



EURORDIS
Rare Diseases Europe

P O S I T I O N P A P E R

EURORDIS Proposal for the Practical Implementation of Policy Principles to Improve Access to Orphan Drugs in the EU

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EXECUTIVE SUMMARY & CRITICAL SUCCESS FACTORS

It has been acknowledged over recent years that, while the EU Orphan Drugs Regulation 141/2000 has stimulated research and development of orphan medicinal products in the EU, equitable and timely access to approved Orphan Drugs 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 (the EU High Level Pharmaceutical Forum conclusions and recommendations: “Improving Access to Orphan Medicines for all affected EU citizens”, the Commission Communication on “Rare Diseases: Europe’s Challenges” and the Council Recommendation on a European Action in the Field of Rare Diseases) have recently called for an increased cooperation between EU level authorities and Member States in order to improve access to Orphan Drugs for people living with rare diseases.

In fact, as acknowledged by the Pharmaceutical Forum conclusions, “the know-how to make the value assessment of Orphan Drugs is fragmented over national procedures within the Member States and their regions. The disconnection of national and regional processes from the knowledge and experience gathered upfront in the centralised processes does add to this fragmentation”. This situation generates detrimental delays in the national decision-making process aimed at making Orphan Drugs available to patients on national markets.

Faced to this major challenge, interested parties - from the patients and industry arena, as well as EU and national decision-makers - have identified the creation at the EMEA of a Working Party for the assessment of the clinical added value of Orphan Drugs as being a key instrument for an increased collaboration between Member States and EU-level authorities. This collaboration is needed to overcome the specific bottleneck created by scarce, uneven and fragmented expertise on Orphan Drugs at national level.

Gathering expertise at EU level for the assessment of the clinical added value of Orphan Drugs would allow timely production of well-informed opinions which will reduce the information deficit for the national Pricing & Reimbursement decisions and lead to non-binding Common Assessment Reports on the clinical added value of Orphan Drugs based on improved information.

The objective of the collaboration on the common assessment of the clinical added value is to “facilitate the national pricing and reimbursement decisions” and has the only objective to “minimise delays to access Orphan Drugs for rare disease patients”, while fully respecting national competences to make their pricing & reimbursement decisions within their respective healthcare and economic environment.

The success of this newly proposed collaboration will depend on carefully, precisely and realistically defined role, mandate and composition of the Working Party. The link between the Working Party and the EU Member States needs to be explicitly stated. It has to be ensured that any newly created process does not interfere with the normal regulatory approval process as this might create additional delays in access to innovative therapies for patients, which would result in the exact opposite of the desired intent.

This EMEA Working Party is specifically intended for the highly distinct field of rare diseases. The methodology of work for the common scientific assessment of the clinical added-value of Orphan Drugs will be performed using the state-of-the-art consensus on relative efficacy and relative effectiveness.

With this in mind, and with the shared goal of improving patient's access, EURORDIS and the below-indicated companies and experts would like to suggest the following to the European Commission and the EMEA concerning the mandate of the Working Party, its composition, its role and how to perform it, its external outputs and the link between Member States and the external outputs, in order to secure an improved outcome compared to the current situation.

The guiding principles crucial to the success of the implementation of the Commission Communication and Council Recommendation on Rare Diseases are:

1. **To facilitate Member States informed decisions** by providing the fullest available set of scientific information available at the time of Marketing Authorisation in one single Assessment Report.
2. **To the use of the existing reviews of scientific data at the time of Marketing Authorisation** and to make them available to Member States at the time of Marketing Authorisation. The Working Party will not ask for new information at the time of Marketing Authorisation but rather compile the existing evaluations that have been conducted by the COMP, the CHMP and/or the PDCO and the CAT. For this reason the Working Party must be established where the relevant knowledge and expertise is gathered: at the EMEA.
3. **The work of the Working Party must not add another hurdle**, or any additional time to the process.
4. **There must be a commitment by the Member States** - in their National Plans on Rare Diseases - **to use the Common Assessment Reports** on clinical added-value.
5. **The impact on patient access** of the Working Party and the Scientific Assessment Reports **should be subject to review** after few years of implementation.
6. **This process is intended to apply to Orphan Drugs** only, as listed on the EU Register of Orphan Medicinal Products. Orphan Drugs have the unique benefit of 10 or 12 years of Market Exclusivity, an EU incentive which does not exist for any other EU regulated products. Orphan Drugs are characterised by specific issues: the rarity of patients and the scarcity of knowledge and experts in this field.

