Pediatric Cluster Terms of Reference

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I. Introduction

This document has been developed and agreed upon in the framework of the Confidentiality Commitments between the following regulatory agencies in the context of regulatory cooperation and transparency: the European Medicines Agency (EMA) of the European Union (EU), the United States (US) Food and Drug Administration (FDA), Health Canada, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, and the Therapeutic Goods Administration (TGA) of Australia. These regulatory agencies have created a confidential forum for discussion of scientific and ethical issues related to pediatric medicinal product development. This is known as the Pediatric Cluster.

The International Council for Harmonisation E11 Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11) states that "Pediatric patients should be given medicines that have been appropriately evaluated for their use in those populations. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages. Obtaining knowledge of the effects of medicinal products in pediatric patients is an important goal. However, this should be done without compromising the well-being of pediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole."

It is the responsibility of the regulatory agencies that are implementing or overseeing the programs for product development in pediatrics to ensure that the rights, safety, well-being, and dignity of children participating in research are protected. As such, children should be included in clinical trials only when it is scientifically and ethically justified.

In the context of the Confidentiality Commitments between the regulatory agencies participating in the Pediatric Cluster and the pediatric legislations and regulations in their respective countries, the engaged parties have taken a further step in agreeing on principles for interactions in relation to pediatric medicinal product matters.

II. Objectives

Commitment to provide a central forum for discussion of pediatric product development activities.

Specifically:

- To facilitate the regular exchange of information related to scientific and ethical issues and other information on pediatric product development programs that have been submitted to regulatory agencies in Australia, Canada, the EU, Japan, and the US. This includes

development programs submitted in response to pediatric legislations and regulations such as Paediatric Investigation Plans (PIPs) [EMA], Pediatric Study Plans (PSPs) [FDA], and Proposed Pediatric Study Requests (PPSRs) [FDA] to avoid exposing children to unnecessary or duplicative trials.

- To encourage global pediatric product development that is compatible with the pediatric legislations and regulations within Australia, Canada, the EU, Japan, and the US.

- To understand the scientific rationale when divergences in opinions exist between regulatory agencies.

- To discuss post-marketing pediatric requirements and issues including risk management and plans for long-term pediatric safety monitoring.

- To discuss general topics of regulatory and scientific interest to the participating agencies.

- To inform the participants of planned scientific meetings or workshops related to pediatric matters with the possibility of attending the meetings.

III. Scope

Discuss issues pertaining to product classes and to product-specific development that arise during the regulatory life cycle (i.e., pre- and post-marketing).

Examples of issues for discussion include:

- Conditions/indications for study
- Deferrals
- Dosing
- Endpoints
- Ethics
- Extrapolation
- Formulations
- Modeling/simulation
- Nonclinical
- Patient population
- Safety
- Study design
- Waivers

Share information on scientific meetings or workshops related to pediatric matters with the possibility for the other agencies within the Pediatric Cluster to attend the meetings.

IV. Participants

Subject matter experts from the following regulatory agencies who have Confidentiality Commitments in place participate in the Pediatric Cluster:

- EMA will include participants from the Office of Paediatric Medicines[1], the Paediatric Committee (PDCO), Scientific Advice Working Party, Committee for Medicinal Products for Human Use (CHMP), and other committee and working parties as appropriate.

- FDA will include participants from the Office of the Commissioner including the Office of Pediatric Therapeutics (OPT), Office of Orphan Products Development, and the Office of Global Policy and Strategy. FDA will include participants from the Center for Drug Evaluation and Research (CDER) including various offices and divisions within the Office of New Drugs such as the Division of Pediatric and Maternal Health and staff from CDER review divisions. FDA will include participants from CDER's Office of Translational Sciences including the Office of Clinical Pharmacology as appropriate. FDA will include participants from the Center for Biologics Evaluation and Research including the Office of the Center Director and review staff as appropriate.

- Health Canada will include participants from the Pharmaceutical Drugs Directorate, Biologic and Radiopharmaceutical Drugs Directorate, and Marketed Health Products Directorate and include other pediatric subject matter experts as appropriate.

- PMDA will include its pediatric subject matter experts as appropriate.

- TGA will include its pediatric subject matter experts as appropriate.

V. Logistics

- FDA's OPT will host and moderate monthly Pediatric Cluster conferences/teleconferences to provide an opportunity for discussion of issues. Each teleconference will be approximately two hours in duration depending on the agenda and issues requiring discussion.

- FDA's OPT will host additional Pediatric Cluster teleconferences and relevant meetings as needed.

- Participating agencies may submit questions or topics for discussion preferably two weeks in advance of the scheduled meeting date when feasible.

- Proposal of agenda topics by the participating agencies, which will be included upon mutual agreement and shared interest.

