EGA POSITION PAPER ON THE EC COMMISSION NOTICE ON THE APPLICATION OF ARTICLES 3, 5 AND 7 OF REGULATION (EC) NO 141/2000 ON ORPHAN MEDICINAL PRODUCTS

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The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.
1. General comments

The EGA, the association representing the generic and biosimilar medicines industries welcomes the opportunity to comment on the EC proposal for the communication on the Regulation (EC) No 141/20001 on orphan medicinal products (“the Orphan Regulation”) which introduced incentives for research, development and marketing of medicinal products for rare diseases.

We fully recognise the importance of available treatment for the patients suffering from life-threatening or chronically and seriously debilitating diseases. The experience and benefit delivered to patients over the last 15 years shows a real added value to patients suffering from orphan diseases.

15 years of use of the orphan legislation also presented some issues with the practical application of the legal and regulatory framework associated with the implementation of the Orphan Regulation.

We appreciate the EC’s efforts to clarify the interpretation of the Orphan Regulation by reviewing the EC Communication.

2. EGA detailed comments on the consultation:

When studying the “Draft Notice from The Commission on the Application of Articles 3, 5 and 7 of Regulation (EC) N° 141/2000 on orphan medicinal products” we noticed that in “B. Criteria for Designation”, the term “rare condition” (line 47) seems to have replaced the term “life-threatening or chronically debilitating” or “life threatening, seriously debilitating or serious and chronic condition” of Art 3 (1) of the Regulation 141/2000 (also being used in Regulation 847/2000 and in the Commission Communication 2003/C 178/02).

If this is an intended replacement, this would broaden the applicability of ‘orphan drug status’ to a much greater number of products and enable a new interpretation. We trust that this was not the intention of the EC.

EGA Recommendation: the term “rare condition” shall be replaced by the wording of the Regulation 141/2000 on the Orphan Medicinal Products and all other related documents.

B. CRITERIA FOR DESIGNATION – ARTICLE 3(1)

3. Clarification of the definition of “significant benefit”

3.1 Major contribution to patient care

The interpretation of the “significant benefit” is critical in view of granting a market exclusivity and defining the moment of first possible follow-on generic/ biosimilar medicine available to patients.
It needs to be a balance between encouraging a real, significant improvement by providing "significant benefit" to patient and the procedure/ legal framework being used to prevent generic/ biosimilar medicines' competition.

In some cases, the conclusion about "significant benefit" seems to be relatively easily granted. It opens a debate about using the criterion of "significant benefit", especially patient's preference/ compliance, as a regulatory tool for an evergreening strategy. The reward/ exclusivity granted thanks to "orphan designation" shall be proportionate to significant benefit being offered to patients by a given medicinal product.

The criteria and current practice related to orphan designation based on "significant benefit" shall be tighten up (for example by requiring proof of clinically relevant effect to the benefit).

**New pharmaceutical forms**

New pharmaceutical forms (e.g. modified released formulation) of already authorised medicinal products should not be qualified for an orphan reward (market exclusivity) even if there are advantages for the patients. This would open the door for evergreening strategies extending the protection provided by the orphan status. Due to evergreening strategies used by the originator companies to block generic competition, the concept of so called "Global Marketing Authorisation" (art 6.1 of the Dir 2001/83) was introduced in 2004 to prevent such practices. All additional pharmaceutical forms, new indications etc. are considered to be part of the "same MA" in view of the data exclusivity provision. The same principle/ same concept shall also apply to the orphan medicinal products.

This is a critical point for the generic medicines industry in order not to be blocked and to be able to provide generic versions of reference products (including orphan) after expiry of the exclusivity period. Therefore, the period of protection shall not be extended/ granted due to, for example, a modified release form replacing the initial one.

**EGA Recommendation**

New pharmaceutical forms (e.g. modified released formulation) of already authorised medicinal products should not qualify for an orphan reward (market exclusivity).

