European Medicines Agency and European Commission (DG Health and Food Safety) action plan on paediatrics

Status/progress last updated: December 2020

Introduction

The EU's regulatory framework for paediatric medicines, the Paediatric Regulation[1], came into force in 2007. In 2017, the European Commission's (EC) issued their ten-year report[2] on the implementation of the Regulation, which showed that the number of medicines developed for children increased during this period. However, it also revealed specific challenges, like developing medicines for diseases that only affect children or for diseases that manifest differently in adults and children. The report also highlighted that the development and later availability at patients' bedside of paediatric medicines is often delayed when compared with adult medicines.

Based on this analysis, the EC's report identified a number of areas where short-term actions could address the identified shortcomings under the current legal framework. In order to follow up on the report's conclusions the EC and the European Medicines Agency (EMA) have developed a detailed plan to boost the development of medicines for children in Europe, in consultation with all relevant stakeholders.

This action plan takes into account the suggestions made at a multi-stakeholder workshop[3] convened by the EC and the EMA on 20th of March 2018, where ways to improve the implementation of the Paediatric Regulation were discussed. It is expected that the implementation of the proposed actions will increase the efficiency of paediatric regulatory processes in the current legal framework and boost the availability of medicines for children.

The actions are grouped according to the 5 topic areas highlighted by the Commission in the ten-year report on the implementation of the Regulation:

Topic areas
• Identifying paediatric medical needs
• Strengthening of cooperation of decision makers
• Ensuring timely completion of paediatric investigation plans (PIPs)
• Improving the handling of PIP applications
• Increasing transparency around paediatric medicines

Actions by topic area

1. Identifying paediatric medical needs

	Action	Objectives	Progress by December 2020	Status
1	Develop overview of selected therapeutic areas to identify paediatric medical needs. Actions include: • Conducting public survey on criteria proposed for determining paediatric medical needs and on perceived areas of needs • Selecting therapeutic areas based on various factors, including experience with PIPs and stakeholder feedback, for further analyses by multi-stakeholder focus groups • Conducting multi-stakeholder workshops in selected therapeutic areas • Publishing reports on the paediatric therapeutic landscape related to selected areas	To raise awareness for paediatric medical needs with a view to providing a basis for strategic decision making on paediatric medicine development.	• Strategies to address needs in children with malignancies were determined at multi-stakeholder forums organised by EMA together with the ACCELERATE platform: ○ ACCELERATE & EMA Paediatric Strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients (09/2018), related publication in Eur J Cancer (11/2019) ○ ACCELERATE & EMA Paediatric Strategy Forum for medicinal product development for acute myeloid leukaemia in children and adolescents (04/2019), related manuscript accepted for publication in Eur J Cancer (05/2020) ○ ACCELERATE & EMA Paediatric Strategy Forum for epigenetic modifiers in paediatric malignancies (01/2020) • Review of the value of Paediatric Strategy Forums for regulatory decision making was published in Clin Pharmacol Ther (06/2020). • Contribution to a Multi-stakeholder workshop on paediatric unmet medical needs (12/2019), which identified the opportunity for disease-focused workshops during 2020/21 in collaboration with the IMI c4c project.	In progress.
2	Develop framework to ascertain paediatric needs in the context of PIP discussions	To improve the systematic and structured assessment of medical need and the potential	• The PDCO set up a dedicated working group to review the discussions around unmet needs, which resulted in the introduction of a new section in the minutes where the discussion on the potential to fulfil an unmet need is reflected since November 2018.	Completed.

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		benefit of a medicine during PIP procedures	• Based on this experience, an article on how to identify and address unmet needs in paediatric developments was published in Reg Rapp (07/2019).	
3	Establish framework for collaboration of EMA/PDCO with the U.S. FDA's Oncology Center of Excellence Pediatric Oncology Program regarding the assessment of relevant molecular targets in paediatric cancers	To maximise synergies and share expertise in the assessment of relevant molecular targets and to address medical needs with a global perspective	• EMA discusses paediatric oncology programmes with the U.S. FDA on a monthly basis via the paediatric cluster. • Both EMA and FDA are represented in ACCELERATE steering committee since 2019 and engage in the organisation of shared paediatric strategy forums addressing needs in children with malignancies. • Article on accelerating the global development of paediatric cancer drugs: a call to coordinate the submissions of Paediatric Investigation Plans and Pediatric Study Plans to the European Medicines Agency and US Food and Drug Administration was published (09/2020).	Completed.

