EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

How to better apply the Paediatric Regulation to boost development of medicines for children

Report on a multi-stakeholder workshop
held at EMA on 20 March 2018

1. Introduction

Topic areas discussed

- Identifying paediatric medical needs
- Further strengthening of international cooperation
- Ensuring timely completion of paediatric investigation plans (PIPs)
- Improving the handling of PIP applications
- Increasing transparency around paediatric medicines

The EU's regulatory framework for paediatric medicines, the Paediatric Regulation[1], came into force in 2007. In 2017, the European Commission (EC) issued a 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 in developing medicines for diseases that only affect children or diseases with different manifestations in adults and children. The report also highlighted that the development and later the availability of paediatric medicines at the bedside 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 identified shortcomings under the current legal framework. The EC and the European Medicines Agency (EMA) committed to develop a detailed plan to boost the development of medicines for children in Europe, in consultation with all relevant stakeholders as a follow up to the ten-year report.

On 20 March 2018, the EC and EMA convened a multi-stakeholder workshop to discuss and identify ways to improve the implementation of the Paediatric Regulation. In their welcome notes Vytenis Andriukaitis, the EC Commissioner for Health & Food Safety, Françoise Grossetête, member of the European Parliament (EP) and former EP rapporteur for the Paediatric Regulation, and Guido Rasi, EMA's Executive Director, acknowledged the achievements of the legal framework but also stressed the importance of the commitment of all stakeholders in improving its implementation. Participants at the workshop were patients and carers, academics, healthcare professionals, and pharmaceutical industry representatives, as well as clinical trial assessors from national competent authorities (NCAs), ethics committees, EMA including representatives of Paediatric Committee (PDCO) and the EC.

This report provides a high-level summary of the main ideas and proposals discussed during the meeting, which will be considered for the development of the action plan. All slide presentations and the recording of the workshop are available on the EMA website.

2. Identifying paediatric medical needs

Main topics discussed

- Assessment of the disease burden
- Characterisation of the properties of medicinal products concerned
- Scientific understanding of relevant research area
- Alignment of actions by national and international partners

The EC's ten-year report showed that most achievements have been made in areas where the needs of adult and paediatric patients overlap. However, the impact of the legislative framework is lower in the area of rare diseases or diseases that occur mainly in children (e.g. certain types of cancer).

To discuss ways of identifying paediatric medical need, introductory perspectives were provided by representatives of patients' organisations (Anne Goeres, Hall Skåra and Virginie Hivert), healthcare professionals and academics (Luca Sangiorgi, Tjitske van der Zanden, Martina Pitzer, and Gilles Vassal), and the pharmaceutical industry (Marie-Yvonne Douste-Blazy). Subsequently, participants at the workshop discussed ways to facilitate strategic decisions on medicine developments to meet paediatric medical needs and help fund bodies to channel resources into neglected areas.

The various suggestions can be summarised in four areas. Firstly, there is a need to properly assess disease burden, including the relevance of a condition in the paediatric population, its seriousness, and the availability and suitability of treatments. Central to the discussion was the understanding that multi-stakeholder engagement is key and that a patient-centred approach (rather than drug-centred approach) is needed. It is also important to build on experience with successful models such as the Accelerate Platform[3] in the area of paediatric oncology.

Secondly, the properties of a given medicinal product, including its mode of action and pharmacological characteristics in various age groups should be taken into account, alongside other considerations such as whether the treatment is potentially curative or disease-modifying, whether it will impact disease progression or mainly target disease symptoms and its impact on quality of life. Patient representatives, industry and other stakeholders also noted that consideration should be given to whether or not there are other available treatments including non-pharmacological interventions.

Thirdly, information and data from research should be shared in a transparent fashion and should be publicly available; such transparency would provide insight on the pipeline of new developments, assist with the design of future trials and help avoid the conduct of unnecessary trials. In this context it was emphasised that standardised terminologies and study methodologies are important in order to permit data merging and avoid fragmentation of data. The importance of registries was highlighted.

Finally, international collaboration is vital in paediatric medicine development. Participants agreed that a global perspective in identifying paediatric medical needs and determining regulatory requirements is very important. This would help to design optimal paediatric development programmes in areas of unmet need, which meet regulatory requirements across regions.

