Process on Corporate Social Responsibility in the Field of Pharmaceuticals
Platform on Access to Medicines in Europe
Working Group on Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA-OMP)

TRANSPARENT VALUE FRAMEWORK[a]

Introduction

In the framework of the Process on Corporate Responsibility in the field of Pharmaceuticals, the Belgian Presidency in 2010 invited the members of the Platform on Access to Medicines in Europe to reflect on creative ways of collaboration in order to improve access to orphan medicines in Europe. Member States, stakeholders and experts volunteered to participate in the project on "UNMET MEDICAL NEED AND SOLIDARITY IN EUROPE: A MECHANISM FOR COORDINATED ACCESS TO ORPHAN MEDICINAL PRODUCTS"[1]

The need for such a project arises from the challenges posed by the specific nature of specific medicinal products: Orphan medicinal products (OMP) are meant to treat rare diseases, which in and by themselves pose a challenge for delivering the right type of healthcare in the right way to the right patients at the right time. Further challenges referred to in the Terms of Reference include:

- Data, information, expertise and knowledge on the therapy or possible alternative/comparative therapies – if available – is often scarce, subsequently limiting evidence on efficacy and (real life) effectiveness, especially at the time of marketing authorisation.
- Registers and registries -again if available -are limited in their capacity of producing solid (high quality) evidence, due to their limited number and limited number of entries.
- Limitations in availability of adequate dosages/packages may result in substantial and expensive 'waste' when therapy protocols are to be adjusted for individual patients.
- The average cost of treatment per year for common ailments or conditions is around 250 Euros per year[b]. In contrast, the average the cost of treatment with an OMP is around 30.000 Euros per year. However, the cost for treating a single patient with an OMP can amount to hundreds of thousands of Euros per year[2].
- Uncertainty on how much the price of existing OMPs will fall when they come to the end of their 10-year marketing exclusivity and are removed from the Community Register. The first approved OMPs are starting to lose exclusivity (as of August 2012).

[a] The present document is without prejudice to any existing or future EU/ national and international legislation.

[b] Austrian reimbursement data

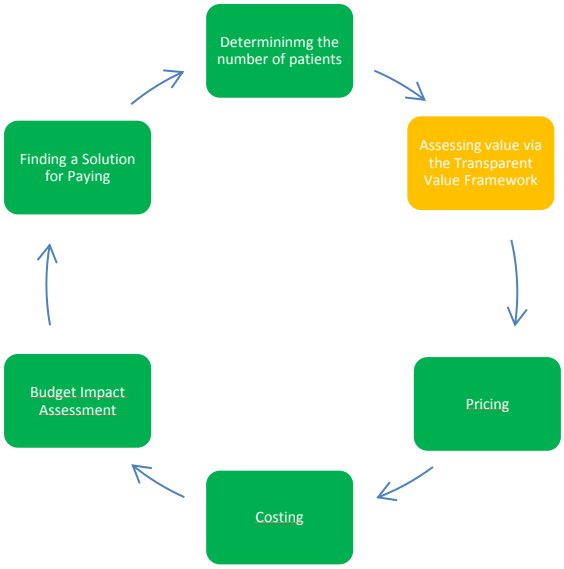
These and other factors described in the Terms of Reference[1] lead to disparities in access to OMPs across the European Union. The current economic situation exacerbates the underlying problem of affordability of high-priced OMPs in the individual Member States.

Decisions on Pricing and Reimbursement are the exclusive competence of the Member States of the European Union. Nevertheless, these Member States foster the same undisputed principles of equity and solidarity, face common challenges when providing urgently needed medicines for their patients and suffer similar burdens when organizing this access[1].

