebastian Vermeersch (sebastian.vermeersch@hict.be)

**Celgene**

Serge De Ruysscher (serge.deruysscher@celgene.com)

# Appendix A: Landscape Analysis Methodology

## 1 Data collection strategy

The research phase data collection strategy consisted of 4 complementary searches: a structured PubMed search, a targeted web search, a targeted stakeholder search and a supplementary quantitative web search. Data collection was performed in August 2016.

### 1 Structured PubMed search

Published literature constitutes the backbone of the landscape analysis. PubMed was searched using a combination of Mesh and regular terms and search results were restricted to publications dating from the last 10 years (2005 – 2015). The following search strategies were used:

- Search terms: Rare diseases [Mesh] AND Belgium;
- Search terms: Orphan drugs [Mesh] AND Belgium.

Articles identified using either of the search term combinations were scanned, first looking at abstracts only, additionally evaluating the full text and were included in the landscape analysis if relevant information on any of the 10 principles was identified. This process finally resulted in the inclusion of 59 articles in the landscape analysis.

### 2 Targeted website search

This involved specific searches covering stakeholders identified prior or during the landscape analysis:

Websites of organizations involved or potentially involved in the reimbursement procedure; e.g. FAGG, RIZIV/INAMI, patient organizations, ...

- Websites of the insurance funds;
- Websites of political parties;
- Belgian government coalition agreement;
- Policy plan of the Belgian Minister of health;
- Published questions and answers of the Belgian Chamber of Representatives.

Targeted websites were searched for any relevant information relating to orphan drugs or rare diseases and manually vetted for inclusion. This process finally resulted in the inclusion of 19 distinct web pages.

### 3 Targeted stakeholder search

For individuals identified prior or during the landscape analysis, a specific Google search was performed in 3 languages:

- “Individual name” + “weesgeneesmiddelen”;
- “Individual name” + “médicaments orphelins”;
- “Individual name” + “orphan drugs”.

The first page of search results was analyzed. Each identified source was additionally checked for cross-references with other stakeholders. Search results were complemented with an additional Twitter search.

### 4 Supplementary quantitative web search

All sources identified in any of the previous search approaches were checked for relevant quantitative data. Data sources identified were then checked for the most recently available data. Additional quantitative data was obtained from the 2012 RIZIV/INAMI MORSE report.

## II Data processing

The raw data desk research results retained from the different search approaches was processed by extracting relevant information. The extracted information was captured in several data extraction sheets. For each relevant element extracted, the following information was registered: date of the search, organization/journal, title, year, website, author(s), people involved, general information of the source and for the website search also whether the data source related to national or international data. These were collected in combination with the actual extracted information to provide context and background for processing.

Data extracted was grouped in different data extraction sheets. A first data extraction sheet covers qualitative data retaining specifically to the 10 principles, an overview of relevant statements found in party programs for most Belgian political parties and an overview of the searches per stakeholder. A second data extraction sheet covers any quantitative data collected during the course of the desk research.

Additionally, contact info for identified stakeholders was collected. Finally, an high-level overview of the price and reimbursement procedure currently applicable for OMP was provided.

All data identified was finally summarized into a single overview excel. This overview omits the contextual information provided in the more detailed data extraction sheets in favor of a more compact and presentable overview of statements presented per stakeholder.

## III References

The following references were consulted as part of the landscape analysis:

[1] A. Denis, S. Simoens, C. Fostier, L. Mergaert, and I. Cleemput, “Beleid voor zeldzame ziekten en weesgeneesmiddelen.” Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE), 2009.

[2] “5 jaar Colleges voor de weesgeneesmiddelen Stand van zaken,” 2009. [Online]. Available:http://www.inami.fgov.be/SiteCollectionDocuments/weesgeneesmiddelen-5jaar-college-programma.pdf. [Accessed: 24-Jun-2015].

[3] "Belgisch plan voor zeldzame ziekten," 2013. [Online]. Available: http://health.belgium.be/internet2Prd/groups/public/@public/documents/ie2divers/19099656_nl.pdf. [Accessed: 24-Jun-2015].

[4] "Info Spot - De Weesgeneesmiddelen," 2007. [Online]. Available: http://www.inami.fgov.be/SiteCollectionDocuments/infospot-2007-04-nl.pdf. [Accessed: 25-Jun-2015].

[5] "Factua Newsletter nr. 151: Samen weesziekten aanpakken," 2009. [Online]. Available: http://www.pharma.be/newsitem.aspx?nid=760. [Accessed: 23-Jun-2015].

[6] "Aanbevelingen en voorstellen tot maatregelen voor een Belgisch Plan voor Zeldzame Ziekten," 2011. [Online]. Available: https://www.kbs-frb.be/start.aspx?q=/. [Accessed: 24-Jun-2015].

[7] A. Denis, L. Mergaert, C. Fostier, I. Cleemput, F. Hulstaert, and S. Simoens, "Critical assessment of belgian reimbursement dossiers of orphan drugs," *Pharmacoeconomics*, vol. 29, no. 10, pp. 883–893, Oct. 2011.