3. International cooperation between regulators

Main topics discussed

- Initiatives to further increase cluster interactions
- Collaboration in the context of molecular targets for paediatric oncology

International cooperation between regulators and international compatibility of clinical research requirements are particularly important in the area of paediatric medicines, for ethical and methodological reasons.

Sandra Kweder, U.S. Food and Drug Administration's (FDA) liaison officer at the EMA, highlighted existing collaboration initiatives involving EMA and FDA, as well as regulators from Canada, Japan and Australia. These initiatives include the monthly paediatric cluster telephone conferences, jointly organised multi-stakeholder expert workshops, multi-stakeholder working groups, joint scientific publications, and collaboration of regulators with international consortia and networks.

To further strengthen the impact of cluster discussions, several suggestions were made by the workshop participants: involvement of investigators and other stakeholders in cluster discussions; interaction between the soon to be launched IMI2 pan-European paediatric research network and its North American counterpart, the Institute for Advanced Clinical Trials for Children (I-ACT for Children); engagement with applicants/sponsors if their product has been selected for discussion at the paediatric regulatory cluster; and more transparency on general topics discussed at the paediatric regulatory cluster.

Sandra Kweder also discussed the implementation of the U.S. RACE (Research to Accelerate Cures and Equity) for Children Act[4] (included in FDARA 2017[5]) which allows the FDA to require the development of paediatric cancer treatments based on their molecular target, in order to address paediatric medical needs. It is expected that the scientific debate stimulated by this new U.S. legislation will also impact PIP discussions and would require even closer international collaboration.

4. Timely completion of Paediatric Investigation Plans (PIPs)

Main topics discussed

- Optimisation of development programmes from early stages onwards:
  - » Early regulatory discussions of trial designs and methodologies
  - » Optimisation of the estimation of patient availability
  - » Consultation and involvement of patients and young people
  - » Knowledge/information sharing between stakeholders
- Support for conduct of clinical trials:
  - » Guidance for planning of clinical trials
  - » Sustainable infrastructure and funding
- Optimisation of dialogue in the context of clinical trial reviews:
  - » Training and exchange of information between assessors of clinical trials from national competent authorities and ethics committees and regulators involved in decisions on PIPs and marketing authorisation

As highlighted in the EC's ten-year report, the timely availability of paediatric medicines is often impacted by the delayed completion of the paediatric clinical trials in PIPs.

Mark Turner, representing academia and health care professionals, highlighted two main obstacles to timely PIP completion: 1) patient availability for a given clinical trial is not always estimated correctly because estimates are often based on non-validated data and 2) clinical sites are not prepared appropriately due to inconsistent trial design and lack incentives for sites. It was suggested that patient availability could be better determined by consulting networks and investigators experienced in the therapeutic area, which may be able to create trial simulations and explanatory flow diagrams. A need for guidance was also identified regarding issues to consider at the planning stage of a clinical trial so that the trial is conducted in a timely manner. Additionally, education and training of research staff at trial sites is important and requests to sites should be consolidated to develop economies of scale in order to incentivize investment.

Heidrun Hildebrand, representing industry, highlighted the importance of best practice sharing and improved infrastructure for paediatric clinical trials, such as that provided by the European Network of Paediatric Research at the EMA (Enpr-EMA) and an IMI initiative creating a pan-European paediatric clinical trial network. Furthermore, the importance of government initiatives in Member States and appropriate funding to ensure sustainability of infrastructure capacities was emphasised. Ensuring harmonisation of local legislative and ethical frameworks for clinical trials with children as well as for patient information and consent/assent procedures was outlined as an important factor to ensure timely conduct of studies. Moreover, the importance of early scientific dialogue and multi-stakeholder interactions, as well as the need for a more pragmatic approach towards PIP generation and approval, allowing an easier adaptation of PIPs to evolving data was highlighted.

