SERVIER'S POSITION ON THE REVIEW OF THE EU'S PAEDIATRIC REGULATION

Servier is at the forefront of paediatric research, putting children at the heart of its R&D process. Paediatric populations have unique needs and characteristics that need thorough scientific investigation and a targeted product development.

Servier looks at paediatric medicines as a stand-alone R&D stream, not solely a spinoff of adult-based research. Driven by our internal expertise and by our focus on cancer treatment, we have carved for the company a growing and unique position in the space of paediatric oncology. As an independent Group governed by a non-profit foundation, we are able to put innovation first at the best service of patients, letting scientific discoveries and medical interest guide our work and product development.

The current paediatric regulatory framework has helped us address the challenges of paediatric research and has paved the way for new children-specific R&D streams that never existed before. We need to enhance the current framework to upscale the development of more tailored treatment options for children and keep up with scientific discoveries in the field of paediatrics.

Children across Europe have greatly benefited from the progress achieved through the EU Paediatric Regulation. The regulatory processes and economic incentives introduced by the Regulation (i.e., paediatric investigation plans (PIP)), paediatric use marketing authorisations (PUMA) and a 6-month extension on supplementary protection certificates) have undoubtedly supported the development of new products for children.

The biggest success of the Regulation arguably lies in making paediatric research an integral part of companies' development programmes. This is demonstrated by the track record of 238 new medicines and new paediatric indications authorized in the EU since the adoption of the Regulation in 2007.

However, the full impact of the current Regulation has not yet allowed to overcome all pitfalls in the availability of paediatric medicines. Developing medicines for children can take several forms, from first-in-child to doing a paediatric development based on an adult indication or repurposing medicines. Each of these avenues are subject to specific barriers that need to be addressed to ensure the paediatric population's needs are met.

This document outlines Servier's position on the challenges faced by the pharmaceutical industry in addressing unmet medical needs for children and puts forward a number of suggestions to ensure the revised regulatory framework for paediatric medicines is fit for purpose.

SERVIER'S SUGGESTED APPROACH INCLUDES:

1. Clarifying and expanding the criteria to define unmet medical needs in order to identify research priorities and eligibility for incentives.
2. Adapting the regulatory processes and adding more dialogue and flexibility by creating a framework for a structured dialogue between appli- cants and regulatory authorities.
3. Maintaining and improving the current framework of incentives to guarantee an adequate economic reward of research efforts for repurposed medicines and to incentivize first-in-child innovation.

ABOUT SERVIER

Servier is a global pharmaceutical group governed by a Foundation. With a strong international presence in 150 countries and a total revenue of 4.7 billion euros in 2021, Servier employs 21,800 people worldwide. Servier is an independent group that invests over 20% of its brand-name revenue in Research and Development every year. To accelerate therapeutic innovation for the benefit of patients, the Group is committed to open and collaborative innovation with academic partners, pharmaceutical groups, and biotech companies. It also integrates the patient's voice at the heart of its activities, from research to support beyond the pill.

01 CLARIFYING AND EXPANDING THE CRITERIA TO DEFINE UNMET MEDICAL NEEDS

Despite recent progress in the field of paediatric medicine, there are still significant barriers to the development of paediatric treatments. First-in-child R&D is hindered by both market-specific and population-specific obstacles, such as the limited size of the population, its high fragmentation – both geographically and per-age groups-, ethical concerns, difficulties in trial designs and in recruiting candidates for clinical trials.

This leads to a general lack of basic research in the field of paediatrics, which consequently hinders the R&D process for paediatric treatments and formulations in particular for first-in-child innovation.

To overcome some of the obstacles, policies put in place should foster a model of open and cross functional innovation, within dynamic Research clusters and through Public-Private Partnerships, to collectively address the pre-competitive barriers that impede the development of specific medicinal products. Additionally, the regulatory framework should facilitate the identification of research priorities.

Article 43 of the Paediatric Regulation provides a short list of criteria according to which the EMA Paediatric Committee (PDCO) shall establish an inventory of therapeutic needs, to identify research priorities. These criteria aim to identify an unmet medical need based on a) prevalence of the conditions in the paediatric population, b) the seriousness of the conditions to be treated, and c) the availability and suitability of alternative treatments.

While such elements must form an integral part of the assessment, they are by no means an exhaustive list of all factors to be taken into account to identify an area of paediatric unmet medical need. Identifying unmet medical needs with areas where no treatment exists, is tantamount to assuming that patient needs are met as soon as a treatment is authorized and placed on the market. This approach does not reflect reality and perpetuates the R&D gap between medicines for adult populations and paediatric treatments.

The Paediatric Regulation should, therefore, include a holistic and broad definition of 'unmet needs' to ensure a more accurate identification of research priorities and improve patient outcomes, looking at additional factors:

- First and foremost, the burden of treatments on patients and their quality of life.
- The availability of treatment suitable for all paediatric ages, including the availability of adapted doses, formulations and/or routes of administration.
- The cost-effectiveness of existing treatments.

To this end, a multi-stakeholder dialogue should be encouraged to continuously update the list of unmet needs and improve the understanding of existing shortcomings in the treatments for and care of paediatric populations.

"At Servier, paediatric research is no longer led only by adult research. Innovation to develop first-in-child medicines is an integral part of our research efforts - especially in the field of oncology - and our R&D pipeline focuses also on the exclusive and unique needs of paediatric populations."

