

**To: European Commission**21st July 2023**COMMENT ON THE “Revision of the EU general pharmaceuticals legislation”**

ESPGHAN welcomes the opportunity to comment on the Proposal for revising the EU pharmaceutical legislation. As stated in the accompanying EU documents, this reform should be considered a significant step forward aiming “*to make medicines more available, accessible and affordable. It will support innovation and boost the competitiveness and attractiveness of the EU pharmaceutical industry while promoting higher environmental standards*”.

With that respect, the Children’s Medicine Regulation (EC) No 1901/2006 was already a significant step forward, resulting in more research on high-quality medicines for children and more authorisations of age-appropriate formulations. Companies were obliged to screen their products for their potential use in children, progressively increasing the number of medicines with paediatric indications. However, significant problems still exist, hampering the development of paediatric medicine and causing a shortage of products for children. Therefore, ESPGHAN, broadly supports the proposed revision. **ESPGHAN exists to protect and promote the gastrointestinal health and nutrition of children, so we are providing comments and suggested revisions relating to children/paediatric patients with diseases of the digestive organs.**

1. Status of Paediatric Medicine and the role of PDCO in the Proposal

1.1 In general, ESPGHAN **positively views and supports that medicinal products for children and for rare diseases are integrated into the “new” regulation**, eliminating the need for separate laws, as this grants unified levels of quality and safety, but also embraces the specific requirements of children, as laid down in Articles 107-120.

1.2 The Paediatric Committee (PDCO) within the European Medicine Agency (EMA), in ESPGHAN’s view, was an important developmental step introduced by the “old” legislation, at least in part responsible for an increasing number of paediatric medicines being registered and obtaining the market authorisation. **Therefore, we do not support the dissolution of PDCO in the new legislation.** The dissolution of PDCO within EMA, justified by streamlining and decreasing the administrative burden, in our opinion, cannot be substituted by the introduction of working groups, working parties, and a pool of experts organised on different domains. Replacing a paediatric scientific committee which is fully engaged in the development of paediatric drugs and comments on issues proactively, with a working group which only provides advice/expertise when asked for, is a step backward, and therefore, ESPGHAN calls against this act.

2. Reasons why the Proposal should address the lack of timely completion of clinical studies in children

One of the major problems responsible for the lack of timely approved paediatric drugs in the EU, which was not alleviated with the “old” paediatric legislation, was the failure to achieve timely completion of clinical studies in children. In those cases, the company could be granted a deferral or a waiver – which is also proposed in this new regulation (Article 81). There are various reasons for Paediatric Investigation Plan (PIP) completion failure, which are addressed in different documents, but we draw attention to – the rarity of the disease in the paediatric population, the requirement for washout periods of other medications, burden on trial participants, accessibility of drugs off-label years before initiation of a PIP resulting in no added value to trial participation, large number of study sites with insufficient workforce and small numbers of patients (as described in ref. 1,2).

All of this is applicable to paediatric medicine in general and inherent to most of the paediatric subspecialties, but to illustrate this further, we provide an example of the problem. At the time of the paediatric inflammatory bowel diseases (IBD) multistakeholder meeting (April 14-15 2021) described in ref. 1, there were 15 PIP’s approved by the EMA in place for multiple classes of drugs, all targeting ulcerative colitis (UC) in children, and all being investigated for adult UC. Only two of these drugs were expected to have completed their paediatric trials in the next 3 years and 10 do not yet have paediatric trials underway (1). Calculation of the number of eligible paediatric patients with active UC in relation to the number of PIP’s and their participant requirements demonstrates this is impossible. This results in an average delay of 7.5 years to 7.7 years from adult to paediatric approval of biologics for UC and Crohn’s disease (CD) respectively, and the situation since this publication is getting worse (1, 2). Pharmaceutical industries are competing with each other to perform ‘their’ PIP and, as a result, most do not manage to enrol the required number of paediatric patients, even after significant study extension.

In summary, the most important consequence of the above-described situation is that the health care of children with chronic disabling diseases is significantly lagging behind care for adults. This is unacceptable anywhere, but particularly in the regulated and well-developed market of the EU countries.