The gathering of expertise at European level can also support the coordination of the national requirements for additional studies after Marketing Authorisation. However, the primary objective of the Working Party should be to gather and make available the results of the existing scientific review of all data available at the time of Marketing Authorisation. This would be already a huge step forward in sharing scientific evaluation outcomes with Member States, enabling them to make the best-informed decisions possible on Pricing & Reimbursement in a timely manner, to the benefit of patients.

I - BACKGROUND & INTRODUCTION

1. **The EU High Level Pharmaceutical Forum¹ conclusions and recommendations – “Improving Access to Orphan Medicines for all affected EU citizens” – adopted by Member States on 2 October 2008** acknowledged that “the overall objective is to promote the sustainable development of valuable orphan medicines and to improve sustainable access to these medicines for all affected in the EU” (p1). This policy document calls for **“exchange of knowledge amongst Member States and European authorities on the scientific assessment of the clinical added value of orphan medicines”** (p4). “Such exchange could improve the flow of knowledge from EU-level authorities (e.g. EMEA Committees) to the Member States’ pricing and reimbursement authorities, in particular with knowledge gathered during the marketing authorisation procedures (quality, safety, efficacy), revision of the orphan designation criteria at the time of the marketing authorisation (significant benefit) and potentially the evaluation of paediatric use (paediatric investigation plans)” (p4). “Bundling the fragmented know-how to assess the clinical value of orphan medicines would **allow the timely production of well-informed opinions**, based on more data, shared information, experiences and in-depth discussion” (p4). “These collaboration 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” (p4). This policy document also calls to “establish early dialogue between companies and pricing and reimbursement authorities, including clinical value assessment authorities regarding orphan medicines in the pipeline and the future needs for these medicines” (p3). “It would offer an early occasion to discuss what clinical data would be required for later clinical added value assessments and pricing and reimbursement decisions” (p3). “Such dialogue might require an upfront coordination between Member States and the European authorities, in full respects of different competences, in order to jointly pass common messages to the individual companies” (p3).

"The High Level Pharmaceutical Forum acknowledges the **distinction between the scientific assessment of the relative effectiveness of medicinal products and health economic assessments of their costs and benefits**. The aim of relative effectiveness assessment is to compare healthcare interventions in daily practice and classifying them according to their added therapeutic value". "It acknowledges the importance for Member States of exchanging information on their respective relative effectiveness assessment criteria, systems and activities in order to: i) consolidate the scientific evidence on relative effectiveness by collecting data, processes and conclusions reached at national level, for purpose of comparison, where appropriate; ii) facilitate the work of the pricing and reimbursement authorities by providing them with consolidated scientific evidence, and iii) inform health-care professionals and patients on the most effective medicines." "It endorses the working definitions on efficacy, relative efficacy, effectiveness and relative effectiveness [...] and calls the Member States to take these definitions into account when developing and implementing systems of relative effectiveness assessment."

2. On 11 November 2008, the **European Commission adopted the Communication from the Commission on “Rare Diseases: Europe’s Challenges”**. In its “operational actions to develop European cooperation and improve access to high quality healthcare for rare diseases”, it identifies specific actions to improve “access to orphan drugs” (paragraph 5.3, p.6) as: “There are specific bottlenecks in access to orphan drugs through the decision-making process for pricing and reimbursement

¹ <http://ec.europa.eu/pharmaforum/>

linked to rarity; the way forward is to increase collaboration at the European level [...]. **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”.**

3. On the same date, 11 November 2008, the Commission has adopted a **Proposal for a Council Recommendation on a European Action in the Field of Rare Diseases**, which has been adopted by the Health Council on 9 June 2009. In the recommendations to Member States, there is a specific chapter on “gathering the expertise on rare diseases at the European level” (Chapter 5) with a specific action on orphan drugs (5): **“Sharing Member State’s 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”.**

The success of this proposed Working Party and assessment reports depend entirely on:

- A carefully, precisely and realistically defined role, mandate, composition and functioning of the Working Party to be in charge of the scientific assessment of the clinical added value of orphan drugs; AND
- An explicitly stated link between these reports at EU level and the Member States.

