WORKSHOP 5 of the EUROPLAN National Conferences

Theme 5: Orphan Medicinal Products and Therapeutics for Rare Diseases

Table of Contents

A. How to read and use these Content Guidelines

The EUROPLAN Content Guidelines cover 6 main Themes. For each Theme, these Content Guidelines cover all the core topics to be addressed in the Workshop dedicated to that Theme. These Guidelines include:

1st column – RESOURCES	**2nd column - TOPICS FOR DISCUSSION**
This column includes the background documents and relevant material that should be referred to in preparation for the discussion. They mainly include: • Articles of the Regulation (EC) n°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products • Specific articles of the EU Council Recommendation on an action in the field of rare diseases; • Specific items of the Commission Communication on Rare Diseases: Europe's challenges • Relevant EUROPLAN Recommendations • EUCERD Recommendations on Clinical Added Value of Orphan Medicinal Products – Information Flow • Extracts from the Synthesis Report of the 15 EUROPLAN National Conferences held in 2010; **NB: Full documents of the sources referenced above can be found in Section C**	**The topics for discussion are questions formulated to stimulate the discussion within the Workshop**. The conference organisers, with the help of their Advisor, will **select those questions that are relevant for the discussion in their countries**. As such, **not all listed questions need to be addressed in a mandatory way**. They rather represent a "menu" from which to pick the questions that address the most relevant topics in the country, having considered the level of advancement of the national policy on rare diseases in the country.

B. Guidelines for discussion for Workshop 5 – Theme Orphan Medicinal Products and Therapeutics for Rare Diseases

RESOURCES	TOPICS for DISCUSSION
B.1 Support to Orphan Drug (OD) development	
Regulation (EC) 141/2000 on orphan medicinal products Whereas: […] (2) patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; […] (7) patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process; sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; in order to facilitate the granting or the maintenance of a Community authorisation, fees to be paid to the Agency should be waived at least in part; the Community budget should compensate the Agency for the loss in revenue thus occasioned; […] Art. 9 […] 2. Before 22 July 2000, the Member States shall communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. That information shall be updated regularly. **Commission Communication on RD** 5.6. Incentives for Orphan Drug development "Pharmaceutical companies invest heavily over a long period of time to discover,	• What type of support is provided to SMEs after designation of their products as Orphan Drug (OD)? Are there **specific programmes that foster further developments of designated ODs**? • Please discuss and explore additional incentives at national level to strengthen research into rare diseases leading to the development of orphan medicinal products**.** • What mechanisms need to be put in place to facilitate the set-up of **clinical trials for small populations** run by academics in centres of expertise? *(see also Theme 4)*

develop and bring to market treatments for rare diseases. They need to be able to show a return on investment. However, the ideal is that they are also able to reinvest that return on investment into discovering more treatments. With more than 45 treatments authorised in the EU – and some for the same conditions – there are still many conditions with no treatment. Exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State awareness with these products should be encouraged in accordance with Article 9 of Regulation (EC) No 141/2000."	
B.2 Access to treatments	
Regulation (EC) 141/2000 on orphan medicinal products Whereas: […] (2) patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry. **Council Recommendation** 17. Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: (e) the sharing Member States' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge and expertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients. **Commission Communication on RD** 5.3. Access to Orphan Drugs "There are specific bottlenecks in access to orphan drugs through the decision making process for pricing and reimbursement linked to rarity. The way forward is to increase collaboration at the European level for the scientific assessment of the (added) therapeutic value of Orphan Medicinal Products. The Commission will set up a working party to exchange knowledge between Member States and European authorities on the scientific assessment of the clinical added value of orphan medicines. These collaborations could lead to non-binding common clinical added	• How to improve and speed up national procedures for pricing and reimbursement of OD so as to minimise delays and improving access to OD? • To this aim, how is my country aware of and ready to support the mechanism for exchange of knowledge between MS and European authorities on the scientific assessment of the **clinical added value for orphan medicinal products (CAVOMP)** as adapted in EUCERD Recommendation? • In particular, this is the mechanisms with 4 timepoints to put in place to ensure the best possible 'information flow' and sharing of assessment reports from different with other EU Member States and the EU authorities: - Timepoint 1: Early dialogue - Timepoint 2: Compilation Report and evidence definition / Evidence Generation Plan (EGP) - Timepoint 3: Follow-up of the EGP - Timepoint 4: Assessment of relative effectiveness How will my country participate to these timepoints? • Please discuss about the importance of adopting a policy on **conditional pricing and reimbursement** with regular revisions, based on revised and updated assessment reports. • Do national **HTA agencies** send representatives to participate in: - Protocol assistance/ scientific advice? - Dialogue mechanisms with the EMA (European Medicines Agency), other