Oana Bernard,
Paediatrics R&D
Director,

02 ADAPTING THE REGULATORY PROCESSES AND ADDING MORE DIALOGUE AND FLEXIBILITY

The complexities of the current regulatory process for paediatric R&D constitute an additional barrier to development. Paediatric investigation plans (PIPs) require companies to submit a large and detailed amount of information at a very early stage, when accurate data may not yet be available. This often obliges companies to submit multiple modifications and corrections to the initial investigation plan as additional data becomes available through clinical trials, creating a significant administrative burden and ultimately delaying authorizations.

A revision of the regulation should introduce regulatory flexibilities and simplified procedures to facilitate market access of paediatric medicines and reduce the administrative burden for companies. These should include the overall simplification of PIPs and the possibility to incorporate additional evidence in the plans as it becomes available (i.e. so-called staggered approach to PIPs), as well as the enhanced use of rolling reviews, extrapolation frameworks, conditional market authorizations and real-world evidence.

In particular, an effective framework to complement the limited data generated in the paediatric population with data extrapolated from adult research should be developed. Maximizing the use of data from adult research whenever the pathophysiology is similar would in fact reduce paediatric data requirements and help speed up the authorization process while minimizing children's exposure to studies.

TIMING OF THE PIP

For one of Servier's treatments, a PIP was submitted in 2011 proposing a detailed design and number of clinical trials in children. The trials started on time, but difficulties led to delays in the R&D process. In the meantime, additional knowledge was acquired on the disease and on the molecule, leading to strategy changes, and several subsequent modifications to the original PIP to improve the feasibility of the studies. Each Requests for Modifications (RFP) to the initial PIP created delays, with the last one taking over a year to be submitted and approved, with limited possibility of dialogue with the authorities due to the constraints of the PIP procedural rules. The regulatory process thus added significant bureaucratic burden and uncertainty to the outcome of the paediatric programme. Ten years later the studies are still ongoing.

In this case, a more flexible, structured and systematic framework of discussion between the PDCO and Servier would have improved the efficiency and cost-effectiveness of the procedure. A staggered approach would have allowed Servier to kick start the paediatric R&D process right after the adult phase I, identifying only the main lines of development. A more detailed study plan and protocol design of phase III trials in children could then have been discussed and submitted for approval at a later stage when more clinical data were obtained, avoiding subsequent multiple modification procedures.

03 MAINTAINING AND IMPROVING THE CURRENT FRAMEWORK OF INCENTIVES

In addition to population-specific barriers, developers are faced with constraints related to the lack of adequate market and regulatory incentives. Pricing decisions for new paediatric formulations hardly ever reflect the added value of the research done to bring a new paediatric indication/formulation to the market. This is especially the case when an older, cheaper medicine with an adult indication is available and can be compounded and used off-label, creating uncertainties in the revenue potential of repurposing adult treatments for paediatric use. Consequently, in the face of competition from both generics and existing products with adult indications, repurposing and reformulating is rarely an economically viable option for developers of paediatric treatments, discouraging companies' engagement in voluntary repurposing programmes in areas of unmet medical need.

A review of the existing incentives is therefore needed to encourage the R&D of medicines for children and ensure their timely access to the market through efficient streamlined authorisation procedures.

The current incentives framework needs to be adapted to improve the economic viability of the repurposing of existing adult products for paediatric indications. This would ensure the market value of new paediatric indications/formulations is appropriately recognized by healthcare systems and reflected in pricing mechanisms. In particular, the Paediatric-Use Marketing Authorization (PUMA) should be revised to guarantee an adequate economic reward of research efforts, encourage value-based health technology assessment and delink the pricing of new paediatric indications from generic prices.

THE CURRENT INVESTMENT FRAMEWORK FOR PAEDIATRICS

When a company completes a Paediatric Investigation Plan (PIP), the rewards can take two alternative forms:

- A 6-month extension to the supplementary protection certificate (SPC), which protects the product
- When the product which is the subject of the completed PIP is an orphan medicinal product, the 10 years of market exclusivity provided by the Orphan Regulation can be extended by a further 2 years.

To incentivize companies to develop off-patent compounds for paediatric indications, a Paediatric use marketing authorization (PUMA) can be granted. A PUMA will only cover the paediatric indication(s) and will benefit from a separate 8+2 year period of data and market protection.

REPURPOSING A MEDICINE FOR A PAEDIATRIC INDICATION

In 2017, Servier started a development project to repurpose an existing molecule to develop the first treatment in a new indication for children and adolescents. While the molecule itself was not new, the development plan was highly innovative and a significant amount of high-quality data and RWE was required in order to demonstrate the efficacy and safety of the drug to treat a completely different condition in a very peculiar population group.

This required:

- Carrying out toxicity studies in animals
- The development of a specific paediatric formulation
- The development of an exploratory Proof of Concept (PoC)
- A phase 2b and two phase 3 clinical studies and a genotoxicity study
- The rollout of a clinical and pharmacokinetic development plan in children and adolescents from 2- to 17-year-old

More than 500 patients were involved in the process. A high level of investment was needed for the project to be launched and completed throughout all the various development stages. Unfortunately, five years later, after many discussions and reviews with the PDCO the clinical studies were terminated as the molecule did not perform as well as expected.

Though the development did not succeed, one of the hurdles identified to bring the product to the market was the level of incentives for repurposed molecules. While the data exclusivity protection granted by the PUMA scheme was one of the essential drivers to launch the project in Europe, early discussions with payers had shown that the price of the product would likely be capped by the price of the off-patent molecule prescribed for a very different indication. This risk could have been mitigated by ensuring that the list of comparators to define the price of the medicine is restricted to products for a similar indication.