2. Strengthening of cooperation of decision makers

	Action	Objectives	Progress by December 2020	Status
1	Establish framework for exchange of information between the EMA/PDCO and the Clinical Trial Facilitation Group (CTFG) as well as ethics committees	To improve dialogue between EMA/PDCO and clinical trial assessors and facilitate mutual understanding of the interplay between assessment of PIPs and of clinical trials	• Co-chair of CTFG attended PDCO plenary meetings in December 2018 and June 2019 to discuss how to further strengthen collaboration between the CTFG and the PDCO. Product-related discussions including CTFG/PDCO took place in January 2020 in the context of safety considerations for a specific class of products. A joint meeting to improve ways of collaboration is planned in 2021/2022 pending business continuity considerations.	In progress.
2	Enhance integration of EMA/FDA paediatric cluster activities	To ensure knowledge and information exchange between PDCO and the	• Establishment of regular reporting at the PDCO plenary meeting to provide timely feedback to members about paediatric cluster activities (11/2018). Paediatric cluster minutes are shared with PDCO members.	Completed.

	Action	Objectives	Progress by December 2020	Status
		paediatric regulatory cluster	• Invitation to paediatric cluster meetings has been extended to all PDCO members and, depending on the topic, also to Scientific Advice coordinators as well as CHMP members concerned (11/2018). • FDA/EMA Common Commentary on submitting an initial Pediatric Study Plan (iPSP) and Paediatric Investigation Plan (PIP) for the prevention and treatment of COVID-19 was published simultaneously by U.S. FDA and EMA (06/2020).	
3	Increase transparency with regard to EMA/FDA paediatric cluster discussions	To better inform sponsors about paediatric cluster discussions and to increase transparency for all relevant stakeholders regarding outcomes of non-product related interactions	• Outcomes of product related paediatric cluster discussions ("action points") are shared with the sponsor concerned.	Completed.
4	Increase global interactions between EMA/PDCO and other stakeholders, including other regulators and paediatric clinical research networks such as the European Network of Paediatric Research at EMA (Enpr-EMA)	To promote a global and holistic approach for paediatric medicine development	• An Enpr-EMA WG on international collaboration was set up (12/2018), including representatives from international regulators, paediatric research networks and EMA/PDCO. Work on a white paper on requirements for paediatric clinical trial authorisation in different legislative regions is in progress. • Collaboration between EMA and Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard was set up in order to promote global clinical research in children (10/2019).	In progress.

3. Ensuring timely completion of paediatric investigation plans (PIPs)

	Action	Objectives	Progress by December 2020	Status
1	Publish recommendations to support the conduct of paediatric clinical trials	To facilitate the conduct of paediatric clinical trials by focusing on identification and resolution of factors impeding the conduct of trials in children	• PDCO adopted a letter addressed to the department on HIV/AIDS of the World Health Organization (WHO) and to the Elizabeth Glaser Paediatric AIDS Foundation, supporting age inclusive research in paediatric HIV whenever scientifically justified (03/2019). • PDCO adopted a letter, addressed to Innovative Therapies for Children with Cancer (ITCC) and Accelerate, supporting age inclusive research in paediatric oncology whenever scientifically justified (04/2019). • Enpr-EMA facilitates connections between paediatric research nurse networks and groups in Europe. As a first step a list of contact details of European paediatric research nurse networks and groups was published (07/2018). • Enpr-EMA published a framework about paediatric clinical trial preparedness (08/2020).	Completed.
2	Make training material on paediatric medicine development publicly available	To raise awareness and understanding of regulatory and scientific aspects of paediatric medicine development among researchers and academia	• Training material on paediatric medicine development has been made available via the EU Network Training Centre (EU-NTC) to EU medicines agencies (12/1219) and is being prepared for making it accessible for public use.	In progress.
3	Develop training resources on clinical research for young people's advisory groups and patients/parents organisations in collaboration with Enpr-EMA and increase opportunities for dialogue between young patients and EMA/PDCO	To educate young people's advisory groups and patients/parents on clinical research in order to enable them to best contribute to and represent their interests	• Building on an Enpr-EMA working group the European Young People Advisory Group network (eYPAGnet) was established and became a member of Enpr-EMA in 2018. eYPAGnet provide a range of services and training resources to young people involved in clinical research. • EMA supported conect4children (c4c) in the development of a video about involvement of young	In progress.

