Final Concept Paper
E11(R1): Clinical Investigation of Medicinal Products in the Pediatric Population
dated 17 July 2014
Endorsed by the ICH Steering Committee on 14 August 2014

Type of Harmonisation Action Proposed

An update of E11 Guideline with an addendum is proposed to address new scientific and technical knowledge advances in pediatric drug development. A full revision of E11 is not recommended at this time.

Statement of the Perceived Problem

Pediatric drug development has been enhanced by advancements in several areas of general adult drug development since the current ICH E11 Guideline was adopted in 2000. Targeted scientific and technical issues relevant to pediatric populations, regulatory requirements for pediatric study plans, and infrastructures for undertaking complex trials in pediatric patient populations has been considerably advanced in the last decade, without a parallel development of harmonised guidance in these areas.

Background to the Proposal

The United States (US) and the European Union (EU) now have permanent legislation in place that mandates plans for pediatric development as part of an overall product development strategy. These plans drive US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to regularly share information related to the development of pediatric drug products. More recently, Japanese Ministry of Health Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada (Health Products and Food Branch) have joined these discussions as observers.

Thus, it is important for E11 to provide drug developers clear and compatible guidance with considerations specific to global product development of pediatric medicines. Although ICH E11 currently covers many of the relevant issues for consideration in pediatric drug development in general terms, there are clear gaps in contemporary guidance on several topics.

An addendum to the current E11 guidance seeks to reflect the latest thinking in both scientific and technical knowledge, and regulatory approaches where possible, taking into consideration that there is ongoing technical and regulatory assessments on key topics where currently no consensus has yet been achieved. Where there is agreement on general principles that are relevant for consideration by sponsors, these will be reflected in the proposed addendum.

Specific topics of pediatric formulation development, extrapolation of data in pediatric drug development, and model informed drug discovery development as it might apply to pediatric subpopulations, are recognised as areas where technical and regulatory assessments and consensus is evolving. The EWG recognises that these topics require the participation of additional scientific expertise beyond the scope of the current EWG at an appropriate future time. It is therefore our recommendation that these topics be considered for future Concept

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Papers after ongoing regulatory and scientific assessments on these topics has matured to provide a consensus position. In the interim, general considerations will be provided in the planned addendum.

Issues to be Resolved

The informal EWG for E11 has selected new and established topics to include in an update to address gaps in the current E11 document.

Acknowledging the innate differences of regulatory requirements in different regions, collaboration is needed on topics of mutual concern to accomplish consistency across various scientific and technical issues that are common to all interested parties in pediatric drug development.

There is agreement that the following topics should be addressed:

- **Timing of pediatric development milestone agreements with regulators and "commonality of content"** in pediatric drug development, especially for important milestone meetings with regulators will be addressed. Existing differences in the timing of presentation of pediatric study plans owing to regional regulations poses a need for more clarity on the commonality of regulatory content to guide the developers of pediatric medicines, recognising that pediatric clinical development programs are multi-national/ multi-regional and are designed and conducted to satisfy regulatory requirements of multiple global regulatory authorities. This is especially necessary for pediatric programs that will include the implementation of clinical outcome assessments or innovative study designs.

- **Age classification and pediatric subsets including neonates** – The addendum will reflect new science in the understanding of the developmental considerations in pediatric subsets, especially for neonates and infants.

- **Ethical considerations in pediatric studies** – The addendum will include an enhancement of the ethical considerations in pediatric studies.

- **Types of studies and methodology of clinical trials –**The addendum will reflect advances in clinical trial and statistical analysis designs especially relevant for pediatric populations. This could include innovative study designs, such as adaptive and Bayesian approaches, utilisation of pediatric clinical trial consortia, development of clinical outcome assessments, development of validated age-appropriate clinical endpoints and surrogate markers (biomarkers), including specific scales particularly for younger age groups such as neonates, and other relevant topics in this category. This would be a step toward encouraging investigators and developers to consider and discuss non-conventional designs with regulatory authorities whenever appropriate.

Recent regulatory guidance in this area will be reviewed and summarised as they might apply to pediatric study plans, including:

- *FDA guidance on "Adaptive Design Clinical Trials for Drugs and Biologics" (February 2010)* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf
- *FDA "Qualification Process for Drug Development Tools" (2010)* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
- *2007 EU Reflection Paper on on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design* www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003616
- *2009 EU procedure: Qualification of novel methodologies for medicine development* http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0
- *EMA/EFPIA workshop on Adaptive Designs in Confirmatory Trials – April 2009* http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2010/04/WC500089206.pdf
- *EMA/EFPIA workshop on Adaptive Designs in Confirmatory Trials – December 2007* http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500011842.pdf

- **Formulation challenges in pediatric drug development –** Pediatric technical research and development experts acknowledge that ICH Q8(R2) does not address formulation development that is specific to the considerations of the pediatric population. Extensive discussion and assessments on this topic by EMA, FDA, and technical experts in formulation development are ongoing, as reflected in the references below. To develop specific comprehensive guidance on this subject, consideration for a future Concept Paper developed by experts in this topic is supported taking advantage of all the work already achieved in this field.