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1 Plenadren- a modified release formulation of hydrocortisone (once a day). Orphan status was granted on the basis of eventual benefit of better compliance, without real data being provided. (EPAR: “Although the clinical data is insufficient to make any claims on improvements with regards to metabolic effects with Plenadren, a once daily dosing regimen could however be of benefit in the context of convenience and patient compliance” There was no evidence that the difference detected in this small study had any clinical relevance whatsoever. This product should not have satisfied the Article 3(1)(b) criteria.
We also agree with the conclusion that significant benefit shall not be considered to be based on:

- A possible increased supply/availability due to shortages of existing authorised products or due to existing products authorised only in one or a limited number of Member States.
- Enhancement of the pharmaceutical quality of a product in compliance with relevant (CHMP) guidelines which are part of the obligation of every marketing authorisation holder;
- An alternative mechanism of action per se, to be sufficient for the assumption of significant benefit.

The criteria and current practice related to orphan designation based on “significant benefit” shall be carefully reviewed and shall not be used as a regulatory tool for evergreening strategies.

4. **Encouraging the development of orphan medicinal products for communicable diseases (e.g. Ebola)**

**Prevalence of a condition outside the European Union**

If the prevalent condition outside the EU is much higher than in the EU (prevalence close to zero in the EU) and the medicinal product can be extensively used outside the EU, there is no justification for the applicant (having a potential benefit and return on investment from the outside the EU) to benefit from the European “orphan status” and rewards associated with it. If the prevalence rapidly increases in the EU, the prevalence conditions as defined in the Orphan Regulation are no longer going to be met. The market exclusivity mechanism also seems to be irrelevant for the EU market (in case of “zero” prevalence” and “zero market potential”).

These kinds of products should be defined as a special category and probably assessed by the CHMP on a case-by-case basis.

5. **Simplifying the procedure for the reassessment of orphan criteria when two authorisation application procedures are pending in parallel for two orphan medicinal products**

With regard to parallel on-going applications, the EGA understands the need for a “tolerance window” and some flexibility as proposed by the European Commission in this respect and we support it. However, this “flexibility window” should be well defined and transparent. Clarity on exclusivity timelines is of high importance to all parties.
6. Introducing reassessment of the orphan criteria for a new subset of conditions when a sponsor extends the use of its product after marketing authorisation

The EGA would welcome some clarification on practices leading to the extension of the exclusivity period and delaying access to generic/biosimilar versions of orphan medicinal product.

A clear interpretation (line 323-332) that a sponsor can only receive one orphan designation per medicinal product and per condition would be welcomed. New subsequent formulations, routes of administration of the already authorised orphan medicinal product fall within the scope of the existing orphan designation. Moreover, it should not be possible to transfer an orphan designation to an applicant who already has a marketing authorisation for the same medicinal product and condition. Any additional pharmaceutical form should be granted by varying the existing marketing authorisation. Where an applicant submits a separate marketing authorisation to provide a distinction between two pharmaceutical forms and to avoid medication errors, this separate marketing authorisation shall be subject to the same market exclusivity period. It is fully in line with the concept of the Global MA (Art 6.1 Dir 2001/83).

**Issue with the interpretation of Art 7 and Art 8.3 (a) and (c) - market exclusivity**

There seems to be an issue with the interpretation of Art 8.1 (acceptance of another application for the same indication in respect of a similar medicinal product, only after expiry of 10 years market exclusivity) in conjunction with Art 8.3 (a) and (c) (derogations) in the context of the follow-on generic/biosimilar medicinal product after 10 years. Some examples from the practice illustrate strategies leading to a delay in access to generic/biosimilar versions of orphan medicinal products after expiry of the 10 year exclusivity period.

We understand the logic and sense of these provisions ("similarity" versus "safer, more effective and clinically superior") fitting the context for “new orphan medicines”, but these are counterproductive for the follow-on generic and biosimilar medicines.

From EGA’s perspective, it is most important to address the issue of market access to generic development of those designated orphan drug products, for which 10 years of market exclusivity have already expired, but for which a similar drug product was approved during the first exclusivity period, which then triggered a new exclusivity period, thereby blocking generic launches of the first product for an additional ten years (e.g. Imatinib versus Nilotinib case\(^2\)). Linking similarity to “mode of action” creates an evergreening strategy for blocking generic competition and patient access to a generic version of orphan medicines after expiry of the exclusivity period. This will block generic version of Imatinib for CML for the next years.