[8] A. G. Dupont and P. B. Van Wilder, "Access to orphan drugs despite poor quality of clinical evidence," *Br J Clin Pharmacol*, vol. 71, no. 4, pp. 488–496, Apr. 2011.

[9] C. A. Gericke, A. Riesberg, and R. Busse, "Ethical issues in funding orphan drug research and development," *J Med Ethics*, vol. 31, no. 3, pp. 164–168, Mar. 2005.

[10] W. Hughes-Wilson, A. Palma, A. Schuurman, and S. Simoens, "Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?," *Orphanet J Rare Dis*, vol. 7, p. 74, 2012.

[11] T. Morel *et al.*, "Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries," *Orphanet J Rare Dis*, vol. 8, p. 198, 2013.

[12] E. Picavet, D. Cassiman, C. E. Hollak, J. A. Maertens, and S. Simoens, "Clinical evidence for orphan medicinal products-a cause for concern?," *Orphanet J Rare Dis*, vol. 8, p. 164, 2013.

[13] S. Simoens, E. Picavet, M. Dooms, D. Cassiman, and T. Morel, "Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum," *Appl Health Econ Health Policy*, vol. 11, no. 1, pp. 1–3, Feb. 2013.

[14] A. Denis, L. Mergaert, C. Fostier, I. Cleemput, and S. Simoens, "Budget impact analysis of orphan drugs in Belgium: estimates from 2008 to 2013," *J Med Econ*, vol. 13, no. 2, pp. 295–301, 2010.

[15] E. Picavet, M. Dooms, D. Cassiman, and S. Simoens, "Drugs for rare diseases: influence of orphan designation status on price," *Appl Health Econ Health Policy*, vol. 9, no. 4, pp. 275–279, Jul. 2011.

[16] A. Denis, L. Mergaert, C. Fostier, I. Cleemput, and S. Simoens, "[Orphan diseases and orphan medicines: a Belgian and European study]," *J Pharm Belg*, no. 4, pp. 131–137, Dec. 2009.

[17] E. Picavet, T. Morel, D. Cassiman, and S. Simoens, "Shining a light in the black box of orphan drug pricing," *Orphanet J Rare Dis*, vol. 9, p. 62, 2014.

[18] S. Simoens, D. Cassiman, M. Dooms, and E. Picavet, "Orphan drugs for rare diseases: is it time to revisit their special market access status?," *Drugs*, vol. 72, no. 11, pp. 1437–1443, Jul. 2012.

[19] Orphanet, "Rare Disease Registries in Europe." 2015.

[20] E. Picavet, L. Annemans, I. Cleemput, D. Cassiman, and S. Simoens, "Market uptake of orphan drugs--a European analysis," *J Clin Pharm Ther*, vol. 37, no. 6, pp. 664–667, Dec. 2012.

[21] "Compassionate use - medical need - Human medicines - FAMHP," 01-Jul-2015. [Online]. Available: http://www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/compassionate_use_medical_need/. [Accessed: 01-Jul-2015].

[22] Orphanet, "List of Research Infrastructures useful to Rare Diseases in Europe (By country of location)." 2015.

[23] Vlaams patiëntenplatform, "Knelpuntennota zeldzame aandoeningen." 2009.

[24] MLOZ, "Debat: Geneesmiddelen, tegen elke prijs?" 2015.

[25] "Terugbetaling van geneesmiddelen Performantie van het overheidsbeheer." Verslag van het Rekenhof aan de Kamer van Volksvertegenwoordigers, Dec-2013.

[26] MLOZ, "Geneesmiddelen tegen elke prijs? Wat met de 'usual suspects' onder de geneesmiddelen?," *Health Forum*, vol. Geneesmiddelen, tegen elke prijs?, no. 22, Jun-2015.

[27] "Advies van de NRZV i.v.m. de organisatie van zorg voor patiënten met zeldzame ziekten in de Belgische ziekenhuizen." FOD volksgezondheid, veiligheid van de voedselketen en leefmilieu; nationale raad voor ziekenhuisvoorzieningen, 16-May-2013.

[28] "INTEGRAAL VERSLAG MET VERTAALD BEKNOPT VERSLAG VAN DE TOESPRAKEN 12/05/2015." BELGISCHE KAMER VAN VOLKSVERTEGENWOORDIGERS, 05-Dec-2015.

[29] "INTEGRAAL VERSLAG MET VERTAALD BEKNOPT VERSLAG VAN DE TOESPRAKEN 10/03/2015." BELGISCHE KAMER VAN VOLKSVERTEGENWOORDIGERS, 03-Oct-2015.

[30] E. Picavet, D. Cassiman, B. Aertgeerts, and S. Simoens, "Development and validation of COMPASS: clinical evidence of orphan medicinal products - an assessment tool," *Orphanet J Rare Dis*, vol. 8, p. 157, 2013.

