Dutch government response to the Public Consultation on the draft Notice of the European Commission on aspects of the application of Articles 3, 5 and 7 of Regulation No 141/2000 on orphan medicinal products.

Introduction
This document contains the response of the Dutch government to the European Commission's draft notice to replace the 2003 Communication from the Commission on the Orphan Medicines Regulation (OJ C178, 29.7.2003). The response has been prepared by the Ministry of Health, Welfare and Sport with input from the Medicines Evaluation Board.

The draft notice specifically provides revised guidelines for the application of articles 3, 5 and 7 of the Regulation, but excludes a review of guidelines on Article 8 of the Regulation. Those guidelines have been revised in 2008. The Dutch government believes that the functioning and application of the Orphan Medicinal Products Regulation should be reviewed integrally. Therefore this response document is built up in two parts. In the first part we respond specifically to the consultation questions posed by the Commission. The second part briefly addresses some important issues in relation to the Orphan Medicinal Products Regulation, other than raised by the Commission, and in particular in relation to (the application of) article 8.

The main items put forward by the Commission in its public consultation query are as follows:

- **n°1: Clarification of the definition of "significant benefit"**
- **n°2: Encouraging the development of orphan medicinal products for communicable diseases (e.g. Ebola)**
- **n°3: Simplifying the procedure for the reassessment of orphan criteria when two authorisation application procedures are pending in parallel for two orphan medicinal products**
- **n°4: Introducing the reassessment of the orphan criteria for a new subset of the condition when a sponsor extends the use of its product after marketing authorisation**
- **n°5: Clarifications on processing the transfer of orphan designations between sponsors**

<u>Part I – response to the questions raised by the Commission</u>

Add N°1. Significant benefit
Overall, we welcome the clarifications made by the Commission in this section.

With regard to the discussion about significant benefit over **authorised medicinal products and methods**, we support the proposal that significant benefit of a new orphan product should not only be discussed vis-à-vis authorised products, but also over existing methods of treatment which are established in clinical practice if these are described and confirmed in clinical treatment guidelines. Whether medicinal products prepared in a hospital pharmacy should also be taken into account in such an assessment depends on the ease of preparation of such products and evidence that this is a general practice in EU, i.e. that if an orphan centrally registered product does not come to the market, patients in EU will still be guaranteed treatment with the pharmacy preparation.

Importantly, the inclusion of this specific significant benefit comparison may also prevent the observed practice in which an accessible magistral product prepared in hospital pharmacies is obtained by a sponsor and subsequently registered and marketed as an orphan medicinal product (OMP), with the potential consequence that it may no longer be accessible for patients in all EU countries because of the market exclusivity and price

setting related to its orphan designation. However, we would welcome that widely prepared magistral preparations obtain a 'normal' marketing authorization within the EU. Lines 154-159 of the proposed text are agreed.

According to the 2003 Communication, a possible argument for significant benefit of a new orphan medicinal product over existing products may be if for the already authorised medicinal products there is a **lack of supply and/or the new product may potentially increase supply.**

We agree with the interpretation in the draft-Notice that the fact that a product is registered in one or a few member states per se is not a sufficient argument for demonstrating a lack of supply. However there have been examples in the past (e.g. the case of Cerezyme and Vpriv), when there were documented and substantiated problems with supply and patients were confronted with situations in which pharmaceutical treatment would not be available.
Therefore, in our opinion the significant benefit may continue to be based on supply-related aspects, but only in cases in which the sponsor is able *to demonstrate with data* that there is serious and documented lack of supply with evidence of patient harm. In this respect the changes as proposed in the Notice should be revised and further specified (lines 188-191). Furthermore, such exceptional circumstances should not be the result of shortages of an existing authorised orphan medicinal product, e.g. as meant in Art 8.3(b) of the Regulation, when it is marketed by a sponsor or marketing authorization holder who is also applying for orphan designation for a new similar medicinal product.

In addition, the issue of the level of evidence required to substantiate **significant benefit over existing therapies at the time of marketing authorisation** (lines 219 – 228) may need some more specific wording. The latest experience with products for oncological indications shows that even indirect comparisons with all existing methods for the same condition may be problematic to provide. Therefore some agreement is needed on the level of evidence and use of historical control data with specific aim at making the most fair and logical comparisons.

