EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

Pharm 791

PHARMACEUTICAL COMMITTEE
12 March 2020

Subject: **Evaluation of the Orphan and Paediatric Regulations**[1]

Agenda item 3

1. BACKGROUND

The Commission is currently finalising its evaluation on the Orphan and Paediatric Regulations under the Commission's Better Regulation principles.[2] We expect to publish the Staff Working Document in spring 2020.

An discussion has already taken place during the Pharmaceutical Committee of 17 December 2019. The outcome of such discussion is presented in the Annex to this document.

In the forthcoming meeting of the Pharmaceutical Committee on 12 March 2020, we would like to provide you with some preliminary outcomes of the ongoing evaluation and brainstorm with you on the results achieved by the current legislations.

2. DISCUSSION

Since the application of the Orphan regulation till 2017, 1956 designations have been granted and 142 orphan medicines have been authorised. However, it has been estimated that the number of new orphan medicines which may be attributed to the EU Orphan Regulation, equates to 18 to 24. While these products would not have been available without the Regulation, the others, instead, would have been introduced anyway, also thanks to their development in other regions, like the US.

The 142 products authorised covers only a limited number of therapeutic areas. Furthermore, it can be observed that over the time the Regulation seem to have become less effective in directing research to areas where there are no treatments: only 28% of the 142 authorised orphan medicines targeted diseases for which there were no alternative treatment option (95% of rare diseases remain still without a treatment). At the same time, especially in the area of oncology, the number of treatment options is expanding and the market is starting to look more and more similar to non-orphans areas.

[1] This document has not been adopted by the European Commission and, therefore, it does not reflect an official position of the European Commission. It is only meant to be a tool for discussion and the views expressed therein do not necessarily reflect those of the Commission and its services.
[2] https://ec.europa.eu/info/law/law-making-process/planning-and-proposing-law/better-regulation-why-and-how_en

This despite more than € 1 billion from EU research programs has been committed to research on rare diseases over the last 10 years. We have observed that it is impossible to establish a direct link between public research funding (both at EU and at national level) and the development of specific new orphan medicinal products.

The same problem is also true for paediatric medicinal products, where, in areas of major therapeutic needs of children, little development is seen. The paediatric pipeline is still strongly dependent from the adult pipeline and the SPC incentive provided by the legislation does not seem to be an efficient tool to direct research in areas of paediatric unmet need.

Coming to the incentives provided by the Orphan Regulation, we have seen that the market exclusivity in most cases allowed companies to recuperate investments made in therapeutic areas, which were not considered as profitable. In fact, we can see that for 50% of the orphan medicines with an annual turnover below €50 million per year in the EEA the market exclusivity reward has helped to increase profitability, without giving the sponsor an unbalanced or unfair compensation. Due to lack of transparency on research & development costs, the evaluation made an assumption of an average cost of development of an orphan medicine of €600 million, based on literature data. However, we have also observed that 14% of orphan medicines had sales turnover well above €100 million per year in the EEA and may have been overcompensated. Only one orphan medicine was authorised based on the "insufficient return upon investment" criterion, but it was withdrawn by the applicant.

The risk of overcompensation exists in particular for orphan medicines authorised for multiple indications, on the basis of well-established use products or known active substances, where the investment was little in relation to the revenues obtained.

Taking into account the observations above, we would appreciate to have your views on the following points:

- *During the discussion at the last Pharmaceutical Committee, one of the ways proposed to better redirect investment in areas of unmet need was to create a list of priorities in therapeutic areas. What would be your solution to develop and agree on such a list taking into account views of different decision makers?*

- *How to increase transparency on research and development costs in order to provide adequate incentives to investments made? How could this help to better analyse return on investment in view of a possible reduction of the market exclusivity period (Article 8.2 of the Orphan Regulation)?*

Annex

Results of the discussion held at the Pharmaceutical Committee on 17 December 2019:

Ideas from Member States
1) We would like the Committee to reflect whether there are ways to improve the use of incentives to redirect investments in areas of unmet need compared to areas where the market offers opportunities for return on investment
Definition of unmet need • List of priorities in therapeutic areas (dynamic) • Change of definition of orphan diseases (unmet need), and patient population <u>Improve use of existing incentives</u> • Stratification (layers) of incentives (unmet medical need, new treatment, related to availability, follow up of obligations) • Link incentives to company's obligation (profitability): shortening rewards once the product is sufficiently profitable • Encourage laboratories to enter certain therapeutic areas with little or no investment: reinforce scientific advice by EMA • Specific incentives for hospitals to encourage the development of ATMPs • SPC extension depends on the number of patients (paediatrics) • Increase market exclusivity • Strengthen/increase the financial penalties provided for in Article 49(1) (national marketing authorisations) and (3) (centralised marketing authorisations) of the Regulation for laboratories which fail to comply with the obligations • Limit the deferrals granted by the European Medicines Agency in the conduct of PIPs • Obligations to report on development costs/on marketing <u>New incentives/mechanisms</u> • Push and pull incentives, life-cycle of product • National/EU level incentives (guarantee revenues) • Incentives for repurposing • Pipeline incentives : connect with milestones • Transferable incentives to other products in the portfolio & link to placing on the market in all MS of the orphan & paediatric medicine • "Staying on the market" incentive • Specific/different solutions for paediatrics & orphans • Special support programmes for academia and research institutions for areas with less commercial interest • Funding –supported research (paediatric rare diseases funding mechanism is an incentive but also scientific advice) • Encourage development in specific indications for children, based on the American Creating Hope Act (particularly in oncology) Improve regulatory processes • Involvement of patients, health care professionals & all stakeholders (research, academia) • Early contacts with HTAs • Worldwide synchronisation of filing of applications

- Decrease of regulatory burden (ePI)

2) We would like the Committee to reflect on the limitations of the legal criteria used in the two regulations to identify products that may receive orphan designations or are subject to the obligations to perform paediatric studies and whether there are ways to improve those criteria.

Limitations

Orphans

- If orphans are linked to biomarkers, we risk to have more neglected areas:
  - innovation, not disease, but technology driven
  - clustering of development around targets and technology
  - other than prevalence, consider technological criteria
- Assumptions of linking prevalence to market failure does not always hold
- Significant benefit may differ within MS-should this be considered for the incentives
- Profitability of companies is a black box (difficult to adapt incentives)

Paediatrics

- Paediatric paradox: paediatric only products not sufficiently supported by Paediatric Regulation
- PIP/waivers: too early in the process
- Innovation, not disease, but technology driven

Ways to improve criteria

Orphans

- Exclude magistral formulas
- Adaptive system with a look in the future: revert the orphan designation, with time, on the basis of specific criteria
- Definition adapted, not to distort generic competition
- Incentives for turning off label and magistral use into marketing authorization
- Definition: consider relevance of diseases, alternatives (case-by-case analysis)
- Criteria: magnitude of benefit
- True orphans VS orphans that just fulfil the definition (for the later prevalence criteria to be combined with added benefit)
- Tax reduction as incentive
- Prevalence & UMN to be combined to show true value for society
- No ever-greening for same condition (once over certain threshold of prevalence, incentives to be adapted)
- Multiple orphan indication-cumulative prevalence (or no indication slicing)
- Full transparency on development costs
- Financial incentives should be adapted to better target ultra-rare diseases.

Paediatrics

- Paediatric only products not sufficiently supported by paediatric regulation: mechanism of action→ obligation for companies to go further?
- Products developed for children outside the scope of the regulation
- Specific incentives for paediatrics to ensure early full development
- Specific incentives/focus for paediatric diseases

- Paediatric research and incentives on pathologies in children only
- Take account of clinical practice and advocacy groups: have specific ways to harvest their inputs (re-purposing)
- Consider better recognition of unmet need
- More dynamic PIP later in the development process like in the US
- Obligation to do further research
- Whenever a medicinal product proposes a new mechanism of action, PIPs should be systematically required from the laboratory to explore the benefit of this mechanism in children

3) We would like the Committee to reflect on **mechanisms** within the scope of the two Regulations that may contribute **to improving access.** This may include measures linked to the supply of those medicines or linked to the incentives/rewards provided?

<u>Orphans</u>

- Link incentive to obligation to put on the market (however, reimbursement is needed)
- Gaming of system (not all MS use reference pricing)
- Parallel distribution (few patients in countries); parallel import (procedure to make it easier)
- Electronic and multilingual PI
- Sunset clause (obligation to place on market in all MS): but what is the effect?
- Early scientific advice (early dialogues with HTA bodies)
- Incentives or obligations to bring to the market
- Regional cooperation (public procurement). Pricing relate to GDP
- Product information (on packages). Link to incentives with supply to cover and keep product on the market
- Access linked to national situation in each MS. Reimbursement decisions at national level have consequence for access
- More flexibility to labelling issues. MS could make national decisions on language
- Local repackaging, national languages. More actors in this field.
- Risk minimisation measures: decisions by e.g. PRAC. They can be an obstacle for the marketing
- Definition of access in relation to availability. Role of O / P Regulations and the premium for these products. Delinking that label and value
- Review of the 10-year period of exclusivity if it appears that, in at least one Member State, the population treated with the medicinal product, at the end of 5 years, does not cover at least 50% of the target population

<u>Paediatrics</u>

- Paediatrics magistral formulations: related to pricing and withdrawals by companies
- Granting of the SPC reward to be made conditional on the marketing of the speciality in all Member States