- Topics can include 1) general topics of interest related to aspects of pediatric medicinal product development, 2) general topics related to pediatric medicinal product development in a particular disease or condition, 3) or a discussion of issues in the pediatric development of specific medicinal products.

- The applicant/company/sponsor can submit a request to one of the participating regulatory agencies that their drug product – or more generally, the appropriateness of potential indications by drug class – be considered for discussion at a Pediatric Cluster teleconference. Such a request will be relayed to the relevant participating regulatory agency's subject matter experts. It is at the discretion of the relevant participating regulatory agency's subject matter experts to decide if the topic should be discussed at the Pediatric Cluster. If the relevant participating regulatory agency's subject matter experts decide the topic should be discussed, it will be scheduled for discussion following the routine process of the Pediatric Cluster. For

FDA, this is usually decided by the appropriate review division. For EMA, this is usually decided by EMA together with the relevant PDCO members.

- FDA's OPT will coordinate the agenda and background materials for each Pediatric Cluster teleconference.

- FDA's OPT will share the agenda and background documents approximately one week prior to the Pediatric Cluster teleconference with the participating regulatory agencies. From the EMA side, these materials may include PIPs, Summary Reports (SRs), agreed Opinions, Requests for Modification of PIPs, CHMP Assessment Reports, and documents from other committees and working parties as appropriate. From the FDA side, background documents may include PSPs, PPSRs, Written Requests, and reviews by the various disciplines such as chemistry (excluding trade secret information), non-clinical and clinical.

- Document exchange between EMA and FDA should be via secure government email but can also be via EudraLink for larger files as needed or as requested by EMA.

- Document exchange between EMA and FDA should be channeled through the proper EMA/FDA contact points.

- Each participating agency will ensure the appropriate pediatric and subject matter experts are participating in the discussions.

- When it is considered helpful to share EMA's and FDA's thinking about specific pediatric medicinal product development plans with the applicant/company/sponsor, a Common Commentary may be written and then shared with the applicant/company/sponsor. A Common Commentary is a brief, 1- to 2-page summary of a topic discussed at the Pediatric Cluster. The Common Commentary does not constitute formal regulatory advice and is not binding. The Common Commentary document is drafted by EMA or FDA's OPT and edited by the relevant subject matter experts at EMA and FDA. When the document has been finalized and agreed upon by mutual consent of EMA and FDA, OPT may send it to the applicant/company/sponsor unless notified otherwise by EMA.

- The applicant/company/sponsor can submit a request to one of the participating regulatory agencies that their drug product and its proposed global pediatric development plan be the subject of a Common Commentary. Such a request will be relayed to the relevant participating regulatory agency's subject matter experts. It is at the discretion of the agency's subject matter experts to decide if a Common Commentary is appropriate. For FDA, this is usually decided by the appropriate review division. For EMA, this is usually decided together with the relevant PDCO members.

- Some general-topic Common Commentaries may be posted publicly by mutual consent of EMA and FDA, provided they do not contain proprietary information.

- High-level action items may be shared with the applicant/company/sponsor after agreement of the high-level action item by the relevant subject matter experts at EMA and FDA. This communication may be handled though OPT when the PIP is already finalized or in clock-stop. When the PIP is under discussion, EMA may elect to include the action item in the PIP SR shared with the applicant/company/sponsor.

VI. Additional Collaborative Activities that are an Extension of the Pediatric Cluster

- Formation of joint working groups and workshops when extended in-depth discussions are needed in specific therapeutic areas.

- Participation in each agency's scientific meetings, subject to agreement from the applicant/company/sponsor when required, pertaining to pediatric therapeutics as resources and availability permit.

- Publication of joint manuscripts, editorials, posters, and reports.

VII. Other

- Mutual participation by EMA and FDA in each agency's pediatric committee discussions can be coordinated. This includes FDA participating in EMA's PDCO monthly discussions and EMA participating in FDA's Pediatric Review Committee (PeRC) and Oncology Subcommittee of PeRC weekly discussions.

- Sharing of meeting minutes between EMA and FDA from the PDCO and PeRC.

- Participation by FDA in EMA's Nonclinical Working Party and Formulations Working Group[2] monthly discussions.

- Sharing of periodic line-listings of pediatric application information between EMA and FDA including deferrals and waivers.

- Sharing FDA's PEDSCLIPS: Pediatric Clinical Pharmacology Weekly Newsletter with EMA, Health Canada, PMDA, and TGA.

- Including a link on the OPT public-facing webpage that directs to EMA, and a link on the appropriate EMA public-facing webpage that directs to FDA, to facilitate the search of information by interested parties.

1. (other) EMA Offices
2. now named now named Paediatric Formulation Operational Expert Group