[31] "ZOOM Zeldzame ziekten: nieuwe perspectieven op gelijke kansen," 2014. [Online]. Available: https://www.kbs-frb.be/nl/Activities/Publications/2014/310000. [Accessed: 13-Jul-2015].

[32] "BELGIUM EUROPLAN NATIONAL CONFERENCE FINAL REPORT." Eucerd, 2014.

[33] "BELGISCH PLAN VOOR ZELDZAME ZIEKTEN VRAGEN & ANTWOORDEN." Koning Boudewijnstichting, 2015.

[34] "Justice & solidarity in priority setting in healthcare." KING BAUDOUIN FOUNDATION BELGIAN ADVISORY COMMITTEE ON BIOETHICS, 2013.

[35] "Kansen en uitdagingen verbonden aan innoverende therapieën." Belgische Senaat, Jul-2013.

[36] "Lotgenoten vormen sterke netwerken." maczima, 2014.

[37] "ZOOM: Burgerlabo - burgers als leidraad bij terugbetalingen in de gezondheidszorg," 2015. [Online]. Available: /nl/Activities/Publications/2015/317348. [Accessed: 30-Jul-2015].

[38] M. De Block, "TOEKOMSTPACT VOOR DE PATIËNT MET DE FARMACEUTISCHE INDUSTRIE," 2015. [Online]. Available: http://www.deblock.belgium.be/nl/maggie-de-block-en-farmasector-sluiten-uniek-toekomstpact. [Accessed: 30-Jul-2015].

[39] "Événement politique EURORDIS pour la Journée des maladies rares 2015," *Eurodis*, 2015. [Online]. Available: http://www.eurordis.org/fr/news/en-influant-sur-les-processus-decisionnels-les-patients-creent-une-situation-gagnant-gagnant. [Accessed: 31-Jul-2015].

[40] "Payers perspective on the pricing debate for orphan drugs," *Total Biopharma*, 2012. [Online]. Available: http://www.totalbiopharma.com/2012/08/28/payers-perspective-pricing-debate-orphan-drugs/. [Accessed: 31-Jul-2015].

[41] "Open Vld'ers willen terugbetaling dure geneesmiddelen op Europees niveau," *Politics.be*, 2014. [Online]. Available: http://www.politics.be/persmededelingen/38766/. [Accessed: 03-Aug-2015].

[42] "Orphan Drugs: Interview With INSERM's Ségolène Aymé," *Orphan Druganaut Blog*, 2014.

[43] "15 years after the Orphan Medicines Regulation, are rare disease patients getting the innovation and treatments they need?", *CONFERENCE SUMMARY REPORT*, 2015. [Online]. Available: http://www.efpia.eu/uploads/FINAL_report_OMP_event_26_May_2015_1.pdf. [Accessed: 03-Aug-2015].

[44] "The high costs of orphan medicine," 2015. [Online]. Available: http://euranetplus-inside.eu/the-high-costs-of-orphan-medicine/. [Accessed: 03-Aug-2015].

[45] "Je geld of je leven? Een pleidooi voor meer kosteneffectiviteit in de Belgische gezondheidszorg." 'Itinera Institue, 2011.

[46] "Remboursement des médicaments orphelins: un pour tous, tous pour un...," 2011. [Online]. Available: http://www.pharma-sphere.be/fr/actualite/remboursement-des-medicaments-orphelins-un-pour-tous-tous-pour-un. [Accessed: 03-Aug-2015].

[47] "Mondelinge vraag aan Maggie De Block: Samenwerken voor goedkopere weesmedicijnen," *Yoleen Van Camp*, 2015. [Online]. Available: http://www.yoleenvancamp.be/nieuws/mondelinge-vraag-aan-maggie-de-block-samenwerken-voor-goedkopere-weesmedicijnen. [Accessed: 03-Aug-2015].

[48] "Orphanet: een portaalsite voor zeldzame ziekten." WIV-ISP, 2012-2011.

[49] M. De Block, "Pacte d'avenir pour le patient avec l'industrie pharmaceutique," 2015. [Online]. Available: http://www.deblock.belgium.be/fr/maggie-de-block-et-le-secteur-pharmaceutique-concluent-un-pacte-davenir-unique. [Accessed: 30-Jul-2015].

[50] J. Paasch, G. Sherwood, and S. Herms, "ASH 2013 HIGHLIGHTS." Torch International Waldenstrom's Macroglobulinemia Foundation, 26-Nov-2015.

[51] J. Sussex, P. Rollet, M. Garau, C. Schmitt, A. Kent, and A. Hutchings, "A pilot study of multicriteria decision analysis for valuing orphan medicines," *Value Health*, vol. 16, no. 8, pp. 1163–1169, Dec. 2013.

[52] P. B. Van Wilder and A. G. Dupont, "Reimbursement of medicines in Belgium: role of evidence-based medicine," *Acta Clin Belg*, vol. 64, no. 2, pp. 120–128, Apr. 2009.

