Final Concept Paper

S11: Nonclinical Safety Testing in Support of Development of Pediatric Medicines
dated 3 September 2014
Endorsed by the ICH Steering Committee on 10 November 2014

Type of Harmonisation Action Proposed

A new guideline on the nonclinical safety studies important to support a pediatric development program is proposed. This guideline is needed to recommend standards for the conditions under which nonclinical juvenile animal testing is considered informative and necessary to support pediatric clinical trials, and to provide guidance on the design of the studies. This will result in streamlined drug development and higher scientific rigor while minimising the unnecessary use of animals.
The following products would be excluded from the scope of the guideline: anticancer pharmaceuticals for serious and life threatening malignancies as defined in ICH S9, cellular therapies, gene therapies, therapeutic and preventative vaccines, and tissue-engineered products.

Statement of Perceived Problem

Conflicting recommendations on major aspects of the nonclinical development program that will support pediatric clinical trials arise among and within regulatory bodies, which makes defining a single nonclinical development plan that satisfies all regulatory regions challenging and can result in unnecessary delay in delivering safe medicines to pediatric patients. Variability also exists in the nonclinical plans proposed by the companies.

The ICH M3(R2) Guideline states, "The conduct of any juvenile animal toxicity studies should be considered only when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support pediatric studies." Criteria are needed to assist in interpreting this statement.

Specific problems include:

1. Lack of harmonised criteria for determining when all previous animal data and human safety date are considered insufficient to support pediatric studies.
2. Lack of harmonisation of specific aspects of design of the juvenile animal studies where it is determined that studies are appropriate.
3. No guidelines describe in detail the studies that need to be performed to support a pediatric only development with no indication in adults.

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Issues to be Resolved

The proposed guideline will provide clarity in determining the situations where non-clinical safety studies are important to support pediatric development. The expectation would be to develop a guideline that results in a clear, consistent and harmonised approach across all regions:

1. The guideline will discuss how previous animal data, including pharmacodynamics, and human safety data can be used to determine if additional animal data are recommended to support pediatric clinical trials.
2. The guideline may outline example scenarios in which additional juvenile animal data are needed to support pediatric clinical trials or scenarios in which additional animal data are not considered informative.
3. The guideline will address design aspects of juvenile animal studies; (for example, the need for toxicokinetic assessments and applicable approaches that can reduce animal use; i.e., microsampling).

It is proposed that the new guideline define criteria for judging the sufficiency of available data to support consistent interpretation and application across industry and regulatory authorities.

The topics that a working group would consider to determine the extent that nonclinical studies are informative for pediatric clinical trials will include, but are not limited to:

- A review of previous pediatric drug development programs with the intent of identifying the criteria used to decide when additional animal data were warranted;
- A review of results from completed juvenile animal toxicity studies to determine what unique findings were identified, and what impact those findings had on the risk assessment for pediatric populations;
- Role of pharmacology in predicting effects in pediatric patients;
- Structural and functional differences between juveniles and adults;
- Pharmacodynamic (receptors) and pharmacokinetic (metabolic enzymes, transporters) differences between juveniles and adults;
- The need for pharmacodynamic and pharmacokinetic (rather than toxicokinetic) juvenile animal studies.

Juvenile animal study design considerations including the dose selection considerations, species selection, developmental stage of animals in relation to pediatric population, administration route, duration of dosing, reversibility, toxicokinetics, the utility of data derived from using young animals in general toxicity studies and its impact (or need for separate juvenile studies), and specific assessment endpoints will be discussed in the guideline.

Any recommendations for timing will be in full alignment with ICH M3(R2). The guideline may elaborate on considerations that impact the conduct of juvenile animal studies such as the duration of the pediatric clinical trial, the therapeutic indication, age of the pediatric population, and available safety data from adult animal and human studies.

The guideline will also include recommendations for drugs in development for pediatric-only indications.

Background to the Proposal

Specific guidance on the need, study design, and/or timing of juvenile animal studies to support pediatric indications is addressed in regulatory guidelines from the ICH, EMA, FDA, and MHLW. The regional guidelines recommend a case-by-case approach for determining the need for a juvenile animal study after consideration of the available data (FDA, 2006; EMA, 2008; MHLW, 2012). The guidelines propose that the study design be "appropriate and scientifically justified", and options are described for both a targeted design and a modification of a repeat-dose general toxicity study or a pre- and postnatal developmental toxicity study. The ICH M3(R2) Guideline, which focuses on the need and, when warranted, the timing of juvenile animal studies, states, "The conduct of any juvenile animal toxicity studies should be considered only when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support pediatric studies. If a study is warranted, one relevant species, preferably rodent, is generally considered adequate." Given the presence of different guidelines, inconsistencies in interpretation and application have sometimes arisen.

Type of Expert Working Group

The Expert Working Group (EWG) will consist of two nonclinical experts nominated by EU, EFPIA, FDA, PhRMA, MHLW, JPMA, Health Canada and Swissmedic. One member can also be nominated by WHO Observer, as well as RHIs, DRAs/DoH (if requested).

Timeline

The request will be submitted to the ICH Steering Committee (SC) in September 2014 with the expectation of the EWG meeting face-to-face in November 2015. It is anticipated that a *Step 2b* Guideline will be completed by 2Q 2016 and that *Step 5* will be reached in 2018.