

Prescrire's response on public consultation on

Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to anotherⁱ

We would like to thank the European Commission for the opportunity to provide comments on the updated guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another.

General comments

Over the last years exorbitant prices of orphan drugs have made the headlines in the media and initiated heated debates over patients' access, affordability and sustainability of healthcare systems. Some voices came up to call for an end to the abuse of orphan drug approvals.

Since the adoption of the orphan drugs Regulation in 2000, pharmaceutical companies developing orphan drugs enjoy regulatory and financial benefits including an accelerated marketing authorisation process, 10 years market exclusivity, the possibility of conducting small and therefore generally less costly clinical trials as well as other advantagesⁱⁱ. The development of drugs with a favourable harm-benefit balance for patients with rare diseases and no other therapeutic options is clearly welcome. Over the years, the development of orphan drugs has become a very attractive business. In the past several years, orphan drugs accounted for a particularly high proportion of newly authorised drugs and indications, i.e. 22 out of 99 as assessed by *Prescrire* in 2018ⁱ. Among these 22 assessments, *Prescrire* rated 11 drugs or new indications as an advance, but in most cases only a minimal advance. One new orphan drug was considered more dangerous than useful and was added to *Prescrire's* list of drugs to avoid: *obeticholic acid* (Ocaliva^o) in primary biliary cholangitis. For 4 new orphan drugs, we obtained insufficient data to determine the harm-benefit balanceⁱ.

Some orphan drugs benefit from subsequent marketing authorisation in several indications. In 2018, *lenalidomide* (Revlimid^o) was authorised in a third indication as an orphan drug for patients with multiple myeloma, after being granted orphan drug status for certain types of myelodysplastic syndrome and lymphoma. In 2015, *lenalidomide* was the ninth highest selling drug in the world, with global sales of 5.8 billion US dollarsⁱ. As regards Orphacol^o (*cholic acid*), one year after its approval for two rare bile acid deficiencies, an EU marketing application was filed for Kolbam^o (*cholic acid*) in three other rare bile acid deficienciesⁱⁱⁱ. This raises the question whether the orphan drug status is granted too generously, which could lead to an "abuse" of the orphan drug incentives.

Due to their very high prices, orphan drugs raise the problem of affordability and ultimately of patient access. We consider that the European authorities have a duty to pay attention to the affordability of orphan drugs, which should be addressed in some sections outlined in this guideline. The sections on “*Medical plausibility*” and “*Other methods, for diagnosis, prevention or treatment of the condition*” deserve special consideration especially regarding the aspects linked to “orphanisation” and magistral formulations.

We invite the European Commission to pay particular attention to the following aspects when finalising the guideline:

- The number of patients concerned by the disease which can vary from very few to many patients. It is time to reconsider the notion of “rarity”.
- The phenomenon of “orphanisation” of common disorders and the endless research of subgroups where the product might be helpful.
- The profitability of orphan products, considering multiple orphan indications approved for a given product, and the related R&D costs, including support from public funding or experience with previous treatment use e.g. through off-label use or ‘magistral’/‘officinal’ formula.
- The expected benefits to the patients, including existing alternative treatment methods.

Specific comments

Timing of submissions

Sponsors are encouraged to request a pre-submission meeting with the EMA before completing the submission file (p. 3). Considering the high numbers of requests for orphan designation, the submission of written questions and if needed e-meetings might be more cost-effective.

Information to be supplied

It is stated that in the case of designation in more than one orphan condition for the same product, separate applications should be submitted for each orphan condition (p. 4). To have a comprehensive view on the company’s use of the orphan incentives, it would be useful to require that the sponsor mentions in its submission if, and which, other orphan designations have been sought for the same product.

Medical Plausibility

We suggest:

“In order to support the rationale for the development of the product in the proposed condition non-clinical **and/or** preliminary clinical data are generally required.”

“The aim, methodology, results of all relevant studies, etc. ~~should~~ **must** be submitted at the time of the application.”