value assessment reports with improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities. Furthermore, the involvement of the EMEA and existing international Health Technology Assessment networks as the Health Technology Assessment. International (HTAi)[1], the European Network for Health Technology Assessment (EUnetHTA)[2] or the Medicines Evaluation Committee (MEDEV) should be considered. **EUCERD Recommendation on CAVOMP Information Flow** See full text below in this document or http://www.eucerd.eu/?post_type=document&p=1446 **EUROPLAN Recommendations** R 5.10 Dissemination of the information about treatment for rare diseases is ensured in the most effective way, to avoid delays of treatment accessibility. R 5.12 An inventory of orphan drugs accessible at national level, including reimbursement status, is compiled and made publicly available. R 5.13 Patients' access to authorised treatment for rare diseases including reimbursement status, is recorded at national and/or EU level. **EUnetHTA** http://www.eunethta.eu/	HTA agencies, notably the EUnetHTA (www.eunethta.eu)? What measures should be put in place to ensure their involvement? Specifically, are HTA bodies in my country participating to the permanent cooperation mechanism for HTA as laid down in the Cross-Border Health Care Directive? What measures should be put in place to ensure their involvement? • Is your country participating to the voluntary ad hoc Working Group **"MOCA" (Mechanisms for Coordinated Access to ODs)** set up between EU Member States on a voluntary basis to discuss the value of new OD based on common European transparent value framework (report to be adopted in early 2013)? • What measures are in place to support the availability and access to orphan drugs through Centres of Expertise? In particular, please discuss the value of **budget allocation for OD at national/central level** (or coordinated at national level) so as to avoid that OD budget be managed by hospitals/centres of Expertise alone, without overall coordination. • **Information and access to OD**. Is the information about treatment for rare diseases is disseminated in the most effective way, so as to avoid delays of treatment accessibility?
B.3 Compassionate use	
Regulation (EC) 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:EN:PDF Art. 83 (2) - DEFINITION of compassionate use **:** *"… making a medicinal product belonging to the categories referred to in Article 3 (1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously*	• How to foster access to compassionate use programmes? Notably, how to best inform patients and their organisations, as well as healthcare professionals of compassionate use[3] opportunities? • How to adopt a compassionate use programme when one does not exist? • As for clinical trials, a Compassionate Use Programmes Facilitation Group could

[1] http://www.htai.org/
[2] http://www.eunethta.net/
[3] A treatment option for European patients suffering from a disease for which no satisfactory authorised alternative therapy exists and/or who cannot enter a clinical trial, may be the use of an unauthorised medicinal product in a compassionate use programme.

debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials." **Commission Communication on RD** 5.4. Compassionate use programmes A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs is needed. Under the existing pharmaceutical legislation, the EMEA* may issue opinions on the use of the product under compassionate use to ensure a common approach across the Community. The Commission will invite the EMEA* to revise their existing guideline with a view to providing patient access to treatment. ***** *Currently renamed 'EMA', European Medicines Agency* **EUROPLAN Recommendations** R 5.11 Participation is ensured in common mechanisms, when available, defining conditions for the off-label use of approved medicinal products for application to rare diseases; for facilitating the use of drugs still under clinical trial; for compassionate provision of orphan drugs. **Final Report of EUROPLAN I Conferences** (Area 5, page 51) - "In order to manage compassionate use programmes, systems of 'temporary authorisations' exist or are evoked by National Conferences, which are or could be granted to drugs used to treat cohorts of individuals before they obtain market authorisation. The application of temporary protocols to cohorts rather than individual patients avoids cumbersome procedures to obtain ad hoc individual authorisations. Protocols for therapeutic use and information collection must be followed. In such cases (see France, for example), it is possible to take advantage of marketing under temporary authorisations to organise the follow up of treated patients with the concerned industry, to collect data on the tolerance and efficacy of drugs in real life, and thus improve knowledge on these products."	be created in the context of the activities of the Heads of National Medicines Agencies, to coordinate actions. Please discuss of the opportunity of supporting the creation of this group and joining it. • Does your country respects the EU legislation and the related obligation to notify the European Medicines Agency (EMA) on compassionate use programmes? • Some Member States need to change their rules/legislations to comply with EU Regulation 726/2004 (see left column on the left). Please consider whether the national provisions on compassionate use reflect the EU Regulation (that prevails on national legislation). *For example, in Romania the Minister of Health requested the drug to be already authorised "somewhere in the world", whereas the Regulation states that either a marketing authorisation application has been submitted (in the EU), or clinical trials are in progress, but does not pre-requisite the product to be authorised somewhere.* • How to best support companies that have difficulties in putting in place compassionate use programmes? • In particular, when drug supply is limited (larger scale manufacturing capacities not yet reached), is there a guideline on how to distribute a limited supply when the demand is greater than the offer? • How to involve patients in the setting up and management of compassionate use programmes?