The objective of the current MoCA project on Mechanisms of Coordinated Access (MoCA), as described in the Terms of Reference[1] is to provide real access to a real solution (orphan medicinal product) for real patients with real Unmet Medical Needs, for which these solutions would otherwise be out of reach - in an affordable and sustainable way. The work was divided into three packages:

Work Package 1:	Identification of the Unmet Medical Need and assessing the relevant OMP
Work Package 2:	Organisation of the general structural access
Work Package 3:	Organization of the (targeted) individual access

Organising the structural access requires to find modalities and conditions for providing access. This includes definition of the patient group, determining conditions for providing the OMP, budgeting and pricing. Whereas such mechanisms already exist at a national level, the aim of the current project is to explore the possible scope and the added value of voluntary coordination and cooperation at the multinational, Member State level[c].



As decisions on pricing and reimbursement are the exclusive competence of the Member States, it is clear that participation, engagement and/or involvement in a coordinated system on a European level can only be organised on a voluntary basis.

[c] Policy recommendations are not made, as they are not mentioned in the Terms of Reference.

The Transparent Value Framework (TVF) should help to coordinate access pathways for orphan medicinal products in EU Member States by providing a simple and consistent terminology and methodology[d].

[d] Trying to achieve harmonization within a consortium is the point of the matrix/framework. Ability to pay is not included, since this cannot be addressed here by achieving consensus.

Use and Benefits of the Transparent Value Framework

The framework lists the elements which are important criteria contributing to the value of a new orphan medicine. It also provides a semi-quantitative framework for determining the degree to which the individual criteria are met. How well new OMPs measure up against each of these elements could also give a better overall picture of their value.

The TVF is intended to be used within the context of value-based pricing discussions. Its added utility is in the context of any voluntary task force or consortium that might decide to collaborate in shared discussions. The list of criteria in the TVF is indicative, non-prescriptive and non-binding. It is subject to change on the basis of experience if it is put to use. Specifically, it is an instrument for making value-based pricing more transparent by defining the criteria of value to payers in a qualitative and semi-quantitative manner. It is based on how payers currently assign value and could serve as a basis for collaborative dialogue.

The TVF is not really new, as most payers already take these issues into account (even if the value placed on them is divergent). This was confirmed by members of MEDEV, which is an informal group of payers and their advisors which also advises ESIP in matters of the reimbursement of pharmaceuticals[e].TVF however, is an instrument to assign value in a consistent way, which ensures equal treatment of patients and providers across the wide range of OMPs. This is a necessary prerequisite if the vision of negotiations within the framework of a multi-country consortium is to be pursued further.

[e] A formal survey was not conducted but would be welcome.

THE TRANSPARENT VALUE FRAMEWORK

Criterion	Lower Degree	Medium Degree	High Degree
Available Alternatives/ Unmet Need, including non-pharmaceutical treatment options	yes, new medicine does not address unmet need	yes, but major unmet need still remains	no alternatives except best supportive care - new drug addresses major unmet need
(Relative) Effectiveness, Degree of Net Benefit (Clinical Improvement, QoL, etc. vs. side effects, societal impact, etc.) relative to alternatives, including no treatment.	incremental	major	curative
Response Rate (based on best available clinically relevant criteria)	<30%	30-60%	>60%
Degree of Certainty (Documentation)	promising but not well-documented	plausible	unequivocal

New orphan medicinal products could be assessed according to how well they fulfilled the different criteria at a given point in time. This could be compared with other therapeutic alternatives and be included as one factor in pricing negotiations in Member States

Individual Elements of the Transparent Value Framework

Assessing the elements of the TVF is part of the Health technology Assessment (HTA) so the data from HTA[f] can be used for value assignment. This could take the relative effectiveness assessment performed at European level a step forward in the process of OMPs reimbursement decision-making.

1. **Unmet need**

   In terms of unmet need, no orphan medicinal product is approved in the EU without a formal assessment that it adds value over existing therapies. However, the degree of addressing unmet need (i.e. the usefulness of existing therapies) can differ widely.

   If alternatives are available, these will, as a rule, be the benchmark for the pricing of the new product. This is even the case for several OMP, which can receive marketing authorisation if they address unmet need, thereby providing significant benefit over existing therapies.

   If no pharmaceutical alternatives are available, non-pharmaceutical treatment such as surgical intervention, physiotherapy or even watchful observation, will be used as a benchmark[3].