Elisabeth Vroom and Begonya Nafria Escalera presented the perspective of patients and young people. Particular emphasis was given to the fact that

clinical trial protocols, as they relate, for example, to eligibility criteria or invasive procedures need to be suitable for the paediatric population and take into account the patients' and their families' quality of life. Age-appropriate outcome measures and trial designs (e.g. minimal use of placebo) were mentioned as main solutions to improve patient recruitment. In order to achieve these solutions it was highlighted that standardised consultation of patients and young people at all steps of a medicine's life cycle and their collaboration with sponsors and ethics committees would be crucial. It was suggested that there is a need to harmonise the rules governing the work of ethics committees regarding paediatric trials. The patient representatives also stressed the need for the exchange of best practices and training on paediatric aspects for all stakeholders involved in clinical trials. The lack of central patient or disease registries and a lack of awareness in the general EU population of the benefits of clinical trials were mentioned as additional obstacles.

Ann Marie Janson Lang, representing the perspective of clinical trial assessors, drew attention to the importance of the open exchange of information and increased interactions between the PDCO and the Clinical Trial Facilitation Group (CTFG), which is a working group representing clinical trial units of NCAs of EU/EEA countries. It was highlighted that CTFG also promotes collaboration between NCAs and ethics committees. It was pointed out that the authorisation of clinical trials is a separate national decision with its own scope and criteria which differ from those used by PDCO in deciding on paediatric development programmes. Therefore, the proposed interactions between PDCO and CTFG would help foster mutual understanding and have the potential to support the respective reviews.

During the discussion several participants mentioned the need to improve the awareness of patients, parents and the general public about the importance of clinical trials to facilitate and fund research and to implement innovative trial designs. Concrete examples of how to accelerate at least some types of paediatric clinical studies were proposed, such as limiting age-staggered recruitment to only essential cases. Stakeholder groups called for interaction of all relevant players in paediatric clinical trials (patients/carers, health care professionals, researchers, industry, regulatory bodies and ethics committees) from the early stages of medicine development.

Another proposal was to improve multi-stakeholder interaction and learn from successful models such as the Accelerate Platform in the area of oncology. A dialogue on the respective therapeutic landscapes with a view to sharing information, identifying the most promising drug developments and defining success criteria and milestones in the development processes was deemed of great importance. The exchange of information between academia/research networks and industry is of particular importance in this regard. Other relevant stakeholders, such as patient organisations and regulatory bodies should contribute to such discussions during development. Finally, the advantage of multi-agent/multi-company trials with a shared control group was mentioned as a means of reducing the number of patients needed in parallel drug developments.

5. Improving the handling of PIP applications

Main topics discussed

- Evolutionary approach to PIP agreement
- Lean and simplified submission requirements
- Optimised procedural guidance
- Increased dialogue before and during the PIP procedure

Geneviève Le Visage, representing industry, and Mark Turner, representing academia, presented the applicants' perspective on procedural and operational challenges posed by PIP applications.

Given the requirement to submit a PIP early in development and keeping in mind the course of pharmaceutical development, a more 'evolutionary' approach to agreeing PIPs was proposed – one that better reflects the knowledge gained over time. With this approach, in certain cases (e.g. for innovative medicines or therapeutic areas for which knowledge is limited) PIPs will only reflect data and knowledge available at a given point in time, but would then need to be enriched subsequently based on the scientific knowledge gained during development.

Participants also proposed that documents and available guidance could be simplified or improved in order to focus on the critical aspects of development (e.g. the key elements), which may also positively impact the efficiency of the PIP procedure.

In addition, extended timelines with multiple lists of questions and clock stops were suggested as possible solutions for challenging PIP discussions, illustrating the need for a flexible case-by-case approach. Overall, participants agreed on the benefits of increased dialogue before PIP submission and during the PIP procedure.

6. Increasing transparency around paediatric medicines

Main topics discussed

- Community register of medicinal products for human use to include PIP information
- Implementation of the Clinical Trial Regulation

Fabio D'Atri from the EC informed the workshop participants about the Commission's plan to improve the paediatric information available on the Community register of medicinal products for human use including the provision of information on PIPs and a link to PIP Decisions.