With regard to the **pharmaceutical form**, it is considered relevant to specify if and in which cases a new pharmaceutical form for a certain active substance and indication represents a significant benefit. Currently if a new pharmaceutical form is considered as sufficient for significant benefit this may result in an orphan medicinal product with ten years market exclusivity which blocks the registration of any generics for the same indication, even if they have another pharmaceutical form. This is due to the fact that the orphan designation is linked to the active substance and the indication, and not to the pharmaceutical form in combination with the active substance and indication. Therefore it is proposed that the orphan status at time of granting a marketing authorisation can be discussed and confirmed to the active substance, its specific pharmaceutical form and indication only. We therefore endorse the proposed change by the Commission, but it is recommended to revise lines 232 – 237 and make this requirement more explicit, providing the possibility that the orphan exclusivity could be bound to the new pharmaceutical form for a certain active substance and indication only. In this way entrance of generics for the same indication but with the 'old' formulation will not be hindered, which is the case for Vantobra.

Add N°2. Encouraging development of products for communicable disease
From the perspective of public health protection and safety, it is important that research and development of medicinal products for potentially serious communicable diseases is promoted. For this reason the Commission proposes that in order to stimulate such research, the threshold criteria regarding prevalence for orphan designation (not more than 5 in 10 000 persons in the European Union) for conditions which affect large numbers of people in Third World countries, but that have a very low prevalence or are

non-existent in EU countries, should also include the option of zero prevalence (lines 85-99). In principle we can support this inclusion for the reasons as discussed in the Notice.

However, the use of the Orphan Medicinal Product Regulation for promoting the development of medicinal products or vaccines targeting highly contagious communicable diseases, needs serious considerations. Some of the benefits of the Regulation can be of great added value for the development of these products, e.g. protocol assistance, reduced fees, etc. But from a public health perspective, the benefit of market exclusivity is not desirable. Orphan designation for a condition such as Ebola would entail that eventually only one product would be available in the EU, which creates dependence of EU Member States towards one marketing authorization holder. If the 'orphan condition' suddenly evolves into a highly prevalent disease within the EU, it is doubtful whether production can follow suit. In such cases it is desirable that several manufacturers can develop the product.

Finally, the market exclusivity for the orphan medicinal product as meant above also means that any similar medicinal product that may have been developed in third countries, which is equally effective but (much) less costly than the orphan medicinal product, can't enter the EU market. In the situation when large numbers of citizens are affected by the disease and mass vaccination is required, the price levels for such an orphan product may pose an unacceptable barrier to public health.

Whether the proposed inclusion of zero prevalence in the prevalence criterion is the proper solution, therefore requires further discussion. It might be useful to draw a parallel to similar concerns that exist around the lack of development of new antibiotics and the proposed solutions to tackle these, e.g. the development of alternative business models.

Add N°3. Assessment of orphan criteria at time of marketing authorisation when two products run in parallel

We can agree with the proposal that some flexibility should be provided in cases where two products run in parallel, because significant benefit cannot be discussed against another product which is still under scientific assessment and neither against an immediately registered product (lines 296-307). However, we suggest that a careful discussion should take place to address some details of this proposal.

One question concerns the "buffer" time and how long this should be. The current proposal for two months difference in CHMP meetings is not clear enough. Is it two months since the CHMP had issued a positive opinion and if yes, what is the rational for this cut off?

If two procedures had started at the same time, but one is delayed due to clock stops and pending questions, does this mean that the second product will not have to defend significant benefit even if approved many months later? Usually such delay indicates incompleteness of the dossier and unresolved questions. Another issue concerns the question how to deal if two products are started at the same time but one goes through an accelerated procedure and the other not.

Add N°4. Reassessment of the orphan criteria for a new subset of the condition

The proposal to introduce a reassessment of any extension of the initial marketing authorisation for an orphan medicinal product has our support because the orphan criteria (including significant benefit over existing therapies at that point in time) should be assessed in the same way as for the initial registration. Lines 357-387 are supported. This reassessment should however not be limited to a review of the orphan designation criteria for the new indication only, but for the initial orphan conditions and the indications and variations that are being added at a later stage.

We welcome the clarification in the draft Notice of what may be considered as a valid subset as an important explanation. The clarification makes clear that the recognition of

a valid subset for the purpose of the orphan legislation requires that patients in a subset should have unique evaluable characteristics, the absence of which would render the orphan medicinal product ineffective in the rest of the population. Lines 108-125 are agreed.

n°5. The transfer of orphan designations between sponsors.
We welcome the proposal made by the Commission, which avoids that one sponsor can extend market exclusivity for a medicinal product and for a condition by registering the same product again in another form or with another route of administration, while also prohibiting that such new registration can be acquired by one sponsor from another (lines 317-332).