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\(^2\) Imatinib (Glivec, Novartis) is authorised for the treatment of chronic myeloid leukaemia (CML) in adults. The orphan designation CML for Imatinib has already expired. However, generic companies cannot apply for imatinib with CML as indication due to the fact that Nilotinib (Tasigna, Novartis) which has been authorised in the EU since 19 November 2007, has an orphan designation for CML (until 2017). Orphan designations for CML with respect to Nilotinib blocks the indication CML for the generic version of much older drug Glivec (Imatinib) for which the market exclusivity has expired. Linking similarity to “mode of action” (next new tyrosine kinase inhibitors for CML are already in the pipelines) creates an evergreening strategy for blocking generic competition and patient access to a generic version of orphan medicines after expiry of the exclusivity period. This will block generic version of Imatinib for CML for the next years. In practice, Imatinib is going to be protected by orphan exclusivity for 17 years, instead of 10 years. We trust that this was not the purpose of Regulation 141/2000.
blocking generic competition and patient access to a generic version of orphan medicines after expiry of exclusivity period.

An application for a “similar” medicinal product with “clinical superiority” by the same MAH or by giving his consent to another sponsor should not create a mechanism of blocking the follow-on generic/ biosimilar after expiry of the exclusivity for the “initial” orphan medicinal product’s designation.

Thus, we call the EC to extend the revision of the Commission Notice to the application of article 8.1. Some orphan drugs approvals have been granted on the basis of slight improvements of non-orphan medicinal products of the same MAH, which have been already marketed at the time of the approval of the orphan drug (having the same active substance and indication but representing some advantages such as better convenience for the patient, etc.) Those generic/ biosimilar applications referring to the existing non-orphan medicinal product should not be deemed as “similar” medicinal products and then be blocked by the market exclusivity of the orphan drug, especially in the case where the MAH of the orphan drug and the non-orphan reference product is the same or where both MAHs are belonging to the same company/ or are linked.

**Second subset of the designated orphan condition.**

Where the MA holder extends the use of his product to other therapeutic indications within the same designated orphan condition, the general condition of orphan designation (as defined in the Art 3) shall apply. An additional point is related to the way of re-calculating a prevalence in case of “slicing” the orphan condition into several subsets (determined by patient subpopulations, genetic subtypes/ profiles, receptor-response etc) as the prevalence of the disease in total. If the total prevalence exceeds the 5/10,000 limit, orphan status shall not be granted.

EGA also welcomes a clear interpretation (line 357-363) related to a second subset of the designated orphan condition. If the same sponsor subsequently varies the marketing authorisation to extend the use of its product for a second subset of the designated orphan condition, the product shall not benefit from any additional period of market exclusivity, for that second authorised indication, i.e. the second authorised indication will be covered by the market exclusivity granted with the initial authorisation. This is also fully in line with the concept of the Global MA (Art 6.1 Dir 2001/83).

**Reassessment of the orphan criteria for a new subset of conditions when a sponsor extends the use of its product after marketing authorisation**

A review of the reassessment of orphan criteria is foreseen (also in the purpose of the Art 8.2). The transparency of the decision making process and justification of the decision is of key importance. Possible intervention by a Third Party, other than a member state, is not clear. It would be welcome if a Third Party could submit its observation in advance of the reassessment by the authorities. ‘
In the context of reassessment of the criteria of Art 3.1 (a) lack of “sufficient return of investment”, it is clear that the assessment is based on all costs (past and future development costs) and expected revenues. However, it is not clear what is considered “sufficient return of investment”.

More clarity and transparency is needed on using this criterion in general.

7. Clarifications on processing the transfer of orphan designations between sponsors

The EGA fully agrees that the practices described in the consultation paper (e.g. some companies asking a third party to apply for the desired orphan designation, which is subsequently transferred to the original applicant) should not be allowed and shall be considered as an attempt to circumvent the legislation and as an intentional delay for placing on the market of generic/ biosimilar medicinal products. We support a proposal to put in place the control mechanisms for the transfer of orphan designations between companies in that respect.

Separate authorisations:

Clarification on the separate marketing authorisations (line 388-397) in case of orphan/ non-orphan indications is also very helpful for legal clarity and the execution of the benefits of market exclusivity due to the orphan status.