B.4 Off label use of medicinal products	
EUROPLAN Recommendations R 5.11 Participation is ensured in common mechanisms, when available, defining conditions for the off-label use of approved medicinal products for application to rare diseases; for facilitating the use of drugs still under clinical trial; for compassionate provision of orphan drugs. **Final Report of EUROPLAN I Conferences** (Area 5, page 51) - "Consistently, the National Conferences called for the improvement and simplification of the procedures for off-label use of approved medicinal products. Such procedures are usually cumbersome and often do not lead to the reimbursement of the drugs." - "In order to manage compassionate use programmes, systems of 'temporary authorisations' exist or are evoked by National Conferences, which are or could be granted to drugs used to treat cohorts of individuals before they obtain market authorisation. The application of temporary protocols to cohorts rather than individual patients avoids cumbersome procedures to obtain ad hoc individual authorisations. Protocols for therapeutic use and information collection must be followed. In such cases (see the Second French NP, for example), it is possible to take advantage of marketing under temporary authorisations to organise the follow up of treated patients with the concerned industry, to collect data on the tolerance and efficacy of drugs in real life, and thus improve knowledge on these products." **EUROPLAN Recommendations** R 5.11 Participation is ensured in common mechanisms, when available, defining conditions for the off-label use of approved medicinal products for application to rare diseases; for facilitating the use of drugs still under clinical trial; for compassionate provision of orphan drugs.	• Can drugs be reimbursed when the possibility of a benefit for the patients exist? • How to improve and simplify procedures for the off-label uses and related reimbursement? • What measures can be put in place to allow the adoption **of temporary protocols** for cohorts of patients treated with drugs outside their authorised use? Please discuss both cases: 1) when clinical trials to better document the efficacy and the safety of the off-label use in question are in progress and a variation of the marketing authorisation can be envisaged at a later stage; and 2) when such trials are not running and are not likely to be conducted, as there are too few patients/off label prescriptions. • How to decide which **post-authorisation efficacy and safety studies** are needed to document the off-label use in question? In particular, is there a threshold (in terms of volume) where such studies should become more systematic? • Please discuss the possibility of Centres of Expertise taking over the task of assessing benefits and risks of drugs currently prescribed off label for the patients they are following.

B.5 Pharmacovigilance	
EU Pharmacovigilance legislation **Regulation (EU) No 1235/2010** http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF **Directive 2010/84/EU** http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF "Whereas […] (21) Union rules in relation to pharmacovigilance should continue to rely on the crucial role of healthcare professionals in monitoring the safety of medicinal products, and should take account of the fact that patients are also well placed to report suspected adverse reactions to medicinal products. It is therefore appropriate to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients, and to make methods for such reporting available to them." **Final Report of EUROPLAN I Conferences** (Area 5, page 52) - "Self-declaration of side effects by patients and their families should be also considered: several pilot experiments of pharmacovigilance in France have demonstrated its merits, for both drugs with or without a specific marketing authorisation. If such experiments were carried out at the European level, the information base could be broadened. - Nevertheless, in many countries, including France, the importance of compulsory collection of data on the efficiency and tolerance of treatments (under compassionate or off-label use) has been stressed: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF	• Spontaneous reports of adverse drug reactions: how to encourage patients and healthcare professionals to report to their national authorities (implementation of the EU Regulation on Pharmacovigilance)? • What measures are being put in place "to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients and to make methods for such reporting available to them**"?** • What other measures are being adopted to ensure the compliance with the existing EU legislation on pharmacovigilance, in particular the establishment reporting, national contact points, reporting tools?