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		in the planning of clinical trials	people in EMA's activities related to medicine development (06/2020). • Discussing the need for feedback of patients' organisations has been included as an integral part of every PIP assessment by inclusion of a respective chapter in the PDCO meeting documents. Feedback from paediatric patients and their carers on their needs in the context of specific paediatric developments has since been sought in 10 cases.	
4	Publish reflection paper on extrapolation methodologies in PIPs	To increase awareness regarding extrapolation methodologies among medicine developers and regulators	• Reflection paper on the use of extrapolation in the development of medicines for paediatrics was adopted and published (10/2018). • Assessors' guidance on the use of extrapolation is under preparation. • Discussions with Health Technology Assessment (HTA) bodies are planned in order to increase mutual understanding of the extrapolation concept, including its application for the paediatric population.	Completed.
5	Revise paediatric aspects of scientific EMA guidelines	To provide more guidance to support sponsors developing medicines for the paediatric population	• Concept paper on the need for revision of the guideline on the investigation of medicinal products in the term and preterm neonate was adopted and published (05/2019). • Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease was published (11/2018) • Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) was published (11/2018). • Guideline on the development of new medicinal products for the treatment of Crohn's Disease including guidance regarding the possibility for extrapolation from adults, or	In progress.

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			the need to generate separate data in children came into effect (01/2019). • Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis Disease including guidance regarding the possibility for extrapolation from adults, or the need to generate separate data in children came into effect (01/2019).	

4. Improving the handling of PIP applications

	Action	Objectives	Progress by December 2020	Status
1	Explore possibilities for a PIP model that allows, in certain cases, for changes to be made to PIPs as more evidence becomes available over time	To identify possibilities for and limitations of a PIP model that allows to develop along with the evolution of scientific knowledge	• Further to internal EMA/PDCO discussions, options regarding PIP models were exchanged between Industry and PDCO at the Industry stakeholder platform on research and development support (01/2019), discussions are ongoing. Further discussions needed based on relevant examples to define the framework for content and the milestones for assessment and decision making.	In progress.
2	Explore opportunities for enhanced dialogue with sponsors in the context of PIP procedures	To foster informed discussions between EMA/PDCO and PIP applicants	• Business pipeline meetings focussing exclusively on paediatric developments have taken place (2020)	In progress.
3	Improve processes for compliance checks	To minimise unnecessary administrative procedures	• Procedural aspects of the compliance check of an agreed paediatric investigation plan were simplified and endorsed by the PDCO, e.g. enabling EMA/PDCO conclusion without the need for PDCO plenary discussions in non-controversial cases (11/2019).	Completed.
4	Revise PIP summary report template	To improve clarity of summary reports and focus on essential information	• A draft revision of the summary report template has been developed based on experience and is under discussion with the PDCO.	In progress.

	Action	Objectives	Progress by December 2020	Status
			• A modified SR template was published in an FDA/EMA Common Commentary to facilitate efficient PIP submissions related to prevention and treatment of COVID-19 (06/2020, see also Action 2.2).	
5	Review key elements (structure and granularity) of PIP opinions	To focus on essential key elements of the PIP opinion and the appropriate level of detail in order to optimise the need for modifications of an agreed PIP.	• Optimisation of key elements of the PIP opinion to be finalised in conjunction with PIP summary report template.	In progress.
6	Improve procedural guidance related to paediatric medicine development	To enable stakeholders to easily find clear guidance on the Agency's website	• New structure and design of EMA website, including the paediatric medicine pages, was implemented (2018). • Guidance on paediatric submissions and Questions & Answers were updated (03/2020).	Completed.
7	Simplify administrative submission requirements	To reduce unnecessary administrative burden	• Adoption of 11 submission deadlines for paediatric applications at regular intervals per year to avoid submission restrictions in the months May and June (04/2020). • Submission requirements for all paediatric procedures were revised and simplified. New simplified form for PIP modifications was published (10/2018). • Abolishment of the need to submit a letter of intent prior to submission of paediatric procedures (04/2020)	Completed.

5. Increasing transparency around paediatric medicines

	Action	Objectives	Progress by December 2020	Status
1	Update Community Register of medicinal products with paediatric	To facilitate the identification of medicinal products for which a PIP	Planned	In progress.

	Action	Objectives	Progress by December 2020	Status
	information (e.g. link to PIP information)	has been agreed and conducted		
2	Provide information on paediatric trials open for recruitment in a public register, as well as results of such trials in lay language (in accordance with Clinical Trial Regulation)	To facilitate recruitment into paediatric trials and improve clarity of published trial data	Planned	In progress.

References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December2006 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. Official Journal L 378, 27/12/2006, 1-19, 2006. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf [Accessed10 April, 2018].
2. Report from the Commission to the European Parliament and the Council. State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation ((COM (2017) 626). Available at: https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf [Accessed10 April, 2018].
3. Multi-stakeholder workshop to further improve the implementation of the Paediatric Regulation (20/03/2018). Documents available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2018/01/event_detail_001570.jsp&mid=WC0b01ac058004d5c3 [Accessed 18/06/2018].