In view of the implementation of the EU Clinical Trial Regulation, Fabio D'Atri together with Fergus Sweeney from EMA discussed improvements in transparency that will be made, such as providing public protocol information with justification for gender and age requirements and the study population as well as reasons for underrepresentation of specific age or gender groups. Furthermore, clinical trial assessors with specific paediatric expertise will have to be involved in assessing paediatric trials, and agreed PIPs will need to be systematically taken into consideration. Furthermore, ethics committees will have to take into account the views of laypersons (patients' organisations). The new clinical trial portal and database will also allow for public access to information on recruitment periods and the actual start and end dates for all trials authorised in the EU/EEA. Public registration of trials at their start as well as publication of study results (including a summary for laypersons) will become mandatory. It is expected that public data and information on clinical trials and medicines will be crucial in generating trust, building stakeholder confidence, and empowering those entrusted to make decisions.

7. Conclusions

This multi-stakeholder workshop was a unique opportunity for an open dialogue and exchange of ideas among all stakeholder groups and a crucial step in the development of an EC/EMA action plan. With more than 160 participants representing all main stakeholder groups, a wide range of perspectives was heard and the breadth of the proposals for concrete actions is reflective of this wide-ranging input.

The open exchange of ideas facilitated the development of a common understanding across different interest groups. However, it is clear that the commitment of all stakeholders will be needed to better apply the legislative framework and ensure that children in the EU have timely access to much needed new treatments. Progress can only be made if all stakeholders take responsibility, work together and learn from each other.

The EC and EMA, including the PDCO, are working on an action plan for the next 2 years, taking into account relevant practical and legal considerations. Information on these actions will be shared with the stakeholders by mid-2018.

8. 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. ACCELERATE – Innovation for children and adolescents with cancer. CDDF-ITCC-SIOPE Multi-stakeholder Paediatric Platform. http://www.accelerate-platform.eu/about-us/ [Accessed 10 April, 2018]

4. RACE for Children Act. A bill to amend the Federal Food, Drug, and Cosmetic Act to establish a program to increase the development of new drugs to treat pediatric cancers, and for other purposes. https://www.gpo.gov/fdsys/pkg/BILLS-115hr1231ih/pdf/BILLS-115hr1231ih.pdf [Accessed 10 April, 2018].

5. Food and Drug Administration Reauthorization Act (FDARA) of 2017. https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDARA/default.htm [Accessed 04 May, 2018].

Appendix—list of chairs, speakers and panellists

Surname, Name	Affiliation
Alteri, Enrica	European Medicines Agency (EMA)
Andriukaitis, Vytenis	Health & Food Safety Commissioner, European Commission (EC)
Bax, Ralph	European Medicines Agency (EMA)
Berntgen, Michael	European Medicines Agency (EMA)
D'Atri, Fabio	European Commission (EC), DG Health and Food Safety
Douste-Blazy, Marie-Yvonne	European Federation of Pharmaceutical Industries and Associations (EFPIA), Servier
Egger, Gunter	European Medicines Agency (EMA)
Goeres, Anne	Fondatioun Kriibskrank Kanner, Luxembourg
Grossetête, Françoise	Member of the European Parliament (EP), former EP rapporteur for the Paediatric Regulation
Hildebrand, Heidrun	European Biopharmaceutical Enterprises (EBE), Bayer
Hivert, Virginie	Rare Diseases Europe (EURORDIS)
Janson Lang, Ann Marie	Clinical Trials Facilitation Group (CTFG)
Kweder, Sandra	U.S. Food and Drug Administration (FDA)
Le Visage, Geneviève	European Federation of Pharmaceutical Industries and Associations (EFPIA), Novartis
Mentzer, Dirk	Paediatric Committee (EMA)
Nafria, Escalera Begonya	European Young Persons Advisory Groups Network (eYPAGnet)
Pitzer, Martina	Drug Commission of the German Medical Association (DCGMA)
Rasi, Guido	European Medicines Agency (EMA)
Sangiorgi, Luca	European Reference Network on Rare Bone Diseases (BOND ERN)
Schmidt, Florian	European Commission (EC), DG Health and Food Safety
Skåra, Hall	European Pulmonary Hypertension Association (PHA Europe)
Sweeney, Fergus	European Medicines Agency (EMA)
Turner, Mark	European Network of Paediatric Research at the EMA (Enpr-EMA)
Van der Zanden, Tjitske	PEDMED-NL (Former Dutch Medicines for Children Research Network)
Vassal, Gilles	Innovative Therapies for Children with Cancer (ITCC) Consortium
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