EURORDIS Position Paper on the
“Centralised procedure for the scientific assessment of the
Therapeutic Added Value of Orphan Drugs”

EURORDIS - the European Organisation for Rare Diseases – represents 310 rare
disease organisations from 34 different countries, 23 of which are EU member states,
and thereby reflects the voice of an estimated 30 million patients affected by rare
diseases in the European Union.

In response to the Commission Public Consultation “Rare Diseases: Europe’s
challenges”, EURORDIS has developed a Position Paper on the scientific
assessment of the Therapeutic Added Value of Orphan Drugs. EURORDIS has
gained expertise and knowledge on this issue mainly through the participation of
patients’ representatives members of EURORDIS into regulatory bodies for Orphan
Drugs development at EU level, through the EURORDIS Surveys on Orphan Drugs
Availability and Pricing and through intense dialogue with all concerned parties such
as patients, experts, industry, National Competent Authorities (NCA), payers, etc.

Summary:

Patients do not have real and equitable access to Orphan Drugs.

In order to improve access to Orphan Drugs, the scientific assessment of the
Therapeutic Added Value of Orphan Drugs should be achieved through a European
centralised procedure, at the EMEA, where the relevant expertise and knowledge is
gathered.

To this end, a dedicated Working Party within the COMP would be in the best
position to deliver an expert opinion on the scientific assessment of the TAV.
1. The issue

Following the recognition that there is a need for specific medicinal products for rare diseases patients based on research and evidence based medicines, the EU has established a regulatory framework aimed at enhancing the development of Orphan Medicinal Products.

In the Regulation on Orphan Medicinal Products 141/2000 of the European Parliament and the Council (16 December 1999), whereas (1) and (2), it is stipulated that “Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients. (…) But “the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions”. “Some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat these conditions would not be recovered by the expected sales”.

Article 1 of the Regulation: Purpose. “The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products”.

Article 9 of the Regulation: Other incentives. Incentives are foreseen in this article to support research into, development and availability of Orphan Drugs

The Orphan Drugs Regulation can be considered a success as it has allowed, up to January 2008, the designation of 521 Orphan Drugs, among which 52 have been granted a Marketing Authorisation. The time of development between the designation and the Marketing Authorisation, as well as the success ratio of around 17% is similar to the one observed in the US in the last 25 years. Based on the 25 years of experience in the US with the Orphan Drugs Act (March 2007: 1749 designations and 315 Marketing Authorisations) and on the 7 years of European experience with the EU Regulation on Orphan Drugs, EURORDIS has developed a mathematic model to forecast the number of new Orphan Drugs to be potentially approved in the coming years: in 5 years (2012), it is anticipated that around 100 Orphan Drugs will be approved. This means an average of 10 to 12 new drugs per year.
The issue that EURORDIS wishes to address in this specific contribution is based on the following unsatisfactory observation: “Patients do not have real and equitable access to the Orphan Drugs they need”. This regrettable situation represents a major issue for rare diseases patients and their families.

- Orphan drugs are not available to patients and their doctors within the legal timeframe of 180 days maximum across the different EU Member States and this poses a legal issue.

- Orphan drugs are made available to patients in a worst time frame and conditions of access than other drugs, although they are intended for rare conditions where there is unmet medical needs, either with no satisfactory method of treatments or a significant benefit over existing therapeutic interventions. This poses an ethical issue and a political issue.

In fact, despite the overall success of the strategy on Orphan Drugs and the encouraging results, the main problem lies in the access to these drugs. The conclusions of the 4th EURORDIS Survey on Orphan Drug Availability in Europe¹

clearly show that the **EU legal timeframe** established by the Orphan Drugs Regulation is not respected (legal timeframe established by the Council Directive of 21 December 1988 on “Transparency of measures regulating the pricing of Medicinal Products for Human Use and their inclusion in the scope of national health insurance systems”).

**EURORDIS Survey on Orphan Drugs availability:**

Geographical coverage: the Survey has been conducted in 28 countries: the 25 EU Member States before the last enlargement as well as in Iceland, Norway and Switzerland.

Sources of information: Marketing Authorisation holders, COMP members, NCAs direct contacts and members of MEDEV, and patients groups.