   Innovation, *per se*, is usually not considered for reimbursement, unless it offers added therapeutic benefit (see 3 and 4 below). This may be the case generally or for a subgroup of patients who cannot be treated with a product or products from an existing therapeutic class. However, developing a new treatment concept *de novo* can be differentiated from developing an existing concept/substance with pre-existing substantial evidence or "repurposing"[4] so that the actual development effort to achieve marketing authorisation is much less. In this case, unmet need may have been previously met by the off-label use of the substance, so the degree of innovation involved in obtaining marketing authorisation is limited[5]. This differentiation is important for considerations on rewarding innovation.

   If the alternatives are not medicinal products, other alternatives may be identified in the context of Health Technology Assessment (conventional or non-conventional).

2. **(Relative) Effectiveness/Degree of Net Benefit (Clinical Improvement, Quality of Life, etc. vs. side effects) relative to alternatives**

   Relative effectiveness can be defined as the net benefit (benefits minus harms) offered by a new treatment vs. current treatment[6]. The degree of relative effectiveness, or, if there is no suitable current treatment, effectiveness "per se", will be a major determinant of the value of a new medicine. HTA assessment will provide the major input in to this parameter. It is a policy issue (and, therefore outside the scope of this paper) whether to assign the same value to the same utility independent of other issues such as age of patients, etc. and whether to consider aspects such as societal impact.

[f] HTA will use all available and pertinent information. However using the framework/matrix for prioritization is not really feasible, as the information needed to populate the matrix is not available at the time of prioritization.

3. **Response Rate**

   Response rates to the same medicine will vary according to which marker is used and over what time frame is considered. For example, progression free survival or overall survival are two measures used for many cancer medicines and can yield differing assessments of response rate. The parameter to be used will depend on the type of clinical data available.

   Further discussion is needed for setting appropriate benchmarks for response rates that are suitable for the disease in question. Response rates to therapies for late stage cancer patients may be lower than response rates in infectious diseases or for diseases treatable with enzyme replacement therapy.

   The response rate is also an important determinant of value. It can be directly considered in the context of managed market entry pricing schemes[8].

4. **Degree of Certainty/Documentation**

   In order to gain regulatory approval, a new medicine needs to convince regulatory agencies that its benefits outweigh its risks, based on the available evidence. However, the certainty of the claim made for a given medicine may vary; medicines with conditional approval may have low levels of evidence at the time, but on the assumption that compelling evidence will be provided in due course. This can be addressed in the context of managed entry agreements.

   Again, this can also be directly considered in the context of pricing ("coverage with evidence development"), if the evidence needs to be developed, as in the case of conditional marketing authorisation. A coordinated approach may be of particular value in these cases, as this provides a larger patient base which facilitates evidence development.

Further Criteria to be considered after a pilot project:

5. **Number of Patients**

   While all patients deserve the same quality of treatment, irrespective of the rarity of the disease they suffer from, it is more difficult to generate evidence for rare diseases, due to the scarcity of patients. Lack of evidence is one of the major barriers for access to treatments for rare diseases, which is precisely the reason for establishing the MOCA project. The MoCA project applies to all OMPs, therefore to all medicines already fulfilling the criterion of 5/10.000. However, there are huge differences to be taken into account between rare diseases potentially affecting up to 200.000 patients in the EU and those affecting only a few thousand or a few hundred or even just tens of patients, meaning extremely few individuals in each Member State. This latter group is precisely the area where cooperation between European countries can add the most value.

   Some Member States tend to see particular value in medicines at the extreme of rarity higher over those at the more prevalent end of the spectrum. However, this cannot be generalized, as other Member States such as Sweden, Norway, Latvia and Austria do not formally differentiate between

treatments for rare and common diseases when assessing the therapeutic value of medicinal products for reimbursement.