C. Background documents

C.1 Regulation (EC) n°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Whereas:
[…]
(1) some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';
(2) **patients suffering from rare conditions should be entitled to the same quality of treatment as other patients**; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; incentives for the development of orphan medicinal products have been available in the United States of America since 1983 and in Japan since 1993;
(3) in the European Union, only limited action has been taken so far, whether at national or at Community level, to stimulate the development of orphan medicinal products; such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited resources; action at Community level is preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Community trade;

[…]

(7) **patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients**; orphan medicinal products should therefore be submitted to the normal evaluation process; sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; in order to facilitate the granting or the maintenance of a Community authorisation, fees to be paid to the Agency should be waived at least in part; the Community budget should compensate the Agency for the loss in revenue thus occasioned;

[…]

Art. 9
[…]
2. Before 22 July 2000, the Member States shall communicate to the Commission detailed information concerning **any measure they have enacted to support research into, and the development and availability of, orphan medicinal products** or medicinal products that may be designated as such. That information shall be updated regularly.
3. Before 22 January 2001, the Commission shall publish a detailed inventory of all incentives made available by the Community and the Member States to support research into, and the development and availability of, orphan medicinal products. That inventory shall be updated regularly.

Full text of the Regulation 141/2000/EC here: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

C.2 Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)

Whereas:

[…]

(19) It is of utmost importance to ensure an active contribution of the Member States to the elaboration of some of the common instruments foreseen in the Commission communication on rare diseases: Europe's challenges of 11 November 2008, especially on diagnostics and medical care and European guidelines on population screening. This could be also the case for the assessment reports on the therapeutic added value of orphan medicinal products, which could contribute to accelerating the price negotiation at national level, thereby reducing delays for access to orphan drugs for rare diseases patients.

(The Council of the EU) hereby recommends that Member States:

[…]

V. GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL

17. Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support:

(e) the sharing Member States' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge and expertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients.

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

C.3 Commission Communication on Rare Diseases: Europe's challenges COM(2008)679

("Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges", 11/11/2008, COM(2008)679)

[…]

5.3. Access to Orphan Drugs

There are specific bottlenecks in access to orphan drugs through the decision making process for pricing and reimbursement linked to rarity. The way forward is to increase collaboration at the European level for the scientific assessment of the (added) therapeutic value of Orphan Medicinal Products. The Commission will set up a working party to exchange knowledge between Member States and European authorities on the scientific assessment of the clinical added value of orphan medicines. These collaborations could lead to non-binding common clinical added value assessment reports with improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities. Furthermore, the involvement of the EMEA and existing international Health Technology Assessment networks as the Health Technology Assessment. International (HTAi)[4], the European Network for Health Technology Assessment (EUnetHTA)[5] or the Medicines Evaluation Committee (MEDEV) should be considered.

5.4. Compassionate use programmes

A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs is needed. Under the existing pharmaceutical legislation, the EMEA may issue opinions on the use of the product under compassionate use to ensure a common approach across the Community. The Commission will invite the EMEA to revise their existing guideline with a view to providing patient access to treatment.

5.5. Medical devices

The Orphan Medicinal Product regulation does not cover the field of medical devices. The limited size of the market and the limited potential return on investment is a disincentive. The Commission will assess whether there is a need for measures to overcome this situation, possibly in the context of the forthcoming revision of the Medical Devices Directives.

5.6. Incentives for Orphan Drug development

Pharmaceutical companies invest heavily over a long period of time to discover, develop and bring to market treatments for rare diseases. They need to be able to show a return on investment. However, the ideal is that they are also able to reinvest that return on investment into discovering more treatments. With more than 45 treatments authorised in the EU – and some for the same conditions – there are still many conditions with no treatment. Exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State awareness with these products should be encouraged in accordance with Article 9 of Regulation (EC) No 141/2000.

[4] http://www.htai.org/
[5] http://www.eunethta.net/

C.4 EUROPLAN Recommendations

54. Clinical trials are also an important area of collaborative action for member states. International collaboration strengthens the power of a study, hence improving the potential to assess treatment efficacy for rare diseases. Collaboration is required among member states also in order to facilitate the design of clinical trials, such as studying possibilities to apply similar approaches to ethical, legal and consensus issues, as well as to set specific tools for assessing the added value of orphan drugs.