We invite the European Commission to keep an eye on the phenomenon of “orphanisation” of common disorders and the chase after patient subgroups where the product is supposed to be effective. The Commission should not tolerate the creation of new ‘sub-categories of diseases’ and the ‘salami slicing’ ploy.

Other methods for diagnosis, prevention or treatment of the condition

As stated above, we call on the Commission to pay particular attention to “*Details of any existing diagnosis, prevention or treatment methods*” (p.9). This information is particularly important for Member states when they assess the affordability and added value of new orphan drugs compared to existing treatment options. To avoid any abuse of the incentives provided by the orphan drug Regulation, it is important to have the necessary information on existing options for the treatment, prevention or diagnosis of rare conditions, including ‘magistral’/‘officinal’ formula and/or off-label use.

We welcome the fact that the Commission invites sponsors to consider other existing ‘magistral’ or ‘officinal’ formula commonly used in the Union. Concerning rare diseases this practice may however vary to a great extent among Member states. According to the proposed text “*magistral or officinal formulations could be considered as satisfactory treatment if they are well known and safe and this is a general practice in the EU*”.

Nevertheless, we are afraid that the statement in the Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products^{iv} outlining that off-label use cannot be considered a satisfactory method might lead to an abuse of the orphan drug incentives:

*“Any reference to an authorised medicinal product must be limited to the terms of the marketing authorisation. Therefore, a product that is administered or applied outside the approved summary of product characteristics (**‘off-label’ use**) **cannot be considered a satisfactory method** for the purposes of Article 3(1)(b).*

*...In certain cases, medicinal products prepared for an individual patient in a pharmacy according to a medical prescription, as referred to in Article 3(1) of Directive 2001/83/EC (commonly known as the ‘magistral formula’), or according to the prescriptions of a pharmacopoeia and intended to be supplied directly to patients served by the pharmacy, as referred to in Article 3(2) of that Directive (commonly known as the ‘**officinal formula**’), **may be considered as satisfactory treatment if they are well known and safe and this is a general practice in the EU**. If the product proposed for designation is not authorised to be placed on the market, patients in the EU may still be treated with it if it is prepared in a pharmacy. On the other hand, a product prepared in a hospital under a hospital exemption scheme (see Article 3(7) of Directive 2001/83/EC) should not be considered a satisfactory method of diagnosis, prevention or treatment of a condition.”*

Experience shows that non-expensive established treatment methods become unaffordable once an orphan drug is authorised^v. We strongly invite the Commission to consider “other treatment” options in a broader context, and to consider if off-label treatments and/or

officinal/magistral formulations are “satisfactory methods” according to a case-by-case analysis. In many cases, off-label use is based on healthcare professionals’ clinical observations which should not be set aside on the sole basis of its “off-label” use. On the contrary it deserves a thorough analysis. France has a system for the prescription of medicines outside regular marketing authorisations called “Temporary Recommendation for Use (RTUs)”. This practice is allowed in cases of unmet therapeutic needs and for products with harm-benefit balances assumed to be favourable.^{vi}

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EU Transparency Register: 982539711698-79

ⁱ https://ec.europa.eu/health/human-use/consultations/2019_guideline_appdes_fr

ⁱⁱ Prescrire Editorial Staff “Drugs in 2018: a brief review” *Prescrire Int* 2019; **28** (203): 105-107.

ⁱⁱⁱ Prescrire Editorial Staff “Orphan drug status: abuse of incentives” *Prescrire Int* 2016; **25** (171): 138.

^{iv} Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03), 11 November 2016, C 424/3 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

^v Medicines Law & Policy blog <https://medicineslawandpolicy.org/2019/01/time-to-put-a-stop-to-the-abuse-of-orphan-drug-regulation-the-latest-scandal/>

^{vi} ANSM information on RTUs [https://www.ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Les-Recommandations-Temporaires-d-Utilisation-Principes-generaux/\(offset\)/0](https://www.ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Les-Recommandations-Temporaires-d-Utilisation-Principes-generaux/(offset)/0)