The figures of the 2007 Survey are the ones observed for the access to the 22 Orphan Drugs authorised before 1st January 2006, namely minimum 1 year after the Marketing Authorisation has been granted. According to the EU law, all these 22 products should be accessible in every Member State. The Survey shows that there are **major differences between Member States** in the availability of Orphan Drugs, from “0 to 5” available Orphan Drugs up to “20 to 21”, with poor scores also in the “old” EU Member States, such as Ireland, Portugal, Belgium and Greece.

**Availability in 2007 at national level of the 22 first ODs authorised at EU level before 1st January 2006**
When looking at the situation of the availability in 2007 of the 12 Orphan Drugs approved before 2004, one can observe that these 12 Orphan Drugs are accessible in almost all EU Member States.

Therefore, **time is the major factor influencing the availability of Orphan Drugs and not the Therapeutic Added Value (TAV) of these products.** As patient representative, EURORDIS does not consider acceptable that the availability of Orphan Drugs is not linked to the TAV of the product – or to its potential value in the therapeutic strategy for the disease but to the time taken by either the pharmaceutical companies to perform the appropriate measures or by the NCA to decide on price and reimbursement.

Furthermore, if one compares the ex factory price for each Orphan Drug in each Member States to its European mean, one finds out that the variations are nowadays surprisingly limited (from −6% to +10%). These variations have been reduced, showing that the **clear and solid trend is a de facto convergence towards an EU ex factory price.** From the reactions that EURORDIS could gather, this also reflects the wish of most EU pharmaceutical companies.

Another interesting observation is the fact that **the lowest price obtained by the NCA, is not in the Member State where the decision was made last.** Therefore, this shows that the strategy consisting in deferring the decision on price and reimbursement does not reduce the economic burden on healthcare systems, in addition to not being based on the real value of the product. When human lives are at stake, this kind of argument and strategy – which is furthermore contradicted by the results – is nor receivable.

If one then compares the price paid for Orphan Drugs to the GDP of different Member States, it appears that the financial commitment varies from 1 to 10; **the ones making the highest financial commitment are not necessarily the richest EU countries.** These countries are: Austria, Czech Republic, Slovenia and Slovakia.

2. **The reasons: why are Orphan Drugs not available to patients in the EU?**

   In the life cycle of Orphan Drugs in the EU, everything is centralised:
   
   - Orphan Drug Designation (COMP / EMEA)
   - Protocol Assistance (SAWP / EMEA)
   - Marketing Authorisation Application (CHMP / EMEA)
• Significant Benefit (COMP / EMEA)
• Paediatric Investigation Plan (PCDO / EMEA)
• Main incentive: 10 or 12 years of EU Market Exclusivity
• 5 Year Review of Market Exclusivity (COMP / EMEA)

The majority of Marketing Authorisations for Orphan Drugs are conditional Marketing Authorisation or Marketing Authorisation under exceptional circumstances, usually at the end of Phase II. Therefore, there are **lots of post-marketing obligations**, such as additional studies and follow-up. The CHMP will evaluate these studies after the Marketing Authorisation has been granted and this means that **important scientific data will exist within the centralised system even after Marketing Authorisation**.

Orphan Drugs have an additional specificity compared to other medicinal products, which is the **Significant Benefit** (SB): if some therapeutic alternatives already exist, the new Orphan Drug shall “do better” in terms of efficacy, safety or contribution to patient care. This **SB assessment is made through EU centralised procedure** by the COMP, based on data provided for the Marketing Authorisation Application. These information are the same ones needed for the scientific evaluation of the Therapeutic Added Value (TAV) and therefore are gathered at European level, within the EMEA.

In the case of Paediatric Drugs, the **Paediatric Investigation Plan** (PIP) is also a **“European level tool”**. It is worthy to remind that 54% of Orphan Drugs are either exclusively intended for a paediatric population or for both paediatric and adult populations. Therefore, the majority of Orphan Drugs may be subject to a PIP within the Paediatric Committee at the EMEA.

To summarise: the whole process of scientific evaluation which leads to a decision bearing an economic impact - namely the granting of market exclusivity of 10 or 12 years - is indeed a process taking place at European level, prevailing on the Member States.