The original argument for developing special rules for orphan medicinal products was to correct market failure: since the development costs, and, to a certain extent, also the production costs of a medicine are fixed, an inverse correlation between the number of units anticipated to be sold and the price per package could be expected – all other things being equal. On the other hand, OMPs are, as a rule, not tested in the same number of patients as other medicines - often they are licensed on the basis of phase II trials, making development costs lower – again, all other things being equal.

The number of patients likely to be eligible to use a new medicine may be smaller than the number of patients who have the disease – patients with contra-indications, different stages of disease or perhaps those currently taking some alternative medication or procedure (transplant) would not qualify or need the new treatment. The number may need to be adjusted during the course of negotiations, e.g. when taking the initially calculated budget impact into account. As additional knowledge about the new therapy emerges, and particularly if other new drugs are produced for the same orphan disease, the usage of the medicine could change still further. This may be needed to be taken into account, e.g. in the context of volume-based agreements.

6. Burden of disease

This is often included as a parameter in the evaluation of health technology interventions. It is already considered (but not quantified) in the definition of orphan medicinal products in the regulation, which defines orphan medicinal products as a medicine which must meet one of these criteria, which both include severity**:**

- *It is intended for the diagnosis, prevention or treatment of a **life-threatening or chronically debilitating** condition affecting no more than 5 in 10,000 people in the EU at the time of submission of the designation application;*
- *It is intended for the diagnosis, prevention or treatment of a **life-threatening, seriously debilitating or serious and chronic condition** and without incentives it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development*[7]*.*

Furthermore, the evaluation of the degree of net therapeutic benefit vs. available alternatives (including no treatment, where no effective alternatives are available) also takes this aspect into account. Conversely, assigning a special value to a treatment for a particularly severe disease would imply that a treatment with a small benefit in terms of outcome or symptom relief would be awarded a high value, simply because the basic condition itself is severe. However, value should be defined in terms of clinical benefit for patients.

7. Added Value of the Transparent Value Framework

Currently, there are multiple approaches for trying to determine whether a medicine has a fair price. Traditional methods applied to utilities, agricultural products and many generic medicines, such as

"cost-plus", i.e. determining the production costs and adding a "fair" profit, are not suitable for pharmaceuticals for a variety of reasons (e.g. intellectual property law, lack of transparency of production costs on the one hand and the unwillingness of payers on the other hand to pay a high price for a product with high production or development costs but which does not provide added benefit vs. a low-priced product). Determining cost-effectiveness based on costs per quality-adjusted life year is used for OMPs in some European countries. The TVF tries to incorporate the information provided by technology appraisals, and sensitivity analysis into the overall value.

Consistent application of the TVF would insure that all members of the consortium use the same set of transparent criteria ("speak the same language"), also for various medicines and diseases. Whilst it is not possible to make a simple translation from the TVF to an agreed price that could apply in multiple countries, starting negotiations from an agreed position of where and how a new OMP has real value would simplify processes and minimize differences in requirements from member state agencies. This increases equity and trust as well as predictability. Ensuring that all OMPs were valued according to the same criteria should lead to more rational prices for payers, more predictable market conditions for providers and, ultimately, for more equitable access for patients.

Conclusion

Currently, there is no consensus among stakeholder on how to apply the TVF, e.g. on how to apply values to the individual criteria (continuous or semi-quantitative as in the current proposal), so further work is needed. If the framework is to be used as a rigorous mathematical model, much further work is needed. This would be worthwhile only if consensus can be achieved on the usefulness of the framework in principle.

It is acknowledged that such an approach is not the perfect solution to the problem of determining a fair and equitable price for new OMPs. Indeed, it may turn out to require major modifications before it can be useful in a multi-national context. Achieving consensus among the members of a multinational consortium on the value to be assigned to the individual criteria may prove difficult. Experience in exchange among individual competent authorities suggests that consensus, at least at the semi-quantitative level proposed in the above table, may be possible, at least in selected cases. Whether it is doable in practice would ultimately need to be tested in a pilot. However, the alternative (i.e. not implementing such a tool) may be a system which is arbitrary, inconsistent and not transparent with regard to how pharmaceuticals are valued by society/payers.

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