[53] "An Interview with an Orphan Drug Payer," *Total Orphan Drugs*, 2013. [Online]. Available: http://www.orphan-drugs.org/2013/08/29/interview-orphan-drug-payer/. [Accessed: 31-Jul-2015].

[54] P. De Backer, "MEP Philippe De Backer explaining EU fund for better reimbursement of orphan drugs," *Euranet Plus Central*, 2015. [Online]. Available: https://soundcloud.com/euranet-plus-official/mep-philippe-de-backer-explaining-eu-fund-for-better-reimbursement-of-orphan-drugs. [Accessed: 03-Aug-2015].

[55] MLOZ, "Zet de terugbetaling van weesgeneesmiddelen het solidariteitssysteem onder druk?," *Health Forum*, vol. Gezondheidszorg: de solidariteit in gevaar?, no. 13, pp. 9–10, Mar-2013.

[56] E. Picavet, D. Cassiman, and S. Simoens, "Reimbursement of orphan drugs in Belgium: what (else) matters?," *Orphanet J Rare Dis*, vol. 9, p. 139, 2014.

[57] E. Picavet, D. Cassiman, and S. Simoens, "Evaluating and improving orphan drug regulations in Europe: a Delphi policy study," *Health Policy*, vol. 108, no. 1, pp. 1–9, Nov. 2012.

[58] S. Simoens, "Pricing and reimbursement of orphan drugs: the need for more transparency," *Orphanet J Rare Dis*, vol. 6, p. 42, 2011.

[59] M. Schlander *et al.*, "Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders," *J Comp Eff Res*, vol. 3, no. 4, pp. 399–422, Jul. 2014.

[60] L. Barham, "Orphan medicines, special treatment required?" 2020health.org, 2012.

[61] S. Simoens, "Health economic assessment: cost-effectiveness thresholds and other decision criteria," *Int J Environ Res Public Health*, vol. 7, no. 4, pp. 1835–1840, Apr. 2010.

[62] M. Le Polain, M. Franken, M. Koopmanschap, and I. Cleemput, "Drug reimbursement systems: international comparison and policy recommendations." Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE), 2010.

[63] I. Cleemput *et al.*, "Incorporating societal preferences in reimbursement decisions – Relative importance of decision criteria according to Belgian citizens." Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE), 2014.

[64] S. Simoens, "How to Assess the Value of Medicines?," *Front Pharmacol*, vol. 1, Sep. 2010.

[65] S. Aymé, C. Rodwell, and Eds., "2012 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE OF THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES." 30-Nov-2015.

[66] S. Stordeur, F. Vrijens, K. Henau, V. Schillemans, C. De Gendt, and R. Leroy, "Organisation of care for adults with a rare or complex cancer." Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE), 2014.

[67] E. Picavet, M. Dooms, D. Cassiman, and S. Simoens, "Orphan Drugs for Rare Diseases: Grounds for Special Status," *Drug Dev. Res.*, vol. 73, no. 3, pp. 115–119, May 2012.

[68] S. Simoens, D. Cassiman, E. Picavet, and M. Dooms, "Are some orphan drugs for rare diseases too expensive? A study of purchase versus compounding costs," *Drugs Ther. Perspect*, vol. 27, no. 10, pp. 24–26, Aug. 2012.

[69] E. Picavet, D. Cassiman, and S. Simoens, "Do ultra-orphan medicinal products warrant ultra-high prices? A review," *Orphan Drugs: Research & Reviews*, vol. Vol. 3, p. p23, Jun. 2013.

[70] L. Luzzatto *et al.*, "Rare diseases and effective treatments: are we delivering?," *Lancet*, vol. 385, no. 9970, pp. 750–752, Feb. 2015.

[71] M. Dooms, H. Pincé, and S. Simoens, "Do we need authorized orphan drugs when compounded medications are available?," *J Clin Pharm Ther*, vol. 38, no. 1, pp. 1–2, Feb. 2013.

[72] C. Rodwell, S. Aymé, and Eds., "2014 Report on the State of the Art of Rare Disease Activities in Europe." Jul-2014.

[73] E. Picavet, "Analysis of market access of orphan drugs for rare diseases," Sep. 2014.

[74] "Prioriteit aan de chronisch zieken!" Oprichting van het Observatorium voor chronische ziekten." RIZIV, May-2012.

[75] L. Annemans, I. Cleemput, F. Hulstaert, and S. Simoens, "Valorising and creating access to innovative medicines in the European Union," *Frontiers in Pharmacology*, no. Volume 2, p. Article 57, 2011.

[76] A. Denis, L. Mergaert, C. Fostier, I. Cleemput, and S. Simoens, "A comparative study of European rare disease and orphan drug markets," *Health Policy*, vol. 97, no. 2–3, pp. 173–179, Oct. 2010.

