MAY 3, 2023

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

For more information, contact:

Geneviève Michaux
+32 2 898 0202
gmichaux@kslaw.com

Chris Markus
+1 202 626 2926
cmarkus@kslaw.com

Georgios Symeonidis
+ 32 2 898 0215
gsymeonidis@kslaw.com

King & Spalding

Brussels
Bastion Tower
5 Place du Champ de Mars
1050 Brussels, Belgium
Tel: +32 2 898 0200

Washington, D.C.
1700 Pennsylvania Ave., NW
Suite 200
Washington, D.C. 20006
Tel: +1 202 737 0500

Currently, the legal regime for pediatric medicinal products is primarily contained in Regulation 1901/2006 on Medicinal Products for Paediatric Use ("Paediatric Regulation").

On April 26, 2023, the European Commission published lengthy legislative proposals for an updated: (i) Directive on the Union code relating to medicinal products for human use; and (ii) Regulation setting out the centralized procedure and establishing the EMA. If finalized, these proposals will replace the current Directive 2001/83 and Regulation 726/2004, respectively.

This note focuses on the main changes that the EU Commission proposes bringing to the current pediatric legal regime. Overall, as it was to be expected, the changes do not improve the situation of the pharmaceutical industry. The most favorable change for the industry is the concept of the adapted or evolutionary pediatric investigation plan ("PIP"), which however has a limited scope. The most detrimental changes are harder to pick. They probably are, from a practice perspective, the EMA's right to modify a PIP on its own initiative and, from a theory perspective, the EU Commission's right to impose financial penalties for the non-submission of a PIP proposal after completion of PK studies in adults.

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- The existing Paediatric Regulation is repealed, and the rules on pediatric medicinal products are divided between the Future Regulation (Ch. VII, Art. 74 to 98) and the Future Directive, which makes it more difficult to have a comprehensive view of that specific legal regime.

- The Future Regulation becomes applicable, and the Future Directive must be transposed into national law 18 months after their entry into force.
- Transitional provisions specific to pediatrics:
  - PIP, waivers, and deferrals granted under the Paediatric Regulation are considered to comply with the Future Regulation and Future Directive.
  - PIP procedures initiated before the date of application of the Future Regulation remain subject to the Paediatric Regulation.

Scope of Application and Derogations

- The scope of the pediatric requirement (i.e., to develop and implement a PIP) is broadened to include new strengths of authorized medicinal products which are still protected by a supplementary protection certificate ("SPC") or a patent that qualifies for an SPC.
- The categories of medicinal products which are exempted from the pediatric requirement remain the same, but the exemption now only applies to hybrids (similar to 505(b)(2) products in the U.S.) and bio-hybrids if the product is not/no longer covered by an SPC or a patent that qualifies for an SPC.
- The EMA may grant a temporary exemption from the pediatric requirement in case of a health emergency, provided that the medicinal product concerns a serious or life-threatening disease and directly relates to the public health emergency. Upon expiration of the derogation, a company must submit an application for a PIP or a full waiver.

Pediatric Investigation Plans (PIP), Waivers, and Deferrals

PIP

- The concept of "evolutionary" or "adapted" PIP is introduced, which permits a PIP to be built progressively:
  - The initial PIP only contains the details and timing of the measures that are known at the time of submission, as well as the timing for regular updates of the PIP and, ultimately, a final PIP.
  - However, the scope of this new type of PIP is limited to two cases: (i) the active substance is new and intended to treat a novel pediatric condition; and (ii) an EMA's authorization. The EMA may give such authorization where it is not possible, based on scientific reasons, to have a complete PIP proposal by the time of its mandatory submission (i.e., completion of PK studies in adults).

  This concept should reduce the number of PIP modification procedures.
- Clarification that the PIP must also include measures to adapt the form, strength, route of administration, and administering device to the pediatric population.
- The EU Commission's guideline on the format and content of the PIP will have to take the specificities of evolutionary PIP, pediatric-only medicinal products, and pediatric use MA ("PUMA") into account.