55. It is advisable to set instruments and measures (e.g. centres) to facilitate planning and performing clinical trials for rare diseases. This can include the provision of scientific, clinical, statistical, ethical and regulatory expertise to such actors as academia, clinical, research bodies and small and medium enterprises. Collaboration of research institutions/organisations with the structures of the National Health System, with particular reference to the Centres of Expertise, is a promising way to improve the quality of health care and accelerate innovation in the field of rare diseases and new treatments for them. A consistent and efficient support to clinical trials on rare diseases would ultimately benefit orphan drug development also at EU level, increasing the amount and quality of dossiers presented for evaluation to the European Medicine Agency (EMA) and the Committee for Orphan Medical Products (COMP). In addition, already available drugs can be used more efficiently and effectively.

82. Despite the incentives for development and marketing of orphan medicinal products provided by the regulation (EC) No. 141/2000, the availability of orphan drugs within the European countries and their access of citizens are very variable and unsatisfactory. The reasons are different and multiple, lying, in some cases, in the fact that companies do not market the drug in some countries (because of scarce market value, e.g. in small countries), or, in other cases, in the national procedures for reimbursement or criteria for special access to drugs. A recent study has been published by the London-based Office of Health Economics investigating pricing and reimbursing schemes and specific orphan drugs policies in some European countries.

EUROPLAN recommendations on Area 5: Gathering expertise on rare diseases

R 5.10 Dissemination of the information about treatment for rare diseases is ensured in the most effective way, to avoid delays of treatment accessibility.

R 5.11 Participation is ensured in common mechanisms, when available, defining conditions for the off-label use of approved medicinal products for application to rare diseases; for facilitating the use of drugs still under clinical trial; for compassionate provision of orphan drugs.

R 5.12 An inventory of orphan drugs accessible at national level, including reimbursement status, is compiled and made publicly available.

R 5.13 Patients' access to authorised treatment for rare disease including reimbursement status, is recorded at national and/or EU level.

http://www.europlanproject.eu/_newsite_986987/_down/results/2008-2011_2.EUROPLANGuidance.pdf

C.5 EUCERD Recommendations on Clinical Added Value of Orphan Medicinal Products – Information Flow

http://www.eucerd.eu/?post_type=document&p=1446

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**[6], as laid down in the EU "Cross-Border Healthcare Directive"[7]. There is also in place **collaboration between the EMA**[8] **and the EUnetHTA**[9], which has already led to the specific cooperation on the improvement of EPARs[10], 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 CAVOMP[11] 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 agencies[12] 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 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**").

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[6] Health Technology Assessment

[7] 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".