  - *EMA "Guideline on pharmaceutical development of medicines for pediatric use", August 2013* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC50 0147002.pdf
  - *Intra-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) Oral Formulations Platform - Report 1* http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/Documents/Formulations_Platform_Report1.pdf
  - *EMA "Reflection Paper: Formulations of Choice for the Pediatric Population", July 2006* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

- *FDA draft guidance "Safety Considerations for Product Design to Minimize Medication Errors", December 2012* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf
- *WHO document "Development of Paediatric Medicines: Points to Consider in Formulation. WHO Technical Report Series, No. 970, 2012, Annex5"* http://apps.who.int/medicinedocs/documents/s19833en/s19833en.pdf

- **Extrapolation for data –** Discussion of the appropriate extrapolation of data from adult populations to pediatric populations, and pediatric subgroups to other pediatric subgroups from both a scientific and regulatory perspective has progressed considerably in the last decade. Both FDA and EMA have actively engaged in workshops on this topic and consensus continues to evolve. A treatment of this topic at a "high level" with some detail on current thinking is considered necessary in the addendum. However, it is acknowledged that there are differences in how regulatory authorities define extrapolation and consider limitations to the utilisation of extrapolated data (i.e. relative to efficacy or safety data). The EWG agrees that reference to current regulatory thinking in the addendum will be informative and can provide sponsors with valuable considerations relevant for their discussion with regulators. These may include:

  - *Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs*. Julia Dunne, William Rodriguez, Dianne Murphy, Nhi Beasley, Gilbert Burckhart, Jane Filie, Linda Lewis, Hari Sachs, Philip Sheridan, Peter Starke and Lynne Yao. Pediatrics 2011;128(5):e1242-9; *doi: 10.1542/peds.2010-3487*.

  - *The EMA Concept Paper on extrapolation of efficacy and safety in medicine development (June 2012)*: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129285.pdf

  - *Proposals for model-based paediatric medicinal development within the current European Union regulatory framework.* Efthymios Manolis & Gérard Pons. Br J Clin Pharmacol 2009; 68(4): 493–501; doi: 10.1111/j.1365-2125.2009.03484.x.

- At present, while this regulatory assessment continues, the EWG recommends that a comprehensive development of a regulatory framework for the use of extrapolation be considered for future harmonised guidance (future Concept Paper) supported by experts on this topic, in a timeframe that reflects the expectation of consensus (over the next 2 years).
  Model-Informed Drug Discovery Development (MID3) – MID3 is a concept currently used to capture a range of quantitative approaches, including pharmacometrics, systems pharmacology and other mathematical/statistical approaches that guide drug development and regulatory interactions.

Again, detailed comprehensive guidance on this topic as it might apply to pediatric drug development, is beyond the scope of an E11 addendum, as scientific and regulatory thinking continues to evolve, and consideration for a separate future Concept Paper developed by experts in this topic for a future guidance is supported.

The addendum will cover general principles for consideration, referencing information useful for developers in the design of pediatric development programs. These may include:

- *The Role of Modeling and Simulation in Development and Registration of Medicinal Products:Output From the EFPIA/EMA Modeling and Simulation Workshop.* Manolis E, Rohou S, Hemmings R, Salmonson T, Karlsson M, Milligan PA. CPT Pharmacometrics Syst Pharmacol. 2013 Feb 27;2:e31, doi: 10.1038/psp.2013.7.

- *Model-Informed Drug Development and Regulatory Review, Contemporary Issues in Clinical Pharmacology.* Sinha V. ASCPT Annual Meeting, March 6, 2013 Open Forum http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM344415.pdf

- *Clinical pharmacology and the catalysis of regulatory science: opportunities for the advancement of drug development and evaluation.* Zineh I, Woodcock J. Clin Pharmacol Ther. 2013;93(6):515-25. doi: 10.1038/clpt.2013.32.

- *EFPIA-EMA Modelling and Simulation Workshop Report EMA-EFPIA Modelling and Simulation Workshop, 30 Nov – 1 Dec 2011, London.* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3

Type of Expert Working Group and Resources

The EWG for the update of E11 should be well represented to develop the proposed topic areas in this Concept Paper. To be included in the roster are members who represent the global regulatory authorities and world guidance bodies (EU, FDA, MHLW/PMDA, Health Canada, WHO, Swissmedic) with experience in and responsibility for guiding pediatric drug development, and members of regulated industry with the relevant pediatric medical and regulatory expertise and who represent the major trade associations (PhRMA, EFPIA, JPMA) that are responsible for collaborating with regulators on drafting regulatory guidance for developers of pediatric medicines and devices. One member can also be nominated by WHO Observer, RHIs and DRAs/DoH (if requested).
Since the topic areas will include general considerations on a "high level", no additional topic experts or interested parties are needed at this time.

Timing

- Approval of Concept Paper by Steering Committee August 14 2014
- A full group work plan following the normal *Step 5* process will be provided to the SC upon adoption of the Concept Paper
- Begin teleconferences 3Q 2014
- Aim for *Step 2* 4Q 2015
- Aim for *Step 4* 4Q 2016