ICH harmonisation for better health

Step 2

ICH S11 - Nonclinical Safety Testing in Support of Development of Paediatric Medicines

Step 2 document – to be released for comments

October 12, 2018

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Background

- **This document has been signed off as a *Step 2* document (September, 2018) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper and a Business Plan (both approved November, 2014)**
- **Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: November 2019**

Concept Paper - 2014

- **Status quo: Several regional guidelines/guidances on nonclinical testing in support of development of pediatric guidances, no harmonised guideline**
- **Specific issues identified**
  - **Lack of harmonised criteria for determining when all previous animal data (juvenile and adult) and human safety date are considered sufficient to support paediatric clinical trials**
  - **Lack of harmonisation of the design of juvenile animal studies**
  - **No guidelines describe in detail the nonclinical studies that need to be conducted to support a paediatric-only development**

See also S11 Concept Paper:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S11/S11_Final_Concept_Paper_10_November_2014.pdf

Business Plan - 2014

- **What are the benefits to the key stakeholders of generating a new guideline?**
  - **Guideline will streamline the drug development**
  - **Unnecessary use of animals will be minimised (3Rs)**
  - **Guideline will provide a harmonised approach on the need and design of juvenile animal studies**
  - **Data from juvenile animal studies will be of higher quality and more informative to the safety of paediatric clinical trials**
- **Planned timeline was to reach *Step 2b* in 2016 - delayed due to complexity of issues**

See also S11 Business Plan:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S11/S11_Final_Business_Plan_10_November_2014.pdf

Gathering the underlying data

- **Collection and evaluation of existing nonclinical data for paediatric development (blinded data)**
  - industry survey from Japan, US and EU
  - EMA analysis of CNS and oncology drugs[1]
  - FDA analysis of all therapeutic areas
- **Comprehensive literature review**

[1] **oncology drugs are published on EMA website:**
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/excipients/general_content_001895.jsp&mid=WC0b01ac0580028e8e

Table of Contents

Section 1: Objectives and Scope

- **Objective: Support development of safe paediatric medicines, facilitate the conduct of paediatric clinical trials, and reduce the use of animals (3Rs principles)**
- **Scope**
  - Drugs intended for paediatric use
  - ICH S9 determines need for nonclinical information for paediatric anticancer pharmaceuticals, S11 provides study design considerations
  - Excluded: tissue-engineered products, gene and cellular therapies, and vaccines

Section 1: General principles

- **Paediatric patients are not small adults - they are a different population compared with adults.**
- **Understanding of the overall clinical development plan is needed to design an appropriate and efficient nonclinical program.**
- **Early consideration of nonclinical support for paediatric medicine development is recommended. Think about changing the design and/ or timing of the traditional nonclinical program → e.g. use of data from reproductive toxicity studies.**
- **Prior to each paediatric clinical trial: weight of evidence (WoE) evaluation should be conducted → would additional nonclinical investigations have added value?**

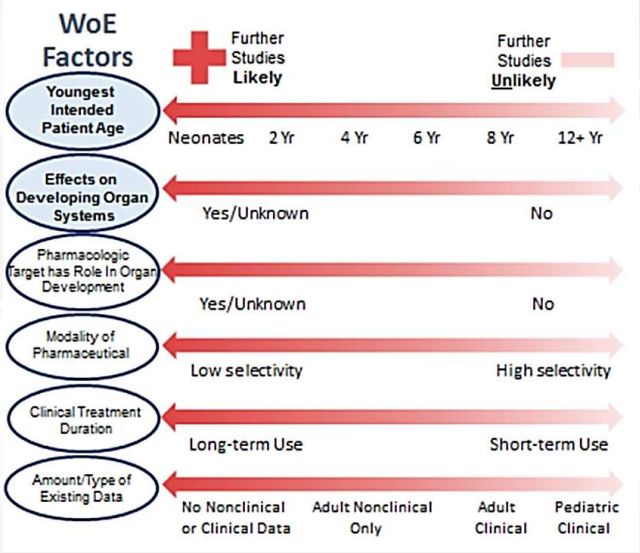
Section 2: Determining the need for additional nonclinical safety investigations

- **Weight of evidence (WoE) approach = integrated assessment**

Based on:

- **Clinical context: indication, intended paediatric age group, treatment regimen, and ability to clinically monitor and/or manage identified safety concerns**
- **Pharmacology and Pharmacokinetics (ADME)**
- **Existing nonclinical (*in vitro* and *in vivo* data) and clinical safety data**
- **Feasibility**

Application of the WoE approach



blue: most important factors
white: factors are not listed in order of weight
arrows indicate a gradient for the weight of each factor
(list is not complete, can be extended as desired)

Figure 1 of the Draft ICH S11

Section 3: Design of JAS (I)

- **Guideline recommends a customised JAS**
  - core endpoints to be evaluated in all studies
  - additional endpoints are added when needed to address identified safety concerns.
- **JAS design including all additional endpoints is not recommended without a rationale.**
- **Understanding the level of maturity and function of organ systems across species during their development is needed (see Appendix A)**
  - To design an appropriate JAS
  - For the translation of nonclinical toxicity findings to a specific human age range

Section 3: Design of JAS (II)

- **Dose-Range-Finding (DRF) studies**
- **Species selection - Appendix A: advantages/ disadvantages of species use in JAS**
- **Age of animals at dosing**
- **Off-treatment period: should be included to understand persistence, progression, reversibility or delayed onset of a specific effect**
- **Route of administration**
- **Dose selection: a dose-response relationship and a no-observed adverse effect level (NOAEL) should be established**

Section 3: Design of JAS (III)

- **Core endpoints: general standard for a JAS: mortality and clinical signs, growth (body weight + long bone length), food consumption, sexual development, clinical pathology (serum chemistry and haematology), anatomic pathology (gross pathology, organ weights, major organ histopathology), and toxicokinetics**
- **Additional endpoints: driven by identified safety concerns e.g. ophthalmologic examinations, CNS and reproductive assessments, expanded histopathology**
- **Allocation of animals to study groups – rodent examples provided in Appendix C**

Section 4: Paediatric-first/ Paediatric-only

- **Special criteria are described when drug will be administered to paediatric patients without any prior adult data: two JAS are recommended (rodent and non-rodent)**
- **Juvenile primate study to be conducted only in exceptional cases**
  - Alternative approaches (in vitro assays, genetically-modified animals, surrogate molecules) should be considered
  - Post-weaning juvenile NHP (9-12 months of age) when it is the only relevant species and needed for paediatric first/only
  - Pre-weaning NHP limited primarily to neonatal use when there are no alternatives

Section 5: Other considerations

- **Excipients**
  - **Separate studies generally not recommended, but safety should be assessed.**
- **Combination pharmaceuticals**
  - **Considerations similar to those for supporting combinations in adults.**
  - **Studies of combination only or of combination in an additional arm of a study of individual drug may be sufficient if warranted.**

Appendices

- **Appendix A**
  - Overview of age-dependent development of organ systems by species
  - Principle advantages and disadvantages of mammalian species for use in juvenile animal studies
- **Appendix B: Case studies applying the weight of evidence approach**
- **Appendix C: Example of an approach to rodent preweaning litter allocation**

Conclusions

- **Agreement on limited request for JAS (based on WoE)**
- **When needed, the JAS study design should contain core endpoints, with additional endpoints added to address identified safety concerns**

Contact

- **For any questions please contact the ICH Secretariat:**

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