[77] S. Simoens, "Health technologies for rare diseases: does conventional HTA still apply?," *Expert Rev Pharmacoecon Outcomes Res*, vol. 14, no. 3, pp. 315–317, Jun. 2014.

[78] A. Denis, L. Mergaert, C. Fostier, I. Cleemput, and S. Simoens, "Issues surrounding orphan disease and orphan drug policies in Europe," *Appl Health Econ Health Policy*, vol. 8, no. 5, pp. 343–350, 2010.

[79] "King Baudouin Foundation | Home," 25-Jun-2015. [Online]. Available: https://www.kbs-frb.be/start.aspx?q=/. [Accessed: 25-Jun-2015].

[80] "Orpha.net - Belgium," 25-Jun-2015. [Online]. Available: http://www.orpha.net/national/BE-NL/index/homepage/. [Accessed: 25-Jun-2015].

[81] "Orpha.net - International," 25-Jun-2015. [Online]. Available: http://www.orpha.net/consor/cgi-bin/index.php. [Accessed: 25-Jun-2015].

[82] "EUCERD," 25-Jun-2015. [Online]. Available: http://www.eucerd.eu/. [Accessed: 25-Jun-2015].

[83] "Policy Rare diseases - European Commission," 25-Jun-2015. [Online]. Available: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm. [Accessed: 25-Jun-2015].

[84] "Radiorg" *Radiorg NL*, 25-Jun-2015. [Online]. Available: http://radiorgnl.squarespace.com/radiorgsplash/. [Accessed: 25-Jun-2015].

[85] "Weesgeneesmiddelen - Menselijk gebruik - FAGG," 25-Jun-2015. [Online]. Available: http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/weesgeneesmiddelen/. [Accessed: 25-Jun-2015].

[86] "Eurordis.org," *EURORDIS*, 25-Jun-2015. [Online]. Available: http://www.facebook.com/eurordis. [Accessed: 25-Jun-2015].

[87] "Rare Disease Day 2015 - Feb 28," *Rare Disease Day - Feb 28 2015*, 25-Jun-2015. [Online]. Available: http://www.rarediseaseday.org/. [Accessed: 25-Jun-2015].

[88] "Luss: Ligue des usagers des services de santé," 25-Jun-2015. [Online]. Available: http://www.luss.be/. [Accessed: 25-Jun-2015].

[89] "Vlaams Patiëntenplatform," 25-Jun-2015. [Online]. Available: http://vlaamspatientenplatform.be/. [Accessed: 25-Jun-2015].

[90] "Weesgeneesmiddelen - RIZIV," 25-Jun-2015. [Online]. Available: http://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/wees/Paginas/default.aspx#.VlxGleI1OXd. [Accessed: 25-Jun-2015].

[91] "Patienten Rat & Treff," 25-Jun-2015. .

[92] "pharma.be," 25-Jun-2015. [Online]. Available: http://www.pharma.be/. [Accessed: 25-Jun-2015].

[93] "ERA-Net E-Rare | ERA-Net for Research Programmes on Rare Diseases," 25-Jun-2015. [Online]. Available: http://www.erare.eu/. [Accessed: 25-Jun-2015].

[94] "Onafhankelijke ziekenfondsen: Debat 'Geneesmiddelen, tegen elke prijs?,'" 25-Jun-2015. [Online]. Available: http://www.mloz.be/nl/event/debat-geneesmiddelen. [Accessed: 25-Jun-2015].

[95] "Rare Disorders Belgium," *Rare Disorders Belgium*, 25-Jun-2015. [Online]. Available: http://rd-b.be/. [Accessed: 25-Jun-2015].

[96] "Onafhankelijke Ziekenfondsen dringen aan op structurele maatregelen geneesmiddelenbeleid," 25-Jun-2015. [Online]. Available: http://www.mloz.be/fr/node/6015. [Accessed: 25-Jun-2015].

[97] "De Belgische Kamer van volksvertegenwoordigers," 25-Jun-2015. [Online]. Available: http://www.dekamer.be/kvvcr/index.cfm?language=nl. [Accessed: 25-Jun-2015].

[98] "INTEGRAAL VERSLAG MET VERTAALD BEKNOPT VERSLAG VAN DE TOESPRAKEN." B ELGISCHE K AMER VAN VOLKSVERTEGENWOORDIGERS, 30-Nov-2015.

[99] E. Tambuyzer, "Rare diseases, orphan drugs and their regulation: questions and misconceptions," *Nat Rev Drug Discov*, vol. 9, no. 12, pp. 921–929, Dec. 2010.

[100] "Quelles méthodes pour (mieux) intégrer la dimension sociale et éthique dans les décisions publiques en matière de santé ?" kbs-frb, 2013.

[101] "Methoden om ethische en maatschappelijke waarden te integreren in beslissingen over de terugbetaling van gezondheidsinterventies." kbs-frb, 2013.

