

EUCERD RECOMMENDATION FOR A CAVOMP INFORMATION FLOW

**RECOMMENDATION OF
THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES
TO
THE EUROPEAN COMMISSION
AND THE MEMBER STATES
ON
IMPROVING INFORMED DECISIONS BASED ON
THE CLINICAL ADDED VALUE OF ORPHAN MEDICINAL PRODUCTS
(CAVOMP) INFORMATION FLOW**

September 2012

BACKGROUND & PURPOSE OF THE RECOMMENDATION

It has been acknowledged over recent years that, while the EU Regulation on Orphan Medicinal Products EC 141/2000 has stimulated research and development of orphan medicinal products in the EU, equitable and timely access to approved orphan medicinal products for rare diseases patients remains an issue. As underlined by the final conclusions and recommendations on Pricing & Reimbursement of the EU High Level Pharmaceutical Forum, *“effective market access and utilisation vary strongly between and within Member States”*.

To address this issue, several policy documents have recently called for an increased cooperation between EU-level authorities and Member States in order to improve access to Orphan Medicinal Products for people living with rare diseases:

- The EU Regulation on Orphan Medicinal Products, adopted on 16 December 1999;
- Final Conclusions and Recommendations of the EU High Level Pharmaceutical Forum⁽¹⁾
- The Commission Communication on “Rare Diseases: Europe’s Challenges”
- The Council Recommendation on a European Action in the Field of Rare Diseases, adopted by the Health Council on 9 June 2009.

In this framework, Ernst & Young was mandated by the Commission to conduct a study into the feasibility of creating a mechanism for the exchange of knowledge on the Clinical Added Value for Orphan Medicinal products (CAVOD) and their final report² was published on 6 December 2011.

The EUCERD was asked to make recommendations to the European Commission on potential ways to facilitate scientific information exchange on orphan medicinal products, in order to support the Member States in their processes of making informed decisions on the scientific assessment of the clinical effectiveness of an orphan medicinal product.

This EUCERD recommendation highlights the fact that the life cycle of an orphan medicinal product is a continuum of evidence generation which is necessary to assessors and decision makers, as well as being necessary to improve the good use of medicines.

In addition there are a number of on-going working groups in this area, such as the one on a Mechanism for Coordinated Access to Orphan Drugs (MoCA) within the Process on Corporate Responsibility in the field of Pharmaceuticals – Platform on Access to Medicines in Europe, initiated by the Commissioner Tajani.

¹ http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum_final_conclusions_en.pdf

² <http://ec.europa.eu/eahc/news/news94.html>

RECOMMENDATIONS OF THE EUCERD TO THE EUROPEAN COMMISSION AND THE MEMBER STATES

ANALYSIS AND GENERAL RECOMMENDATIONS

- 1) The EUCERD welcomes the creation of a mechanism for the exchange of knowledge between Member States and the European authorities with the intention of facilitating the ability of Member States to make informed decisions on access to orphan medicinal products and, most notably, to bridge the knowledge gap at the time of Marketing Authorisation.
- 2) The policy implementation approach should focus on addressing the objective of being a **process for the exchange of knowledge between Member States (MS) as well as between the national level (MS) and EU level (e.g. European authorities and other EU bodies)**, without creating new hurdles and respecting both the legislative framework and the current and emerging roles and responsibilities of all actors at all levels of the process.

The EUCERD notes that there is now an agreement between Member States to create a **permanent cooperation mechanism for HTA**³, as laid down in the EU “Cross-Border Healthcare Directive”⁴. There is also in place **collaboration between the EMA**⁵ **and the EUnetHTA**⁶, which has already led to the specific cooperation on the improvement of EPARs⁷, and which opens the way to other future areas of collaboration, such as: early dialogue and scientific advice, including multi-stakeholder pilots; post-launch collaborative data collection; exchange of and comments on methodological guidelines; and, potential collaboration in areas such as the assessment of significant benefit, added clinical benefit, and clinical superiority.

- 3) The CAVOMP⁸ information flow does not exist independently of these on-going, existing and actual developments. It is vital, however, that all these and other steps and emerging processes within the pharmaceutical sector take account of the specificities of orphan medicinal products within their implementation.
- 4) EUnetHTA and, in future, the permanent network of HTA agencies⁹ should cooperate with the different elements / authorities / institutions within the current and existing orphan medicinal product “journey”. The EUnetHTA / cooperation between Member States’ HTA bodies have a role to play at the appropriate moment in the information flow, however, other bodies also have a role to

³ Health Technology Assessment.

⁴ Article 15, Directive 2011/24/EU of 9 March 2011 on the application of patients’ rights in cross-border healthcare “The Union shall support and facilitate cooperation and the exchange of scientific information among Member States within a voluntary network connecting national authorities or bodies responsible for health technology assessment designated by the Member States”.