With this in mind, and with the shared goal of improving access, EURORDIS and the below-indicated companies and academic leaders in the field of orphan drugs would like to put forward the following proposals to the European Commission, EMEA and Member States.

II- PROPOSAL TO THE EUROPEAN COMMISSION AND EMEA FOR THE ESTABLISHMENT OF A WORKING PARTY FOR THE SCIENTIFIC ASSESSMENT OF THE CLINICAL ADDED VALUE OF ORPHAN DRUGS

1. **Recommendation 1: The Working Party should be created as soon as possible with the clear aim to reduce delays in accessing EU-approved orphan drugs.** It is an essential measure foreseen by the Commission Communication, the Council Recommendation and the adopted outcomes of the EU High Level Pharmaceutical Forum. Patients, healthcare professionals, biopharmaceutical companies and policy-makers alike are waiting for this opportunity to address the main challenge of orphan drug policy in the EU.
2. **Recommendation 2: The Working Party should be created at the EMEA.** All the scientific data are already available from the EU centralised regulatory procedures through the COMP, CHMP, PDCO and CAT. All the relevant knowledge and expertise is built up during the Scientific Advice, Protocol Assistance and Post-Marketing studies. Through these procedures, the scientific and medical expertise on Orphan Drugs in the EU is gathered at the EMEA. The Agency has more than 10 years of experience in pooling together the limited expertise of Member States on Orphan Drugs and is, therefore, the best place to situate the Working Party. It has experience of working on confidentiality aspects, and with marketing authorisation holders, companies developing medicines, medical experts and patient representatives. Additionally, it is in

the EMEA remit to provide information on approved medicinal products within the EU. It is proposed that this **Working Party be established at the level of EMEA - and not as a Working Party of one of the EMEA Committees - in order to ensure that it will involve all the relevant EMEA Committees (COMP, CHMP, CAT and PDCO).**

3. **Recommendation 3: The creation and activity of the Working Party should focus on improving the situation for patients in terms of access to innovative therapies.** This essential point should be kept in mind when developing the mandate, composition and internal rules of procedure.
4. **Recommendation 4: The scope and mandate of the Working Party is to focus on the scientific data of relative effectiveness such as clinical, epidemiologic and therapeutic aspects.** These data are the same and are valid across the EU and their assessment is very much the same in all Member States. The scope and mandate of the Working Party is not to pre-empt or replace activities that are legitimately carried out at Member State level, e.g., health technology assessments or health economic assessments. This is clearly stated in the Commission Communication “Rare Diseases: Europe’s Challenges”, (paragraph 5.3, p.6) which stipulates that the Working Party should not pre-empt the respective roles of the authorities. The mandate should expressly state what the Working Party is for and what its role is. This must be a scientific party to review scientific data and should not become involved in economic discussions or evaluations that are the responsibility of the Member States. The mandate and rules of procedures of the Working Party should be drawn up in such a way to ensure that this is very clear and is not used in future as a “slippery slope” to gradually move away from its scientific focus.
5. **Recommendation 5: The main tasks of the Working Party should be to:**
 - (a) Produce well-informed opinions in the form of non-binding Common Assessment Reports on the Clinical Added Value of Orphan Drugs approved at the EU level;
 - (b) Establish a dialogue between Member States to facilitate an upfront coordination of possible additional national requirements (eg. registries, real life studies) and to articulate them with the CHMP post-marketing obligations to avoid duplication and make the most of available resources;
 - (c) Regularly revise and update these Common Assessment Reports based on knowledge generated after Marketing Authorisation. As above, the Working Party is not intended to conduct new reviews of scientific studies or to request new submission of data. This point is important in order to respect the remits of the COMP, CHMP, CAT and PDCO.
6. **Recommendation 6: The Common Assessment Reports on the clinical added value of orphan medicines should state that the evaluation and pooling of information is intended to “facilitate national pricing and reimbursement decisions” and to “minimise delays for access to orphan drugs for rare disease patients”.**
7. **Recommendation 7: The Report should be made available in the 60 to 90 days period between the CHMP Positive Opinion on an Orphan Drug and the Commission granting of a Marketing Authorisation.** The preparation of this Report should not impact on the timeline of decisions of the EC on Marketing Authorisation, nor on the publication of the EPARs.
8. **Recommendation 8: The Common Assessment Report and related Annex should be endorsed by the COMP and CHMP.** This would enhance the consistency of scientific assessments across the EMEA. It would also reinforce the legitimacy of these reports towards Member States authorities.