Comments on section D –Scope of Union Marketing Authorization (Article 7(3))

The Commission does not request input on this part of the Notice. However, we would like to raise a specific concern regarding the possibility for sponsors to obtain a separate marketing authorization for non-orphan medicinal products or vice versa. The Commission stresses that it is important to handle these authorizations (and their enforcement) separately to ensure legal certainty for the product that benefits from market exclusivity. This is understandable from the perspective of the market authorization holder. However, from the perspective of the accessibility and availability of affordable medicinal products, this issue also raises questions. As orphan medicinal products are granted on the basis of closely defined orphan conditions and related indications for small patient groups, it is difficult to understand that a marketing authorization holder can market the same medicinal product for medical conditions that include large patient groups (example: the orphan medicinal product Revatio and the non-orphan Viagra).

Part II - Additional comments on the Orphan Medicinal Products Regulation:

Despite the general appreciation of the Orphan Medicinal Products Regulation, there is a growing concern in the Netherlands and in other European countries that this legislative framework also has some unintended and/or unwanted adverse consequences that challenge its purpose and that may jeopardize future availability and affordability of orphan medicinal products for EU citizens.

The draft-notice that is the subject of this public consultation reviews the guidelines for application of Articles 3, 5 and 7 of the Orphan Medicinal Products Regulation. In 2008, the Commission reviewed the application of Article 8 of the Regulation, which concerns the rules on market exclusivity, and adopted guidelines into a Communication on derogations from market exclusivity (C(2008) 4077 final) and in a Communication on the review of the period of Market Exclusivity (C(2008) 4051 final).

Orphan medicinal products that benefit from market exclusivity enter the EU market – almost without exception - at very high price levels compared to medicinal products with a 'normal' marketing authorization. Governments are willing to pay for medicinal products that provide effective treatment for patients with serious chronic or life threatening conditions. However, various recent studies in the Netherlands have highlighted the growing influx of new OMPs that reach the market with limited added value for the patient and an increasingly greater budgetary impact.

The Dutch government would like to highlight three important issues:

Expansion of Market authorization. Article 7(3) of the Regulation concerns states that the market authorization granted for an orphan medicinal product shall cover only those therapeutic indications which fulfill the criteria set out in Article 3. As indicated in our response to the consultation questions of the Commission above, we have concerns

that the initial marketing authorization for an orphan medicinal products related to a specific active substance expands over time through the introduction of new indications, subsets and variations, or by introducing a separate marketing authorization. It may be worthwhile to examine the extent to which a sponsor or pharmaceutical company benefits from marketing such an active substance through various channels and marketing authorizations. It may show that the combined authorizations are such that the criteria for orphan designation related to the initial product are no longer met, and that orphan designation may no longer be justified.

Reinforcing the review of market exclusivity. The main incentive for pharmaceutical companies in the orphan medicinal products Regulation concerns the market exclusivity of up to 10 years for medicinal products that are designated as orphan medicinal product (art. 8(1)) and that are granted market authorization. Article 8(2) describes a process through which market exclusivity can be reviewed after five years. Even though Member States can take the initiative to call for a review process, in practice this seldom happens. The procedure for review as adopted in Communication C(2008) 4051 places the burden of proof, to prove that market exclusivity is not longer justified with the Member States – who often lack overview and data - and the COMP. We think it is necessary to discuss how the review process can be improved.

Addressing lack of choice and unreasonable profits. The market exclusivity for orphan medicinal products established under Art. 8(1) offers sponsors unique benefits as competition is eliminated for similar medicinal products for identical therapeutic indications for a specific orphan condition. This incentive has worked well, as over 110 products have been marketed in recent years, while over 1200 registrations for orphan designation have been made. However, there are also less beneficial consequences. The market exclusivity ensures that patients do not have much choice of medicinal product for their specific (subset of a) condition, as there is only one product allowed on the market. Furthermore, orphan medicinal products are all marketed at very high price levels across the EU. In the original proposal of the European Commission from 1999 on the Orphan Medicinal Products Regulation, the review at five years of market exclusivity referred to above included a criterion that the period of exclusivity could be reduced if the criteria for orphan designation were no longer met or if the price charged for a product resulted in unreasonable profits. The latter argument hardly plays a role in the current Regulation.

Considering the above, we think it is important that a debate is initiated if market exclusivity as it is currently applied in the Orphan Medicinal Products Regulation is benefiting patients in a proper way, both in terms of product variety as well as affordability.

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