# Appendix B: MCDA Framework Overview

## I MCDA frameworks specifically for orphan drugs

| Name | Date | Type | Country | Validated framework |
|---|---|---|---|---|
| TVF | 2012 | European Commission | Europe | No |
| Hughes-Wilson | 2012 | Publication in JoRD | Europe | |
| Sussex | 2013 | Publication in Value in Health | EU | Yes, by industry stakeholders |
| Fedyaeva | 2014 | Conference abstract | Russia | |
| Paulden | 2014 | Publication in Pharmacoeconomics | International | |
| Schey | 2014 | Poster presented at ECRD 2014 | International | Yes, validated against drug average annual cost |

## II MCDA frameworks for non-orphan indications

| Name | Date | Type | Country | Validated framework |
|---|---|---|---|---|
| Thokala | 2012 | Publication in Value Health | International | |
| Kanavos | 2013 | Working paper of LSE (London School of Economics) | International | |
| Tanios | 2013 | Publication in International Journal of Technology Assessment in Health Care | International | Survey (not a framework ) compiling criteria used by policy and clinical decision-makers |
| Endrei | 2014 | Letter to the editor of Value in Health | Hungary | |
| Williams | 2014 | Publication in Journal of Market Access & Health Policy | Europe | Yes, tested by payers and payer advisors in the UK, Germany, Spain |
| Wahlster | 2015 | Publication in Health Research Policy and systems | Germany | Yes, validated by a mix of non-industry stakeholders |
| ESMO | 2015 | Publication in Annals of Oncology | Europe | |
| ASCO | 2015 | Publication in Journal of Oncology | International | Yes |

# III Summary of criteria used in existing MCDA frameworks

| MCDA criteria | OD specific | | | | | | Non OD specific | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hughes-Wilson | Sussex | Fedyaeva | Paulden | Schey | TVF | Kanavos | Tanios (survey) | Endrei | Wah-lster | Williams | ESMO | ASCO |
| ***Impact of the disease*** | | | | | | | | | | | | | |
| Disease rarity | ✓ | | ✓ | ✓ | ✓ | | | ✓ | | | ✓ | | |
| Disease severity (mortality/survival) | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Disability and disorders resulting from the disease (morbidity) | | ✓ | ✓ | | | | ✓ | | | ✓ | ✓ | | |
| Unmet need/available alternatives | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Identifiability /size of target population | | | | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Impact on quality of life | | | | | ✓ | | | | ✓ | | ✓ | | |
| Social impact on patients and carers* | | ✓ | ✓ | | | | | | | | | | |
| Impact of disease upon the distribution of health in the population | | | | ✓ | | | | | ✓ | | | | |
| Disease economic burden | | | | | | | | ✓ | | | | | |
| ***Impact of the disease – prioritisation based on population characteristics*** | | | | | | | | | | | | | |
| Age of target population (very young or elderly) | | | | | ✓ | | | ✓ | | | | | |
| Low socioeconomic status | | | | | | | | ✓ | | | | | |
| Patients in productive age | | | | | | | | ✓ | | | | | |
| Women of reproductive age | | | | | | | | ✓ | | | | | |
| Remote communities | | | | | | | | ✓ | | | | | |
| People avoiding risky behaviour | | | | | | | | ✓ | | | | | |
| ***Impact of the new technology*** | | | | | | | | | | | | | |
| First in class | | | | | | | | | | | | | |
| Clinical efficacy, impact on life expectancy | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Magnitude of treatment benefit | ✓ | | | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ |
| Response rate | | | | | | ✓ | | | | | | | |
| Type of medical service (preventive, curative, disease modifying, etc..) | | | | | | | | ✓ | | ✓ | | ✓ | ✓ |
| Impact on quality of life of patients | | | ✓ | | | ✓ | ✓ | | | | ✓ | ✓ | |
| Social impact on patients and carers (includes impact on productivity)* | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | | | |
| Safety/toxicity | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| Quality of evidence | | | | | | ✓ | | ✓ | | ✓ | ✓ | | |
| Endpoints selected (eg: OS vs PFS, etc...) | | | | | | | | | | | | ✓ | ✓ |
| ***Impact of the new technology*** | | | | | | | | | | | | | |
| Treatment-free intervals | | | | | | | | | | | | | ✓ |
| Uniqueness of indication | ✓ | | | | ✓ | | | | | | | | |
| Drug innovation | | ✓ | | ✓ | ✓ | | ✓ | ✓ | | | | | |
| Direct impact: cost of treatment / budget impact | | | ✓ | | | | ✓ | | ✓ | ✓ | ✓ | | ✓ |
| Cost-effectiveness | | | | ✓ | | | | ✓ | ✓ | ✓ | ✓ | | |
| Impact on healthcare system (eg: impact upon the distribution of health in the population) | | | | ✓ | | | ✓ | ✓ | | | | | |