9. **Recommendation 9: The Common Assessment Reports should be made public and translated** in all languages of the Member States. This is very important for national decision makers, prescribing doctors and patients.
10. **Recommendation 10: The National Plans on Rare Diseases should include the explicit intent of the Member States to use the non-binding Common Assessment Reports** on the clinical added value of orphan drugs.

III- ROLES AND RESPONSIBILITIES OF THE NEW PROPOSED WORKING PARTY TO PRODUCE NON-BINDING COMMON ASSESSMENT REPORTS ON THE CLINICAL ADDED VALUE (RELATIVE EFFECTIVENESS) OF ORPHAN DRUGS

The objective of the Working Party is to make the most of the existing scientific data at the time of Marketing Authorisation and to make this transparently available to Member States and all interested parties at the time of Marketing Authorisation. This will avoid duplication and wasting of existing scientific evaluations in the EU orphan legislative process.

To this end the Working Party: 1. Brings together the existing evaluations that have already been conducted by the COMP, the CHMP and/or the PDCO and the CAT, as well as outcomes of other relevant studies; and 2. Compiles them into well informed opinion on the place of the product in the therapeutic strategy.

One of the challenges is that these evaluations are currently not collated and are not made fully public in a transparent way. The Working Party will perform these tasks and will continue to revise and update its Common Assessment Reports using the data generated by the post-marketing studies, which are evaluated by the CHMP or the PDCO and CAT.

11. **Recommendation 11: The aim of the common assessment report should be to provide a well-informed opinion on the place of the product with the authorised therapeutic indication in the therapeutic strategy of the rare condition**, to the best of current knowledge. The Common Assessment Reports should be updated regularly as new information is made available after Marketing Authorisation.
12. **Recommendation 12: The documentation on which the Working Party will produce its Common Assessment Reports should be that already existing at the EMEA.** No new documentation should be requested at the time of Marketing Authorisation, since all scientific data on the Orphan Drug has been made available and reviewed extensively by various Committees at the EMEA each of them being composed of national experts from all Member States. The Working Party should, therefore, be responsible for collating all the existing reviews of the scientific data carried out by those experts from the Member States into one single document.
13. **Recommendation 13: The format of the Common Assessment Report** should be a rather short document, structured in a usable way for national decision makers, written in a clear and easy to understand language, thus avoiding ambiguities in translation and enhancing the usefulness for doctors and patients.
14. **Recommendation 14: The content of the Common Assessment Report should cover: the description of rare condition, the available methods of treatment and care, the description of the product, its mechanism of action, the summary of its risk vs. benefit assessment and other relevant data aimed at assessing its relative effectiveness and the place of the product with this therapeutic indication in the therapeutic strategy** of this rare condition to the best of current

knowledge at the time of assessment. The prevalence of the designated condition and the prevalence of the authorised therapeutic indication will also be included in this Report to allow Member States to have a **realistic estimate of the likely number of patients**, as currently, this is not the case.