Waivers

- No new ground for waiver has been added. Hence, there still is no official ground for waiver for cases where conducting pediatric trials are not feasible, for whatever reason.
- An express reference to the mechanism of action of the active substance is added to the ground for waiver relating to the adult disease/condition. This ground for waiver does not apply when the product is directed at a molecular target which, based on existing scientific data, is responsible for a pediatric disease/condition that is different from the adult disease/condition in the same therapeutic area. This codifies the current practice for oncology and neurodegenerative diseases.

Deferrals

- Deferrals may be granted for a maximum of 5 years. A prolongation of the maximum 5 years may be requested at least 6 months before expiration of the time period (60-day procedure).
- Clarification that deferrals concern initiation as well as completion of measures.

Modification of a PIP

- The EMA has the right to request modifications of the PIP if, based on new scientific information, it considers the PIP (or any of its elements) is no longer appropriate. In such a case, a company must propose changes to the PIP within 60 days, and the EMA has 30 days to accept/refuse the proposed changes. This is a key change to the current system that will empower the EMA even more regarding the development of pediatric medicinal products.

Procedures

- All pediatric procedures remain free of fees (except for the application for a PUMA).
- Mandatory submission of the PIP or full waiver proposal
  - The deadline remains the same: before the initiation of the safety and efficacy clinical studies (i.e. completion of PK studies in adults (except in duly justified cases)).
  - Non-compliance with this obligation is now subject to financial penalties. This is also a key change to the current regime, especially because many companies file their PIP proposal after proof-of-concept. While the authorities did not impose financial penalties for 15 years, this could change in the future.
- The Paediatric Committee ("PDCO") is replaced by a scientific working party to be established by the CHMP (the EMA's main scientific committee).
- The EMA may consult the CHMP or one of its working parties before adopting its decisions.
- Clarification that pediatric scientific advice may be requested before submission of a PIP.
- The duration of the procedure has been extended:
  - PIP/Waiver: 90-day procedure.
  - Adapted PIP: 70-day procedure.
  - Update of adapted PIP: 30-day procedure (implicit agreement if the EMA does not request modifying the new elements).
  - Final PIP: 60-day procedure.
  - Modification of the PIP: 90-day procedure.
  - All time limits are doubled when the EMA proposes modifications to the PIP or asks for additional information.
- Re-examination: 20 days for a company to submit a request for re-examination and 20 days for the EMA to decide on the request.

Pediatric Rewards

- 6-month SPC extension.
- No more specific reward for orphan medicinal products (+2 years orphan exclusivity).
- Data exclusivity and marketing protection for PUMA.

Marketing Authorization (MA)

- Clarification that the compliance statement must be included in the MA.
- Regulators may vary the MA and update the SmPC based on pediatric clinical studies received under Article 45(1) of the Paediatric Regulation, but only for 5 years from the date of application of the Future Regulation.

Other Obligations

- *Mandatory marketing*: The scope of the obligation is clarified. A medicinal product authorized for a new pediatric indication following completion of a PIP must be marketed within 2 years of approval of the pediatric indication in all the national markets where the medicinal product is already on the market.
- This is a very burdensome requirement in cases where the pediatric formulation is different from the adult formulation.
- Codification of the concept of "*discontinuation of the PIP*": Companies wanting to discontinue a PIP must inform the EMA (including the reasons for discontinuation) at least 6 months beforehand. This concept already exists *de facto*, but companies have neither been obligated to inform the EMA nor to comply with a specific time limit.
- *Publication of clinical trial results*: Summaries of results of pediatric clinical trials must be submitted to the EU Database of clinical trials within 6 months of the end of the trial.
  - This requirement also applies to pediatric clinical trials conducted in third countries which are part of a PIP. For those trials, the Future Regulation also requires providing specific information, which it enumerates, before staring the trial.
  - Submission may be done after 12 months (vs 6 months) for justified scientific reasons. It however is unclear whether this applies to all pediatric trials or to pediatric trials conducted in third countries.
  - The EMA and the national competent authorities may vary the MA and update the SmPC/patient leaflet based on the results of pediatric studies.
- *Setting-up of a European Network* (patient representatives, academies, medicine developers, investigators, research centers in the EEA) to discuss priority in pediatric development.

***

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.