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

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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 data 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:
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:

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
  ▪ FDA analysis of all therapeutic areas
• Comprehensive literature review

1 oncology drugs are published on EMA website:
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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**

### WoE Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Youngest Intended Patient Age</th>
<th>Effects on Developing Organ Systems</th>
<th>Pharmacologic Target Has Role in Organ Development</th>
<th>Modality of Pharmaceutical</th>
<th>Clinical Treatment Duration</th>
<th>Amount/Type of Existing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neonates 2 yr</td>
<td>4 yr</td>
<td>6 yr</td>
<td>8 yr</td>
<td>12+ yr</td>
<td>Yes/Unknown</td>
</tr>
<tr>
<td></td>
<td>Long-term Use</td>
<td>Short-term Use</td>
<td>No Nonclinical or Clinical Data</td>
<td>Adult Nonclinical Only</td>
<td>Adult Clinical</td>
<td>Pediatric Clinical</td>
</tr>
</tbody>
</table>

- 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

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**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
  o Alternative approaches (in vitro assays, genetically-modified animals, surrogate molecules) should be considered
  o Post-weaning juvenile NHP (9-12 months of age) when it is the only relevant species and needed for paediatric first/only
  o Pre-weaning NHP limited primarily to neonatal use when there are no alternatives

Section 5: Other considerations

• Excipients
  o Separate studies generally not recommended, but safety should be assessed.

• Combination pharmaceuticals
  o Considerations similar to those for supporting combinations in adults.
  o 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
  o Overview of age-dependent development of organ systems by species
  o 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

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