| MCDA criteria | OD specific | | | | | | Non OD specific | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hughes-Wilson | Sussex | Fedyaeva | Paulden | Schey | TVF | Kanavos | Tanios (survey) | Endrei | Wah-lster | Williams | ESMO | ASCO |
| Intervention cost to patients | | | | | | | | ✓ | | | | | |
| Impoverishing impact on patients | | | | | | | | ✓ | | | | | |
| Impact on forgone health services | | | | | | | | ✓ | | | | | |
| ***Other decision factors*** | | | | | | | | | | | | | |
| Impact on specific patient groups | | | | | | | | ✓ | | | | | |
| Convenience of administration | | | | | ✓ | | | | | | ✓ | | |
| Feasibility of diagnosing the disease | | | | ✓ | | | | | | | | | |
| Feasibility of providing the treatment | | | | ✓ | | | | | | | ✓ | | |
| Socioeconomic policy objectives / Health care Priority | | | | ✓ | | | | ✓ | ✓ | ✓ | | | |
| Industrial and commercial policy considerations | | | | ✓ | | | | | | | | | |
| Legal considerations | | | | ✓ | | | | ✓ | | | | | |
| National and international reputation | | | | | | | | | ✓ | | | | |
| ***Other decision factors*** | | | | | | | | | | | | | |
| Manufacturing complexity | ✓ | | | | ✓ | | | | | | | | |
| Recent development in the therapy area of interest | | | | | | | | | | | | | |
| Reimbursement in other countries | | | | | | | | | | | ✓ | | |
| Level of research undertaken | ✓ | | | | ✓ | | | | | | ✓ | | |
| Level of effectiveness uncertainty | ✓ | | | | ✓ | | | ✓ | | | | | |
| Follow-up measures of monitoring | ✓ | | | | ✓ | | | | | | | | |
| Patient co-payments | | | | | | | | | | | | | ✓ |
| Reach whole target population/region | | | | | | | | ✓ | | | | | |
| Risk of inappropriate use | | | | | | | | ✓ | | | | | |
| Organisational requirements | | | | | | | | ✓ | | | | | |
| ***Other decision factors*** | | | | | | | | | | | | | |
| Clinical guidelines (eg impact of new treatment on guidelines or current recommendations) | | | | | | | | ✓ | | ✓ | | | |
| Skill requirements | | | | | | | | ✓ | | | | | |
| Barriers to uptake | | | | | | | | ✓ | | | | | |
| Mission of the healthcare system | | | | | | | | ✓ | | | | | |
| Cultural acceptability | | | | | | | | ✓ | | | | | |
| Stakeholder pressure/interest | | | | | | | | ✓ | | | | | |
| Congruence with decision | | | | | | | | ✓ | | | | | |
| Capacity to stimulate research | | | | | | | | ✓ | | | | | |
| Partnership and collaboration among stakeholders | | | | | | | | ✓ | | | | | |

# Appendix C: Stakeholder questionnaire

PLEASE COMPLETE THIS SURVEY

**Q1. Please indicate the extent to which you feel:**

| | | Strong | Moderate | Neutral | | | |
|---|---|---|---|---|---|---|---|
| Access to OMPs in Belgium is: | *Sufficient* | ☐ | ☐ | ☐ | ☐ | ☐ | *Insufficient* |
| Access to OMPs in Belgium is: | *Sustainable* | ☐ | ☐ | ☐ | ☐ | ☐ | *Unsustainable* |
| Access to OMPs in Belgium should be: | *A priority* | ☐ | ☐ | ☐ | ☐ | ☐ | *Not a priority* |

**Q2. Please indicate whether you (a) strongly agree, (b) agree, (c) disagree or (d) strongly disagree with each of the statements below. Please also provide any comments, in particular regarding your motivation to agree or disagree with the provided statements.**

| | *Strongly agree* | *Agree* | *Disagree* | *Strongly disagree* | *Comments* |
|---|---|---|---|---|---|
| OMPs have specific elements of value in comparison with drugs in more prevalent indications | ☐ | ☐ | ☐ | ☐ | _____ |
| Some value elements, relevant for OMPs, are not formally considered or valued by current pricing and value assessment tools | ☐ | ☐ | ☐ | ☐ | _____ |
| Some value elements, relevant for OMPs, are more difficult to quantify using current tools used in price and reimbursement, such as cost-effectiveness, budget impact or patient-reported outcomes | ☐ | ☐ | ☐ | ☐ | _____ |
| The lack of appropriate tools to objectively appreciate the value of OMPs leads to a lack of consistency and transparency of pricing for different products (price requested by manufacturer) | ☐ | ☐ | ☐ | ☐ | _____ |
| The lack of appropriate tools to objectively appreciate the value of OMPs leads to a lack of consistency and transparency of pricing for different products (price decision from authorities) | ☐ | ☐ | ☐ | ☐ | _____ |
| There is a need for an objective value framework for OMPs, covering three immediate needs: (1) establish a reference of what value elements could and should be included in the presentation of a product's value; (2) provide a means for objective, inter-product comparable quantification of these value elements; and (3) provide a means for integration of | ☐ | ☐ | ☐ | ☐ | _____ |
| Cost-effectiveness analyses should be mandatory for OMPs | ☐ | ☐ | ☐ | ☐ | _____ |

