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Client Alert

FDA and Life Sciences

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EUROPE – REVISION OF EU GENERAL PHARMACEUTICAL LEGISLATION: Legal Regime for Orphan Medicinal Products

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Currently, orphan medicinal products are primarily governed by Regulation 140/2000 on Orphan Medicinal Products ("Orphan Regulation").

On April 26, 2023, the European Commission ("EU Commission") published legislative proposals for an updated: (i) Directive on the Union code relating to medicinal products for human use ("Future Directive"); and (ii) Regulation setting out the centralized procedure and establishing the EMA ("Future Regulation"), which will replace the current Directive and Regulation, respectively.

This note focuses on the main changes that the EU Commission proposes bringing to the current orphan legal regime. Besides the changes which codify the EMA's current guidelines and practices and the European Court of Justice's rulings, most of the key changes concern the orphan designation and orphan exclusivity. Overall, the regime becomes stricter on companies and orphan exclusivity because: (i) orphan exclusivity is reduced by one year unless the orphan product addresses a high unmet medical need or is launched in all national markets within 2 or 3 years of approval; and (ii) the pediatric exclusivity (2 additional years of orphan exclusivity) is abolished. Moreover, entry of generics and biosimilars is accelerated.

The legislative process, which will likely be completed in 2025 at the earliest (as new European elections will take place in 2024), will provide stakeholders with opportunities to impact the proposed changes.

General Comments

- The Orphan Regulation is repealed and the rules on orphan medicinal products are moved to the Future Regulation (Ch. VI, Art. 63 to 73) for simplification and increased coherence of all measures applicable to orphan medicinal products. Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product is not repealed.
- The Future Regulation becomes applicable 18 months after its entry into force (Date of Application).
- Transitional provisions:
  - Orphan designations ("OD") entered into the Community Register of Orphan Medicinal Products and not granted a marketing authorization ("MA") before the Date of Application are considered to comply with the Future Regulation.
  - As such, they will be entered into the new Register of Designated Orphan Medicinal Products. All other OD will not and thus will be "lost" for their holders.
  - For those OD which are maintained under the Future Regulation, the 7-year period of validity starts from the Date of Application.
  - Orphan designation procedures initiated and still pending before the Date of Application remain subject to the Orphan Regulation.

Orphan Designation

Designation Criteria

- The prevalence criterion is maintained, but the financial criterion (i.e., no sufficient return on investment) is abolished.
- Prevalence is still 5 in 10,000 in the European Economic Area (i.e., EU, Iceland, Liechtenstein, and Norway). However, if this requirement is not appropriate due to the specific characteristics of certain conditions (e.g., short duration or high mortality) or any other scientific reasons, the EU Commission may set specific criteria for certain conditions on the EMA's recommendation.
- The concept of significant benefit is maintained, but the term "significant" is specified by reference to "a substantial part of the target population."
- Recital 93 of the Future Regulation indicates that preparations may be considered as satisfactory treatments if they are well known and safe and this is a general practice for the relevant population in the EEA.

Procedure of Orphan Designation

- Decisions on OD are now taken by the EMA instead of the EU Commission. This key change seeks to facilitate and accelerate the OD procedure.
- The Committee for Orphan Medicinal Products ("COMP") is replaced by a scientific working party to be established by the CHMP (EMA's main scientific committee).
- The EMA may consult the CHMP or one of its working parties on the fulfilment of the OD criteria.
- More details are provided on protocol assistance and research support.

Orphan Designation

- The OD is valid for 7 years. This period may be extended by the EMA if the sponsor proves that promising studies are ongoing. This key change seeks to push companies to accelerate their drug development, but it could also negatively impact the funding of innovative SMEs.
- The OD becomes invalid when an MA corresponding to the OD is granted. Thus, an active substance may be granted several OD, but each OD may only lead to one orphan MA.

- A new Register of Designated Orphan Medicinal Products will be set up and replace the current Community Register of Orphan Medicinal Products.
- OD may be transferred with the EMA's prior approval. However, the Future Regulation does not set out grounds for refusal or approval.

Orphan Marketing Authorization

- The current practice to review the fulfilment of OD criteria once again at the time of marketing authorization is codified. This assessment is made the CHMP and now included in the European Assessment Report ("EPAR").
- New concept of "high unmet medical need" ("HUMN")
  - Criteria: There is no existing treatment or the product presents an exceptional therapeutic advancement and a meaningful reduction in disease morbidity or mortality. This last criterion is meant to ensure that only the most effective medicinal products are covered.
  - Relevant evidence to be included in the marketing authorization application ("MAA").
  - Does not apply in cases of bibliographic MAA.
  - Assessment by the CHMP.
  - May benefit from PRIME, which the Future Regulation codifies (Art. 60).

Orphan Exclusivity

- **Duration of Orphan Exclusivity**
  - 10 years in case of a medicinal product addressing an HUMN.
  - 5 years in case of a medicinal product approved on the basis of a bibliographic MA.
  - 9 years for all other medicinal products.
  - +1 year if the medicinal product is launched (i.e., is released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients) within 2 years of the MA, in the Member States where the MA is valid (i.e., in all Member States given that designated orphan medicinal products are authorized through the centralized procedure).
    The launch period is 3 years for SMEs, not-for-profit entities, and companies/groups of companies that do not hold more than 5 centralized MA.
    The prolongation does not apply to orphan medicinal products authorized on the basis of a bibliographic MA.
  - +1 year if a new orphan MA is granted at least 2 years before the expiration of the orphan exclusivity period. This incentive is available twice but may not accumulate with the +1 year data exclusivity arising from the approval of a new indication which brings a significant clinical benefit in comparison to existing therapies.
  - No more 2 additional years of orphan exclusivity in case of completion of a pediatric investigation plan (PIP).
- Application of the concept of "global" orphan MA: No new orphan exclusivity for a new orphan MA granted for the same active substance. The orphan exclusivity of all orphan MA starts from the date of the first orphan MA.

- The legal definition of "clinically superior," which is one of the conditions for breaking orphan exclusivity, is now defined by reference to a substantial part of the target population.

Access to Market – Similar, Generic/Biosimilar

- Submission of an MAA or granting of MA for a generic or biosimilar of an expired orphan medicinal product may not be prevented by the orphan exclusivity of a similar medicinal product.
- The MAA for a similar medicinal product (innovative or generic/biosimilar) may be submitted 2 years before expiration of orphan exclusivity.

Data Exclusivity

- Orphan medicinal products also benefit from regulatory data protection ("data exclusivity"), which applies in parallel to orphan exclusivity.
- For data exclusivity purposes, designated orphan medicinal products are legally considered as addressing an unmet medical need, which entitles them to an additional 6-month data exclusivity period.

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King & Spalding's regulatory Life Sciences lawyers can help you better understand the changes that may result from the Revision, and anticipate their impact on the development and, in the future, marketing of products in Europe.

Companies involved in the development of orphan and pediatric medicinal products, as well as antibiotics, should closely follow future discussions around revision of the legislative framework and, whenever needed, be involved in those discussions.

Companies also should anticipate evolution of the EU legal framework and its impacts on current development and investment.