EUCOPE

European Confederation of Pharmaceutical Entrepreneurs AISBL

EUCOPE POSITION ON EUROPEAN UNION (EU) PEDIATRIC REGULATION

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1. The EU Paediatric Regulation[1] has had a positive effect on the development of paediatric medicines, based on a set of obligations and rewards

- Since the implementation of the Regulation in 2007, over 230 new medicines for use by children have been authorised[2] (new marketing authorisations and new indications)
- Paediatric development has become an integral part of companies' product development process
- Biopharmaceutical companies have hired paediatric clinicians in order to develop specific Paediatric Investigation Plans (PIPs), generating the best scientific evidence possible to progress innovations in this field
- Substantial knowledge is being built with regard to children's physiology and new methodologies (modelling & simulation, and extrapolation), which helps tremendously to further facilitate paediatric drug development
- The Regulation is an example of how the EU has taken action in a field where incentives are needed to foster innovation
- Paediatric Research & Development (R&D) remains challenging due to the complexity of paediatric indications in terms of ethics and clinical study feasibility, which can lead to longer development times and is impacting the availability of therapies for children.

2. However, the implementation of certain aspects of the Regulation has resulted in unnecessary complexities which are contrary to the intent of this legislation

- The tight and strict early timeframe for the initial PIP submissions is challenging because :
  - Many unknowns existing at the time of PIP agreement making it necessary for companies to frequently request plan modifications due to emerging research data impacting the development
  - Large and early investment of technical expertise and resources is needed from industry before any 'Proof of Concept' data for the adult development is obtained for a product, resulting in uncertainty about the future use of the product at that time
  - A coordination of the EMA and the FDA submission to enable a joint discussion of a global paediatric development program is challenging

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF

[2] European Medicines Agency, "10-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation", 27 October 2016: http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

- The huge administrative and operational regulatory burden is hampering the efficient execution of new paediatric medicine development plans, for example; there are unclear responsibilities and overlaps in the assessments made by different expert committees and working parties within the European Medicines Agency (EMA), duplication of the number of trials due to differing EMA and Food and Drug Administration (FDA) requirements, and need to complete all studies and develop all pharmaceutical forms requested by PDCO in time to be eligible for a reward
- Many paediatric clinical trials required by the Paediatric Committee (PDCO) can be either unnecessary or unfeasible to conduct and/or complete due to the lack of children participating in the studies (especially in rare diseases)
- There is a need to clarify the system for granting PIP waivers and deferrals:
  - ***Waivers:*** they are important to ensure that there are no unjustified or unethical clinical trials in children. They are only granted after thorough review by the PDCO. There is always a possibility to submit a voluntary PIP for a waived condition for PDCO review.However, there are currently no clear guidelines that help applicants to determine which documentation is required to support a waiver application. This creates uncertainties for both sides
  - ***Deferrals:*** they are necessary to protect children from unnecessary or unsafe clinical trials. Although there generally is a positive dialogue between the PDCO and companies to clarify the reasons for requesting a deferral, there is still a lack of predictability that arguments provided by a company will be listened to.
- Rewards for successfully completing agreed PIPs by companies are often not granted or even achievable due to lengthy timelines for paediatric research, complex development programmes requested by PDCO and long recruitment challenges (especially in rare diseases). This has resulted in:
  - Less than half of all completed PIPs leading to any type of reward
  - Less than 40% receiving a 6-month Supplementary Protection (SPC) extension
  - Only 4 being granted a 2-year orphan market exclusivity extension
- Furthermore, these rewards, in particular, SPC extensions do not cover the investment costs needed to complete an average PIP[3].

3. EUCOPE believes that non-legislative guidance will improve the implementation of the Regulation, to enable more development of paediatric medicines in oncology, rare diseases and other areas of high unmet medical need

- There should be a multistakeholder discussion to agree on the inventories of unmet medical needs that will better guide paediatric developers development plans
- Industry would welcome systematic early interactions with the PDCO and other committees at the EMA, as well as stakeholders, such as patients and parents, to have meaningful discussions on the scope of PIPs

[3] estimated costs by European Commission is approximately €20million – up from €4million originally anticipated in 2007

- Clear established criteria should be developed with all stakeholders to document the feasibility of clinical trial conduct in children
- The level of detail within PIPs should match the development phase. The earlier the PIP is submitted, the less data will be available. Hence, less level of detail for initial PIPs is needed to avoid multiple modification procedures, risking unnecessary delay of marketing authorisation applications and patient access to important life-saving therapies. The use of a 'lean PIP' that lists basic studies and essential measures, which would be updated only once with accumulated data nearer to the time of the execution of the clinical trials , could mitigate these challenges
- The assessment of PIPs and modifications should include more experts, such as epidemiologists, key clinical opinion leaders (KOLs), Patient Advocacy Groups (PAGs) and paediatric networks
- European regulators should thoroughly investigate the reasons for waiver requests with multi-stakeholder involvement. A more standardized approach towards the granting of deferrals would reduce the uncertainty for companies and simplify the process
- Alignement of requirements and processes between regulatory agencies - e.g. EMA and FDA - would ease global paediatric medicines development and streamline scarce resources.

4. Therefore, EUCOPE believes that a reopening of the Paediatric Regulation at this stage is premature due to the following reasons:

- The framework set up by the Regulation has stimulated a lot of paediatric medicine development and is appropriately balanced
- Key measures to even improve the current situation can immediately be introduced via soft law
- A reopening would create legal uncertainty for a prolonged period of time and dealy improvements for children.

About EUCOPE

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) is Europe's principal trade body for small-to-medium sized innovative companies working in the field of pharmaceuticals and medical devices. EUCOPE represents 900+ mid-sized innovative pharma and biotech companies, directly and national trade associations. It provides a platform for owners and CEOs of pharmaceutical companies to discuss solutions to improve the quality of life for patients and to strengthen the competitiveness of the European pharmaceutical industry.

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