**EURORDIS wishes to underline that there is a fundamental disruption between on the one hand, the scientific evaluation and the major economic decisions - Orphan Drugs Designation and Market Exclusivity - which both belong to the European level and, on the other hand, the evaluation of the TAV and other pharmaco-economic aspects, which belong to the national level, leading to pricing and reimbursement decisions.**
This disruption creates some major difficulties, both at Member State and company levels:

- **For Member States:** there is not the same level of expertise within the 27 Member States, because Orphan Drugs are intended for rare conditions, some being extremely rare, and it is not surprising that there is a lack of medical expertise to perform a scientific assessment of the TAV, especially in medium-sized and small countries. This is why it has been decided that for designation and Marketing Authorisation decisions, the scarce existing expertise shall be brought together in one place at European level, within the EMEA.

- **For companies:** the vast majority of companies developing Orphan Drugs are small companies. For these companies it is difficult to follow 27 different procedures in 21 languages, for extremely small markets, often only a few patients. This does *de facto* delay placing on the market by marketing holders mostly in medium-sized and small countries. The observation of reality shows that 6 to 7 countries (making up to 50% of the EU population) are fast served, while the others will have authorised Orphan Drugs placed on their market little by little, at an average “speed” of 3 new countries per year.

### Reality of placing OMPs on the European market

- **The smaller the country, the less attractive it is:**
  - Drugs available in 7 countries: 50% of the global population
  - Drugs available in 14 countries: 75% of the global population
  - Drugs available in 21 countries: 90% of the global population
  - Drugs available in 28 countries: 100% of the global population

- **A dynamic process: the older the M.A., the higher the # of countries**
  - Overall: 6 countries fast served, then 3 new countries/year
    (# countries = 5.7 + 0.24 months;  p<0.02)
Furthermore, **diverging requirements** between Member States, such as additional comparative studies, observational studies, registries, new health or quality of life measures, **are not always feasible and increase the overall costs** of Orphan Drugs Development.

### 3. The rationale

The specificity of Orphan Drugs is linked to the rarity of patients (small populations), the scarce expertise (need to pool expertise together) and the **overall rarity of the knowledge base**. In this context, clinical trials needed for the development of Orphan Drugs always take place at European or even international level and their scientific assessment is performed through the EU centralised procedure.

**The development of Orphan Drugs does not stop at Marketing Authorisation:**

Because 50% of Orphan Drugs get the Marketing Authorisation at early stage, mostly at the end of phase II, there are many **post marketing obligations** and the assessment of post marketing studies is performed by the CHMP at EU level. These new data are reflected in the revised EPARs. Concerning the PIP, as recalled above, they are also assessed at EU level by the Paediatric Drugs Committee, at the EMEA.

In parallel, the National Competent Authorities (NCAs) are often also asking for additional data, such as **observational studies and registries**, to answer some of their concerns. The national level has diverging requirements concerning these additional post-marketing studies and data. EURORDIS strongly believes that these data should usefully be managed at European level, in a centralised coordinated way, to avoid duplication of efforts and increased costs, as well as unjustified and unacceptable delays for patient access to Orphan Drugs.

Orphan Drugs are mainly developed by small or medium-sized companies and are very innovative pharmaceutical products, mostly derived from biotechnology. The price and added-value of these products should only be compared to other highly innovative biopharmaceuticals. The conclusion of this comparison is that the **TAV of Orphan Drugs is superior to the TAV of other medicinal products approved during the same period**, as shown in the slide below.
4. The proposal

To address the overall situation as described above and the disastrous consequences it has on patient’s access to Orphan Drugs, EURORDIS proposes that the **scientific assessment of the TAV of Orphan Drugs is performed through an EU centralised procedure**, in the same way in which both the designation as Orphan Drug (at COMP) and the decision for Marketing Authorisation (at CHMP) take place at European level.

The assessment of the TAV of Orphan Drugs (TAVOD) should be performed where the expertise is gathered, and this is not at national level, but within the EMEA.

A Working Party of the COMP within the European Agency would be in the best position to deliver an expert opinion on the scientific assessment of the TAV, which would support and speed-up decisions on pricing and reimbursement at national level.