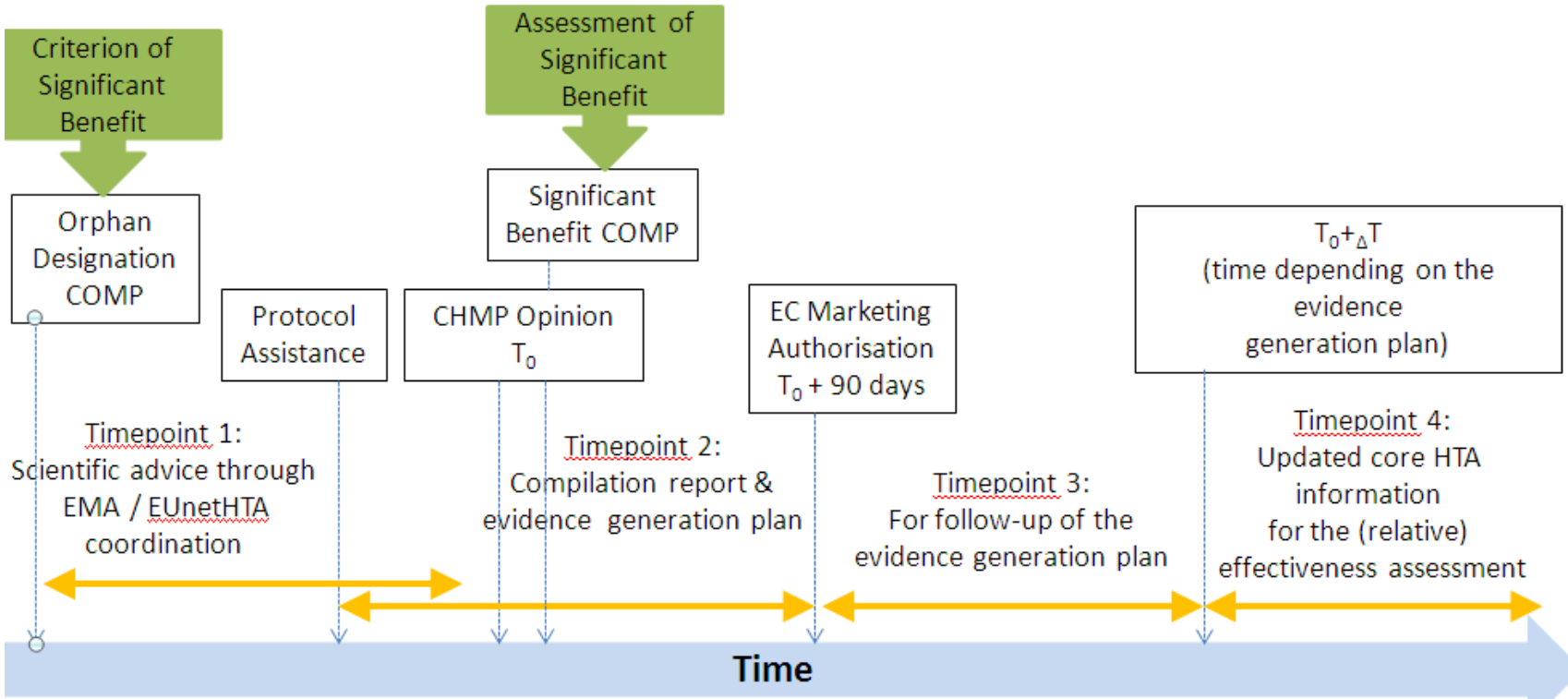
[8] European Medicines Agency

[9] http://www.eunethta.eu/

[10] European Public Assessment Report

[11] Clinical Added Value of Orphan Medicinal Products

[12] See reference 3.



Early Dialogue	Information exchange and defining the evidence generation plan	Evidence generation	Assessment
• EMA • EUnetHTA • Sponsor • Patients • Experts	• EMA • EUnetHTA • Sponsor • Patients & treating physicians	• EMA • EUnetHTA • MAH • Centres of Expertise (CE) & European Reference Networks (ERNs)	• EUnetHTA • EMA • MAH • Patients & CEs/ERNs
• Could be implemented already	• Could be implemented immediately	• Could be implemented immediately	• Adapted methodologies / tools for OMPs to be developed

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 (CHMP[13]), the Orphan Designation Review Reports (COMP[14]), the assessment of Significant Benefit at the time of Marketing Authorisation (COMP), and the Paediatric Investigation Plan (PDCO[15]) – 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 MAH[16]. 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.

[13] EMA Committee for Medicinal Products for Human Use
[14] EMA Committee for Orphan Medicinal Products
[15] EMA Paediatric Committee
[16] Marketing authorisation holder

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 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).

C.6 EUROPLAN Indicators

Area to be explored	Aims	Actions		Indicators	Type of indicator	Answers
Gathering the expertise on Rare Diseases at European level	To ensure and accelerate accessibility to Orphan Designated Drugs (ODD)	Ensure the mechanism that facilitates ODD access and the reimbursement of their cost to patients after they got the market authorization by EMEA	**5.9**	**Number of ODD market authorizations by EMEA and placed in the market in the country**	Outcomes	*Index based on Number of ODD placed in the market by total of ODD approved by the EMEA*
			5.10	**Time between the date of a ODD market authorization by EMEA and its actual date of placement in the market for the country**	Outcomes	*Average days since the date of market authorization by EMEA until the official date of placement in the market in the country*
			5.11	**Time from the placement in the market in the country to the positive decision for reimbursement by public funds**	Outcomes	*Average days since the date of placement in the market until the reimbursement decision date in the country*
			5.12	**Number of ODD reimbursed 100%**	Outcomes	*Number ranging 0 to 1,000*
		To develop mechanisms to accelerate ODD availability	**5.13**	**Existence of a governmental program for compassionate use for Rare Diseases**	Outcomes	• *No* • *Yes* • *In process*