PLEASE COMPLETE THIS SURVEY

**Q1. Please indicate the extent to which you feel:**

| | | Strong | Moderate | Neutral | | | |
|---|---|---|---|---|---|---|---|
| **Access to OMPs in Belgium is:** | *Sufficient* | ☐ | ☐ | ☐ | ☐ | ☐ | *Insufficient* |
| **Access to OMPs in Belgium is:** | *Sustainable* | ☐ | ☐ | ☐ | ☐ | ☐ | *Unsustainable* |
| **Access to OMPs in Belgium should be:** | *A priority* | ☐ | ☐ | ☐ | ☐ | ☐ | *Not a priority* |

**Q2. Please indicate whether you (a) strongly agree, (b) agree, (c) disagree or (d) strongly disagree with each of the statements below. Please also provide any comments, in particular regarding your motivation to agree or disagree with the provided statements.**

| | Strongly agree | Agree | Disagree | Strongly disagree | Comments |
|---|---|---|---|---|---|
| **OMPs have specific elements of value in comparison with drugs in more prevalent indications** | ☐ | ☐ | ☐ | ☐ | |
| **Some value elements, relevant for OMPs, are not formally considered or valued by current pricing and value assessment tools** | ☐ | ☐ | ☐ | ☐ | |
| **Some value elements, relevant for OMPs, are more difficult to quantify using current tools used in price and reimbursement, such as cost-effectiveness, budget impact or patient-reported outcomes** | ☐ | ☐ | ☐ | ☐ | |
| **The lack of appropriate tools to objectively appreciate the value of OMPs leads to a lack of consistency and transparency of pricing for different products (price requested by manufacturer)** | ☐ | ☐ | ☐ | ☐ | |
| **The lack of appropriate tools to objectively appreciate the value of OMPs leads to a lack of consistency and transparency of pricing for different products (price decision from authorities)** | ☐ | ☐ | ☐ | ☐ | |
| **There is a need for an objective value framework for OMPs, covering three immediate needs: (1) establish a reference of what value elements could and should be included in the presentation of a product's value; (2) provide a means for objective, inter-product comparable quantification of these value elements; and (3) provide a means for integration of** | ☐ | ☐ | ☐ | ☐ | |
| **Cost-effectiveness analyses should be mandatory for OMPs** | ☐ | ☐ | ☐ | ☐ | |

PLEASE COMPLETE THIS SURVEY

| | Strongly agree | Agree | Disagree | Strongly disagree | Comments |
|---|---|---|---|---|---|
| Cost-effectiveness analyses should apply to OMPs, but with modified ICER thresholds | ☐ | ☐ | ☐ | ☐ | |
| Multi-criteria decision analysis frameworks should be considered for OMP value assessment | ☐ | ☐ | ☐ | ☐ | |

**Q3. In your opinion, what specific elements of value could be considered particular to orphan medicinal products?**

**Q4. Please indicate whether you (a) strongly agree, (b) agree, (c) disagree or (d) strongly disagree with each of the statements below. Please also provide any comments, in particular regarding your motivation to agree or disagree with the provided statements.**

| | Strongly agree | Agree | Disagree | Strongly disagree | Comments |
|---|---|---|---|---|---|
| Uncertainty on value should be considered while making abstraction of budgetary reality | ☐ | ☐ | ☐ | ☐ | |
| For OMPs, uncertainty disproportionately impacts price and reimbursement evaluations | ☐ | ☐ | ☐ | ☐ | |
| Dealing with budgetary and value uncertainty requires different approaches | ☐ | ☐ | ☐ | ☐ | |
| There is merit in careful consideration of the nature and typology of uncertainty in considering the need for its management | ☐ | ☐ | ☐ | ☐ | |

PLEASE COMPLETE THIS SURVEY

| | Strongly agree | Agree | Disagree | Strongly disagree | Comments |
|---|---|---|---|---|---|
| Real-life data collection should be organized from a disease point of view rather than from a product point of view | ☐ | ☐ | ☐ | ☐ | |
| Real-life data collection should be organized by the manufacturer | ☐ | ☐ | ☐ | ☐ | |
| Real-life data collection should be organized by the authorities | ☐ | ☐ | ☐ | ☐ | |
| The cost or complexity of generating additonal data should be balanced against the additional value they contribute | ☐ | ☐ | ☐ | ☐ | |

**Q5. What *opportunities/strengths* do you see for static versus dynamic risk management approaches in dealing with value or budgetary risk uncertainty?**

**Q6. What *threats/weaknesses* do you see for static versus dynamic risk management approaches for dealing with value or budgetary uncertainty?**

**Do you have any additional comments or suggestions?**

**THANK YOU FOR YOUR PARTICIPATION!**