⁵ European Medicines Agency

⁶ <http://www.eunetha.eu/>

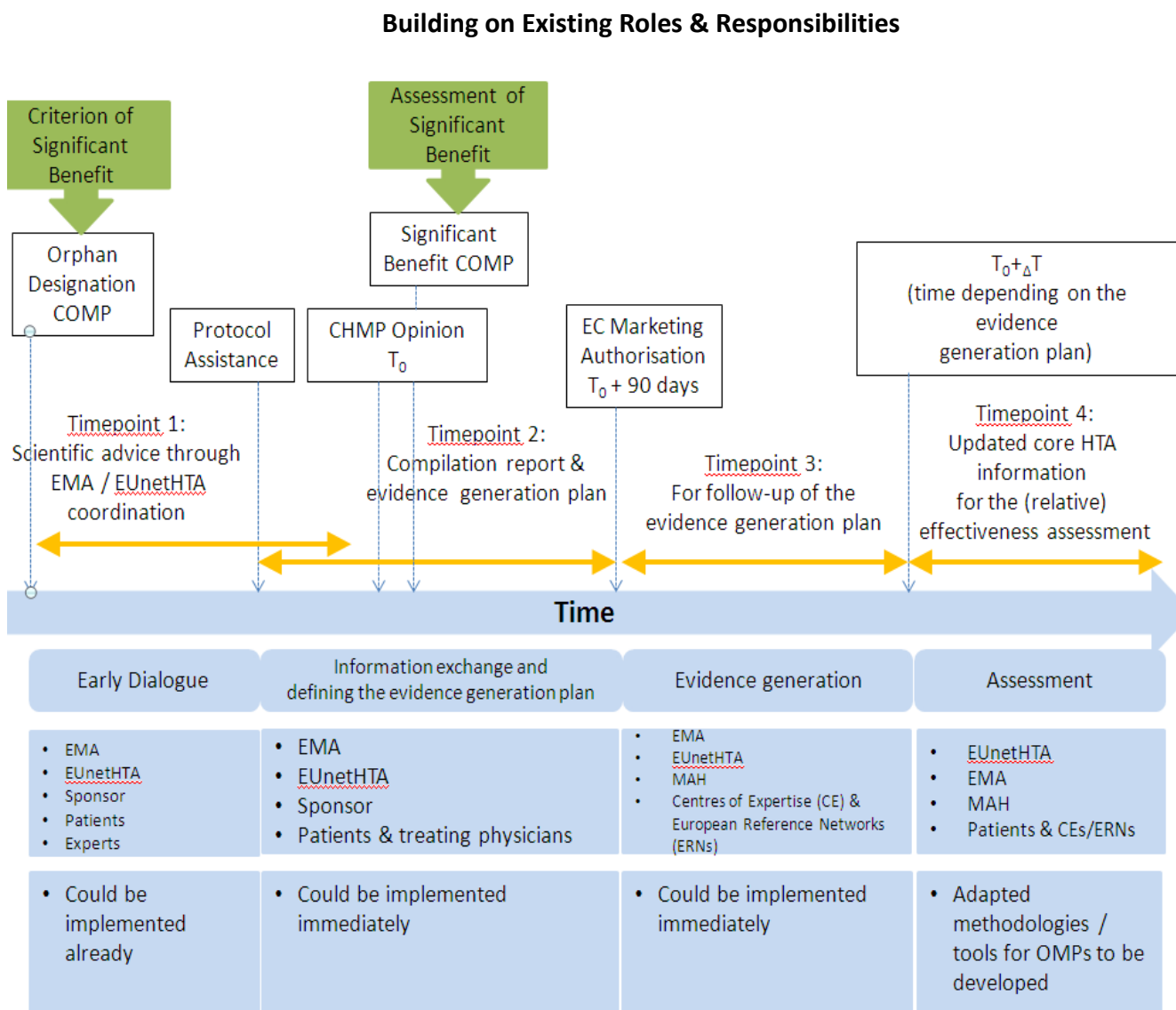
⁷ European Public Assessment Report

⁸ Clinical Added Value of Orphan Medicinal Products

⁹ See reference 3.

play at other times. Each of these **actors should remain responsible for their own area and their own time-point in the journey based on existing roles, responsibilities and also expertise.**

- 5) The concept can be summarised in the diagram below, with the listing of actors to be included in more detail as the information flow is refined. Each step and actors are described in more detail in the corresponding sections below (“**PROPOSED TIME POINTS, ACTIVITIES & INVOLVEMENT**”).



- 6) The CAVOMP information flow will “fit into” the existing processes – regulatory, clinical development, HTA, pricing and reimbursement. The different elements within each time point of the **CAVOMP information flow will be “hosted” by the organisation that is responsible for that particular activity within the time point**, using the funding and the facilities of that organisation as in the normal course of events. If the process is successful, additional resources/funding in the medium term will have to be identified to support adequately the process.

