
This document summarises the comments regarding the content of the draft Notice from the Commission on Regulation (EC) no 141/2000.

- **B.3 – Intention to diagnose, prevent or treat (Medical plausibility)**

The following statement was discussed:
‘Sub-setting a condition with the use of biomarkers (e.g. personalised medicine) will not be acceptable unless it is proved that the product is ineffective in the rest of the population.’

We would welcome clarification from the Commission as to whether sub-setting occurs only in the setting of conditions which exceed the prevalence threshold of 5 in 10,000 (as according to the format and content guideline), or whether this is also relevant for conditions that already fall under the threshold (e.g. gene therapy for epidermolysis bullosa caused by several different genes).

It is supported to have the clarification on the non-acceptability of sub setting based on biomarkers but has to be pointed out that the section as it currently stands could be interpreted as actually opening up this possibility, and may create divergence on the use of the term ‘condition’ with other committees such as the PDCO.

- **B.5. – Significant Benefit**

- The following statement was discussed:
‘A possible increased supply due to shortages of existing authorised products or due to a national marketing authorisation in one or a limited number of Member States.’

We believe that there are exceptional circumstances (e.g. like in the case of Cerezyme and Vpriv), when there are documented and substantiated problems with supply and patients are suffering from the long-term interruption. It is suggested that serious and documented lack of supply with evidence of patient harm should remain as a ground for significant benefit.

We agree that all other examples of limited availability are to be removed.

- **B.5 – Significant Benefit and B.6 – Maintenance of the orphan designation at the time of the Marketing Authorisation**

D. The examples on "a major contribution to patient care" should be reconsidered. The second example mentions that major contribution to patient care could only be acceptable if “there are data showing better clinical outcome”. However, it should be noted that at the time of designation the COMP would still regard this as a clinically relevant advantage even if there is no
data available at the time. This speaks in favour of making a clearer distinction on what are the expectations in terms of data at designation vs. maintenance.

E. Comparator at MAA
With regard to the following statement:

‘In exceptional cases, if it is not possible to generate a sample size big enough to provide statistically comparative evidence or due to the heterogeneous patients population, it would be possible to adapt clinical trials designs and alternative methods (such as indirect comparative data, historical data).’

It is rather the rule than exception that it is not possible “to generate a sample size big enough to provide statistically comparative evidence or due to the heterogeneous patients population”. This is also not only because the population is heterogeneous but rather because it is too small.

Section C. Procedure for Designation and Removal from the Register – Article 5

- **C.1. – Justification of continued fulfilment of the criteria by the applicant**

Maintenance will be assessed in parallel to the marketing authorisation

This is indeed the case, however, we would suggest to clarify that the COMP cannot adopt an opinion until the CHMP has issued an opinion on the granting of the Marketing Authorisation. We would therefore recommend that this aspect is clarified in the notice as this is something that most sponsors do not currently understand.

‘For the orphan medicinal products approved under the conditional marketing authorisation, further data will be generated post authorisation as part of the specific obligations and are reviewed on an annual basis in the context of the review of the benefit risk balance by the Committee for human medicinal products. In the light of the updated data at the end of the fifth year as provided in Article 8.2 of Regulation 141/2000, a Member State may inform that the criterion on the basis of which market exclusivity was granted may not be met and the agency shall then initiate the procedure laid down in Article 5.’

The legislation foresees in specific cases marketing authorisations can be granted on less complete data than is normally required. These authorisations are subject to certain specific obligations that are to be reviewed annually by the agency. However, the limited data available at the time of authorisation may prevent COMP from confirming the significant benefit. The current legislation does not support the re-assessment of significant benefit at the time of the fulfilment of the specific obligations.

- **C.3 – Re-evaluation of orphan designation criteria at time of Marketing Authorisation – pre-authorisation phase**

1. ‘On the other hand, when the procedures for the simultaneous marketing authorisation applications do not remain in parallel and the positive opinion for the second product compared to the first product is delivered by the CHMP with a difference in time of two CHMP meetings or more, the second sponsor should show data supporting the significant benefit over the first product.’

We would agree with the EC that if the CHMP opinions are adopted in the same month, there is no need to reassess the orphan designation criteria. However, from a legal point of view, if this
is not the case, then reassessment of the orphan designation criteria would in our view need to be triggered taking into account the recently authorised product(s). This approach is also followed in other areas and should be consistent across different legal provisions. Once a product has received a marketing authorisation that product must be considered within ongoing applications for the purpose of demonstration of new active substance status, demonstration of significant clinical benefit in comparison with existing therapies for the +1y marketing protection, demonstration of major therapeutic advantage in the framework of a conditional marketing authorisation etc.

Section D. Union Marketing Authorisation – Article 7(3)

- **D.1 – Designated condition vs. authorised indication**

Introducing a review of the orphan criteria once an applicant modifies the therapeutic indication based on Article 7(3) of the Orphan Regulation

While we understand the intent of the EC behind this proposal, we have concerns as this would introduce a significant change with respect to the current practice and may have implications on public health.

The main concern is that this proposal will discourage development in the area of rare diseases. If companies do not have the certainty that their proposed new indication will benefit from Market exclusivity they may refrain from further developing the product in that indication. We believe this may also promote off-label use rather than stimulating the authorisation of new indications. Otherwise this may lead to a delay the application and access to patients until the company is reassured that enough data has been generated to justify significant benefit in the new indication.

This brings an additional regulatory burden on companies to maintain separate MAs for products which would nevertheless be intended for a small number of patients. It should also be borne in mind that any extension of the indications (in certain cases very small changes in target population) within the same orphan condition will not be rewarded with new periods of market exclusivity but rather benefit from the remaining period of market exclusivity that was previously granted.

We would also like to highlight the possible implication with regards to the access to the paediatric reward for orphan medicinal products in case significant benefit may not be demonstrated for the paediatric population.

Additionally, this proposal may also have an impact on other initiatives aimed at promoting early access of medicines for a small indication with subsequent expansion of the therapeutic indication, such as the Adaptive Pathways.

Finally, such a procedure would further distance the EU orphan system from the US and be counterproductive to the attempts to facilitate the global development and marketing of orphan medicinal products on both sides of the Atlantic.
**General comments:**

In addition to the above we would like to take this opportunity to raise some additional points:

**Interpretation of medicinal product as “active substance”**

The COMP has over the last 15 years designated active substances/combinations of active substances rather than medicinal products. As the orphan designation usually takes place at an early stage and the medicinal product is not yet defined. Lately companies have challenged this approach arguing that the orphan regulation refers to the notion of medicinal product rather than active substance. In this regard, we would like to bring to your attention this matter so that you can reflect whether a clarification in the Communication in this respect would be useful.