3. Measures suggested to streamline paediatric clinical studies, and to provide regulatory frame for paediatric extrapolation of adult data

3.1 **ESPGHAN welcomes the introduction of the “developmental” PIP in the Proposal.** In the previous legislation, an obstacle leading to the non-completion of the PIPs was the requirement to submit a full clinical development plan already at the initial stage. This was problematic, particularly for molecules that have never been used before. In the “new” legislation, the introduction of developmental, initially simplified PIPs (covered in Article 74), which can be completed when new information is obtained, will reduce administrative effort and costs and facilitate the whole procedure.



3.2 **ESPGHAN strongly supports the novel regulatory concept created in this Proposal for a “not-for-profit” entity**, to be able to submit clinical evidence for a new therapeutic indication, which is expected to fulfil an unmet medical need – covered in Article 48. This is necessary to create an efficacious and broader regulation of paediatric extrapolation of adult data. In that respect, and with the same purpose of fostering the process of extrapolation, **ESPGHAN also proposes to:**

- a. Provide additional incentives to improve the Paediatric Use Marketing Authorization (PUMA) whenever and wherever possible (covered in Article 92).
- b. Enable legal regulatory support **to use real-world evidence and post-marketing long-term extension studies for monitoring safety and efficacy**, the importance of which cannot be overemphasised. The argument that this creates “unsafe” conditions for children cannot stand critical appraisal when considering the common practice in various paediatric conditions of unlicensed use of adult-approved therapies “off label” when the approved paediatric drugs do not work. Furthermore, “off label use” practice incurs significantly increased costs to health systems.

3.3 Lastly, with the aim to diminish the burden of participation in numerous clinical trials, for the same molecules or comparable drugs with the same mechanism of action (4 trials required currently), and to further streamline the marketing authorisation of paediatric medicine alongside diminishing the costs, **ESPGHAN proposes to establish an “active paediatric patients’ data master file”**. This can be obtained through previous/concurrent clinical trials for the same active substance being made open to subsequent market authorisations by future companies (the possibility described in general in Articles 121-123), and to academia, particularly concerning pharmacokinetics and pharmacodynamics). We also suggest encouraging industry and academia to use, especially in paediatrics, joint clinical trials sharing the pool of patients for testing more than 1 drug within one administrative process - the so-called "**platform study**" concept.

4. **Proposals of further incentivizing measures for obtaining marketing authorisation of paediatric and orphan medicines**

4.1 ESPGHAN is aware of and welcomes the basic concept of this EU proposal to ensure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines, but also, to offer an attractive environment for innovations, development, and production of new medicines in Europe. In practice, new developments should be incentivized, for example, by offering regulatory data protection and market exclusivity, but also to enable the timely introduction of generics. However, when addressing paediatric and orphan medicine, *per definition*, conditions occur infrequently, and the costs of developing and bringing medicinal products to the market usually cannot be covered by expected sales of the medicinal product. Furthermore, satisfying specific requirements for the prolongation of market exclusivity (covered in Article 72) is much easier for large pharmaceutical companies with sufficient resources and workforce compared to small entities that may consequently abolish the EU market for products that do not offer adequate economic returns such as medicine for children



and rare diseases. In addition, shortening the standard regulatory protection period from 8 to 6 years, and market exclusivity from 10 to 9 years for orphan designation, could result in higher average prices for health systems during the protection period. **ESPGHAN, therefore, recommends retaining the standard 8 years of regulatory protection period for medicine for children, and the market exclusivity of 10 years for newly developed orphan medical products, in addition to granting more liberal supplementary protection certificate (SPC) extensions or regulatory protection vouchers for developing PIPs.**

4.2 ESPGHAN also advises the following revisions:

- a. Less demanding requirements for medicinal products for children and for rare diseases to be classified as medicinal products, addressing unmet medical needs.
- b. Accelerated assessment procedures, currently reserved for medicinal products of major therapeutic interest, and the procedures for obtaining conditional marketing authorisations to become more accessible for paediatric and orphan medicine.

ESPGHAN hopes that the suggested comments and revisions will be useful for creating better conditions in the EU for medicine for children and rare diseases, and appreciates the opportunity to provide them. Furthermore, we offer our direct ongoing support by whatever means are found to be necessary.



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Cited sources:

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2. Andrew E. Mulberg, Laurie S. Conklin, Nicholas M. Croft, and the I-ACT for Children Pediatric Extrapolation Working Group. Pediatric Extrapolation of Adult Efficacy to Children Is Critical for Efficient and Successful Drug Development. Gastroenterology 2022;163:77-84