- 7) The CAVOMP information flow is a **voluntary process**, and should be conducted on a case-by-case basis. Each approach will be adapted to the specific disease and potential orphan medicinal product in question.

PROPOSED TIME POINTS, ACTIVITIES & INVOLVEMENT

- 8) The vision of the EUCERD is that it is optimal to follow the four time points of the information flow outlined below. The different actions at the different time-points can be implemented as soon as they become possible, rather than waiting for the entire process to be established.
- 9) **Time point 1 – Early dialogue:**
Early dialogue between the sponsor, EMA and EUnetHTA members/HTA bodies, is encouraged from orphan designation, in particular through protocol assistance where parallel scientific advice from EMA and HTA agencies can be sought. This early dialogue should address the continuum of data generation, leading to a common understanding of data available at marketing authorisation and data possibly available post-authorisation. This will allow the dialogue between regulators and HTA bodies on core common protocols.
- 10) **Time point 2 – Information exchange: Compilation report & Evidence Generation Plan:** This dialogue and exchanges of information between involved parties should occur at the appropriate time, before marketing authorisation. The exchange of information between regulators and HTA is formalised by compiling the assessment reports of the scientific committees of the EMA – such as the European Public Assessment Reports (CHMP¹⁰), the Orphan Designation Review Reports (COMP¹¹), the assessment of Significant Benefit at the time of Marketing Authorisation (COMP), and the Paediatric Investigation Plan (PDCO¹²) – and the core HTA information of the EUnetHTA. This should include a confirmation of the prevalence of the approved therapeutic indication of the orphan medicinal product in question, as defined by the CHMP in its opinion for Marketing Authorisation. The evidence generation plan includes the requirements of the PRAC/CHMP, which will be a condition of the marketing authorisation; in defining these requirements, the contribution of HTA bodies would be beneficial to ensure that the evidence generation plan results in a coordinated and comprehensive approach for the MAH¹³. In addition, it will be important that requirements from individual MS, both regulatory agencies and HTA, should be compiled through this evidence generation plan. The objective should be that post-Marketing Authorisation studies are thoroughly defined and relevant (in terms of evidence generation on safety, (relative) efficacy, effectiveness and efficiency), and that the overall evidence generation plan is truly aimed at building understanding of the role of the medicinal product in the therapeutic strategy.
- 11) **Timepoint 3 – Follow-up of the Evidence Generation Plan:** The progress with the data generation in accordance with the evidence generation plan needs to be monitored. While compliance with the

¹⁰ EMA Committee for Medicinal Products for Human Use

¹¹ EMA Committee for Orphan Medicinal Products

¹² EMA Paediatric Committee

¹³ Marketing authorisation holder

post marketing requirements are followed-up, the MAH can request follow-up dialogue between EMA and HTA bodies on the evidence generation plan when necessary.

- 12) Timepoint 4 – Updated core HTA information for the assessment of (Relative) Effectiveness:** The EUCERD recommends that under the future permanent network of HTA agencies it will be possible to reassess the core HTA information based on the additional evidence generated.

SITUATING THE CAVOMP INFORMATION FLOW IN THE WIDER CONTEXT OF THE EU PHARMACEUTICAL FRAMEWORK

- 13)** Adapted methodological tools for orphan medicinal products are foreseen within the EUnetHTA “mainstream” methodology;
- 14)** There should be an adapted approach that covers each orphan medicinal product in question – the medicinal products and conditions are heterogeneous;
- 15)** There should be stakeholder involvement – including patients, clinicians, researchers, and industry concerned by the treatment in question – in the development of both the preceding points (13) and (14).
- 16)** One of the secondary benefits of the entire information flow has been identified as that of building up **knowledge on an orphan medicinal product** on an on-going basis. The EUCERD recommends that this knowledge could be **housed in the existing EU-funded rare disease database, Orphanet**.
- 17)** The EUCERD recommends that the European Commission mandate the EMA to request information from the Sponsor on the **prevalence of the approved therapeutic indication** for the orphan medicinal product, as defined in the CHMP opinion.
- 18)** The **EUCERD will conduct an evaluation report on the basis of appropriate measures** to establish whether the Clinical Added Value of Orphan Medicinal products Information Flow has been successful in generating relevant and useful additional evidence in the lifecycle of the product, whether the cooperation between different actors at different time points of the information flow is functioning correctly and whether the early dialogue and sharing of information is providing a benefit in practice. If this is not the case, improvements to the information flow should be considered. To facilitate measurement of success of the proposed information flow, both process and outcome indicators have to be defined (e.g. process indicators such as number of times the information flow has been triggered compared with the number of orphan medicinal products designated and/or approved, and outcome indicators such as reduction of delays of patient access and reduction of discrepancies between MS).