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**Example: France Health Technology Agency’s (HAS) assessment of Orphan Drugs (July 2007)**

- 28/28 : favourable opinions
- Assessment of added value (ASMR level) => Improvement over existing therapies

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Orphan drugs</th>
<th>All drugs (2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>3 = 11%</td>
<td>2%</td>
</tr>
<tr>
<td>Important</td>
<td>10 = 36%</td>
<td>12%</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 = 18%</td>
<td>18%</td>
</tr>
<tr>
<td>Minor</td>
<td>4 = 14%</td>
<td>14%</td>
</tr>
<tr>
<td>No improvement</td>
<td>1 = 4%</td>
<td>46%</td>
</tr>
</tbody>
</table>
The proposed TAVOD Working Party\(^2\) - composed of COMP members, NCAs representatives, payers and patient representatives - would perform a common scientific assessment of the TAV for each Orphan Drug and deliver an “opinion document”. In this way Member States would pool their scarce scientific expertise to assess the TAV and would also recognise the value of this common assessment and opinion document. This system would avoid duplication of procedures at national level.

**Pricing and reimbursement (P&R) decisions will be facilitated and accelerated,**

improving the overall coherence, with the following advantages for all parties involved:

- P&R decisions will remain at national level, within NCAs.
- P&R decisions will be based on the Common assessment report of the Therapeutic Added Value of orphan drugs, therefore reducing diverging decisions, helping convergence throughout the EU and optimising resources.
- P&R decisions will be regularly revised on the basis of revised EPARs and European assessment report of therapeutic added value, as well as according to post-marketing studies and observational studies.

The opinion documents can evolve progressively, according to post-marketing obligation and further data produced through registries and observational studies.

The TAVOD Working Party will regularly re-assess the TAV thereby helping to define the most appropriate role of each Orphan Drugs in the therapeutic strategy in real life setting.

**Conclusions:**

1. **Orphan drugs are specific and different from other drugs**

Because of their rarity:

- The clinical development of orphan drugs is specific because of the hurdles of clinical trials with small, very small and extremely small populations of

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\(^2\) Committee for the assessment of the Therapeutic Added Value of Orphan Drugs

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patients, scarce scientific expertise, limited knowledge on the diseases (e.g. issues natural history, relevant endpoints, etc)…

- Orphan Drugs have a specific profile at marketing authorisation: mostly conditional approval, end of phase II, lots of post-marketing obligations…
- There are also specificities related to Orphan Drugs for placing on the market: small production, stocks, packaging, leaflets for very small quantities, etc.

Because of their specific status in the EU:

- Orphan drugs are, by nature, specific and different within the European market given the Market Exclusivity (10 years + 2 years if paediatric studies)
- Specificity of Significant Benefit
- Specificity of the scientific and economic model: mostly innovative, mostly SMEs, often biotechnology companies.

2. **The lack of access to Orphan Drugs is critical and requires coordinated action**

The Orphan Drugs Regulation adopted by EU policy makers and Member States aims at improving the conditions of an underprivileged category of the EU population. The following pieces of legislation, strategies and policies confirm this orientation. However experience shows that rare disease patients do not have timely and equitable access to Orphan Drugs. They do not access them within the legal timeframe, have different access according to the country where they live and irrelevantly of the national GDP. Furthermore, delays of access are not linked to the real value of the drug and Member States are not really saving any money in the long term by delaying their decision on P&R.

The situation is worsening:
- Affecting patients and population health outcomes
- Undermining the EU competitiveness
- Affecting EU capacity to provide an environment supportive of innovation

3. **A specific EU approach for orphan drugs is feasible**

- EUnetHTA has developed « core principles » in its WP5 for common scientific HTA;
- The MEDEV is supportive and encourages collaboration at EU level;
Many representatives of NCAs have experienced the limits of the current situation and are calling for collaboration at EU level;  
10 to 12 new orphan drugs are approved each year in EU

4. **Orphan Drugs can be a model for future products with very small markets or highly innovative**

The adoption in 2007 of the EU Regulation on Advanced Therapy Medicinal Products (gene therapy, cell therapy, tissue engineering), will generate the same kind of issues and will have its own specificities requiring collaboration at EU level to have a common ground for scientific HTA and common rationale for pricing.

The implementation from 2007 of the EU Regulation on Medicinal Products for Paediatric Use may also generate the same needs.