15. **Recommendation 15: The Annex on agreed coordinated national post-marketing requirements.** Each product is reviewed on a case-by-case basis. In some cases, products will be required to generate more scientific data on the basis of in-use evidence. If this is the case, the Working Party, in an Annex to the Common Assessment Report, should also propose a strategy and timelines to develop an **agreed minimum sufficient set of data for demonstrating the clinical relevance and effective place of the product in the therapeutic strategy** and, therefore, the continuance of its availability to patients. This would avoid the current situation where Member States individually request follow-up measures, resulting in a series of potentially differing national requirements. This would also promote better medical practice, better targeting of patients who can effectively benefit the authorised product and for the right dose and regimen.
16. **Recommendation 16: The agreed minimum sufficient set of data, defined on the Annex, should focus on generating the knowledge on the place of the authorised product in real life so to promote the best possible use of the product and care for this condition.** Given that: (i) scientific data at the time of Marketing Authorisation will always be limited in the case of orphan drugs; (ii) the extent of data available is directly linked to the rarity of the disease or condition in question and to the inclusion criteria; (iii) and that there is high heterogeneity of patients affected by a same rare condition, the Working Party should also capture what the minimum sufficient data to demonstrate clinical use would be and to identify an agreed programme and timeline for the sponsor to gather this data set from in-use clinical experience. This would lay down timelines – potentially based on the timelines contained in the regulatory processes that grant the product authorisation developed by the CHMP, e.g., exceptional circumstances, conditional authorisation or full authorisation – and methodologies to develop an agreed sufficient minimum data set and how this should be developed. Timelines must be realistic – depending on the rarity of the disease, for example – to ensure that they can be met.
17. **Recommendation 17: The COMP Opinion** of the reviewed criteria of Orphan Medicinal Products at the time of marketing authorisation **should provide an evaluation of the prevalence of the finally authorised therapeutic indication**, in order to support the work of the new Working Party. The report on the revision of designation criteria already exists, but it is only used internally, for the purpose of recommending whether or not the product being granted Marketing Authorisation should remain also on the EU Registry of orphan medicinal products. The Report by the COMP at the time of Marketing Authorisation includes the actual significant benefit demonstrated by the development plan between designation and Marketing Authorisation, the actual standard of care and available therapeutic intervention in the EU. In addition it should also include the actual prevalence of the authorised therapeutic indication, which is often smaller than the prevalence of designation criteria.
18. **Recommendation 18: The Common Assessment Report should be regularly revised.** This process should follow the existing review periods foreseen in the regulatory approval process in order to gain the maximum efficiencies from the system while at the same time avoiding creating new procedures. The revision of the Common Assessment Report of the clinical added value should aim at defining the place of the product with the authorised therapeutic indication in the therapeutic strategy of the rare

condition, to the best of new knowledge generated, both from the specific post-marketing studies on the product in this rare condition and from the additional knowledge generated by other academic and clinical work on the condition and its best practices of care.

IV- WORKING PARTY COMPOSITION & ESSENTIAL RULES OF PROCEDURE

The composition should secure the best possible articulation between Member States and the European authorities. The composition of the Working Party should reflect the expertise that has been built up during the evaluation of the product through the EU centralised procedures at the time of a positive opinion for designation, of a positive opinion for Marketing Authorisation, of the opinion for paediatric use, and following post-marketing evaluations. The rules of procedure should allow to bringing in the best possible expertise available from medical experts treating the concerned patients and patient representatives as well as a direct dialogue with the marketing holder.

- 19. Recommendation 19: Permanent members of the group should comprise COMP members, CHMP members, PDCO members and CAT members.** For instance, three or four members from each of these four committees should be appointed by their respective committees to this new Working Party. COMP members, because they may have provided Protocol Assistance and performed the significant benefit evaluation. CHMP members, because they have performed the Quality, Safety & Efficacy evaluation as well as the evaluation of the post-Marketing Authorisation commitments. Members of the PDCO could be involved so that there is good use of positive or negative studies on paediatric use. Also, members of the CAT could be permanently involved or invited if necessary, because for a same rare condition, both pharmacologic and advanced therapies may be available.
- 20. Recommendation 20: Member States should be involved as permanent members of the Working Party.** For instance, 10 representatives could be **appointed. Not every Member State needs to be represented** in order to achieve a successful and good exchange of knowledge for three reasons:

 - (a) Several Member States will be participating already through their appointment by one of the four EMEA committees;
 - (b) Member States may consider appointing experts either from their drug agencies or from their HTA agencies;
 - (c) Not all Member States (particularly medium and small size Member States) are willing to take part in this common assessment of the clinical added value and cannot afford to delegate their experts to too many EU committees and working parties;
 - (d) Having all Member States represented in addition to appointees of EMEA committees will make up a group of too many members.
- 21. Recommendation 21: Patient representatives should be involved as permanent members of the Working Party.** For instance, three patient representatives should be appointed. Their appointment could be based on an EMEA call for Expression of Interest to patient groups which already have official relationships with the EMEA.
- 22. Recommendation 22: External experts should systematically be involved in the discussion for the scientific assessment of the clinical added value of each orphan drug.** Three categories of external experts should be involved:

 - (a) Medical experts who are treating physicians for the rare condition in question;
 - (b) Patients' representatives from the rare condition in question;

(c) Leaders of the European Reference Network of Centres of Expertise or of the European Research Projects when one exists for the rare condition in question. This is essential for a good articulation between the Common Assessment Reports of the clinical added value and the European best practices on diagnostic and medical care.

23. **Recommendation 23: Existing international Health Technology Assessment networks should be involved as Observers to the Working Party.** These networks could include the Health Technology Assessment International (HTAi), the European Network for Health Technology Assessment (EUnetHTA) or the Medicines Evaluation Committee (MEDEV). Involvement of these networks is important to enhance the upfront dialogue at EU level on orphan drugs after the marketing authorisation, to exchange on methodologies to assess the scientific data on the therapeutic and clinical added value, to ensure the best possible line of continuation between the process at EU level and at Member State level which, at national level, may also include economic aspects.
24. **Recommendation 24: Other countries may be invited to join the Working Party as Observers.** These include Switzerland, Norway, Iceland and Liechtenstein. It may also include countries which have already expressed an interest in sharing the expertise, such as Canada.
25. **Recommendation 25: For any discussions relating to the updating and collation of future, in-use information** (relating to gathering of future information and updating of the Common Assessment Reports), **the Marketing Authorisation Holder should systematically be invited to an oral hearing based on the draft timeline and on a possible list of questions.** The discussion should aim to provide the best possible Annex for the agreed strategy and timelines between Member States for the generation of the additional minimum data set.
26. **Recommendation 26:** In the case of the discussions on updating and collation of future, in-use information a procedure should be foreseen, whereby the **Marketing Authorisation Holder could appeal** the assessment made by the Working Party.
27. **Recommendation 27: This new process will require financial support.** This financial support should come either from the EMEA budget, or from the EU Health Programme.

V - PROPOSALS TO MEMBER STATES ON RELATED MEASURES TO BE INCLUDED IN FUTURE NATIONAL PLANS ON RARE DISEASES

There needs to be a strong link to the Member States to encourage them to use the Common Assessment Reports. Without such a link, the assessment reports would create extra work without being used in any constructive way to facilitate access. In the worst case, they could be regarded when negative and disregarded when positive. If the new process is to add value, there must be a commitment by the Member States to mention the reports in their individual National Plans on Rare Diseases.

National Measure 1: The Council Recommendation and National Plans should include an explicit reference to the Common Assessment Reports, stating that they intend to use the collated evaluation of the data available to facilitate orphan access. The partners in the EU funded project EUROPLAN should also include a clear reference to the reports in their recommendations, and this should be discussed in the EUROPLAN national Workshops.

National Measure 2: The Common Scientific Assessment Reports on the Clinical Added Value of Orphan Medicines, which will be prepared as well-informed opinions at Community level in the Working Party at the EMEA, are used by the national competent authority to facilitate the national pricing and reimbursement decisions, in order to minimise delays of access to orphan drugs for rare disease patients. The annual budget estimations can then be based on the prevalence of the authorised therapeutic indication, not on the prevalence of the rare condition.

National Measure 3: The national competent authorities will base their requirements to generate additional data set on the Annex of the Common Assessment Report.

National Measure 4: The national competent authorities on pricing and reimbursement will promote the initial uptake of orphan medicines through conditional pricing and reimbursement decisions.

National Measure 5: These national conditional pricing and reimbursement decisions will be revised based on the shared outcomes included in the Revised and Updated Common Scientific Assessment Reports at the review points laid down in the regulatory approval process (1, 3 or 5 years).