#4_S11

Title	**S11: Nonclinical Paediatric Safety** **소아용의약품 개발지원을 위한 비임상 안전성 시험**
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Bio	About 17 years of experience for new drug discovery and development of small molecule new chemical entities with expertise for pharmacology, toxicology (GLP tox) and R&D strategy in JW Pharmaceutical. Currently, I'm in charge of open innovation and research funding as a leader of research innovation group in JW Holdings.
	17년간 JW중외제약에서 저분자 화합물 기반 신약 연구 개발 업무를 담당하고 있으며, 비임상 효능 평가, 비임상 독성 평가 (GLP tox) 및 연구 기획 등의 업무를 수행했습니다. 현재는 Research Innovation실 리더로 오픈 이노베이션 연구 및 연구 투자 관련 업무를 맡고 있습니다.
Summary	In order to support preclinical safety study of paediatric pharmaceuticals, it will be explained the information and examples of ICH S11 guideline (adopted on 14 April 2020).
	소아용 의약품 개발 비임상 안전성 시험을 위해 새롭게 개정된 ICH 가이드라인 (S11)의 주요 내용과 사례를 설명한다.

소아용의약품 개발지원을 위한 비임상 안전성 시험

[Preclinical Safety Study of Paediatric Pharmaceuticals]

2020. 11. 05

차주영

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ICH S11 Guideline (Adopted on 14 April 2020)

NONCLINICAL SAFETY TESTING IN SUPPORT OF DEVELOPMENT OF PAEDIATRIC PHARMACEUTICALS

❖ Document History

Code	History	Date
S11	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation (document dated 9 July 2018).	18 September 2018
S11	Adopted by the Regulatory Members of the ICH Assembly under *Step 4* (document dated 10 March 2020).	14 April 2020

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Table of Contents: ICH S11 Guideline

1. Introduction

1.1 Objectives

- To recommend international standards for, and promote harmonization of, the **nonclinical safety assessments** to support the **development of pharmaceuticals intended for paediatric use**

1.2 Background

1.3 Scope

- **Small molecule therapeutics and biotechnology-derived pharmaceuticals** as defined in ICH S6 are within the scope of this guideline
- **Tissue engineered products, gene, cellular therapies, vaccines are excluded** (dedicated juvenile animal safety studies are generally not warranted for such products)

1. Introduction

1.4 General

- **Paediatric patients**
  - **Immaturity of organ systems** and maturation of systems during drug treatment can **affect drug pharmacokinetics (PK), pharmacodynamics (PD), and/or off-target effects of pharmaceuticals, potentially leading to differences in safety and/or efficacy profiles.**
- **An early consideration of nonclinical support for paediatric pharmaceutical development is recommended.**
  - **Changing the design and/or timing of the traditional nonclinical program** is one way to address potential safety concerns for the paediatric patient.
  - For example, **dosing can be initiated at a younger age in a repeated-dose toxicity study** to support the corresponding developmental stages in paediatric patients.
  - Another approach could be to conduct the **Pre- and Postnatal Development (PPND) study earlier than the normal drug development paradigm.**

2. Consideration for additional nonclinical safety investigations

2.1 Clinical context

- The paediatric clinical development plan for a pharmaceutical (cf. ICH E11 guideline)
- The clinical development of a pharmaceutical for paediatric patients usually follows initial adult clinical studies but can occur in parallel or can be conducted without any adult clinical studies
- Whether **additional nonclinical investigations** are advisable, and their design and timing, will **depend on the identified safety concerns** and **the intended paediatric clinical use**.

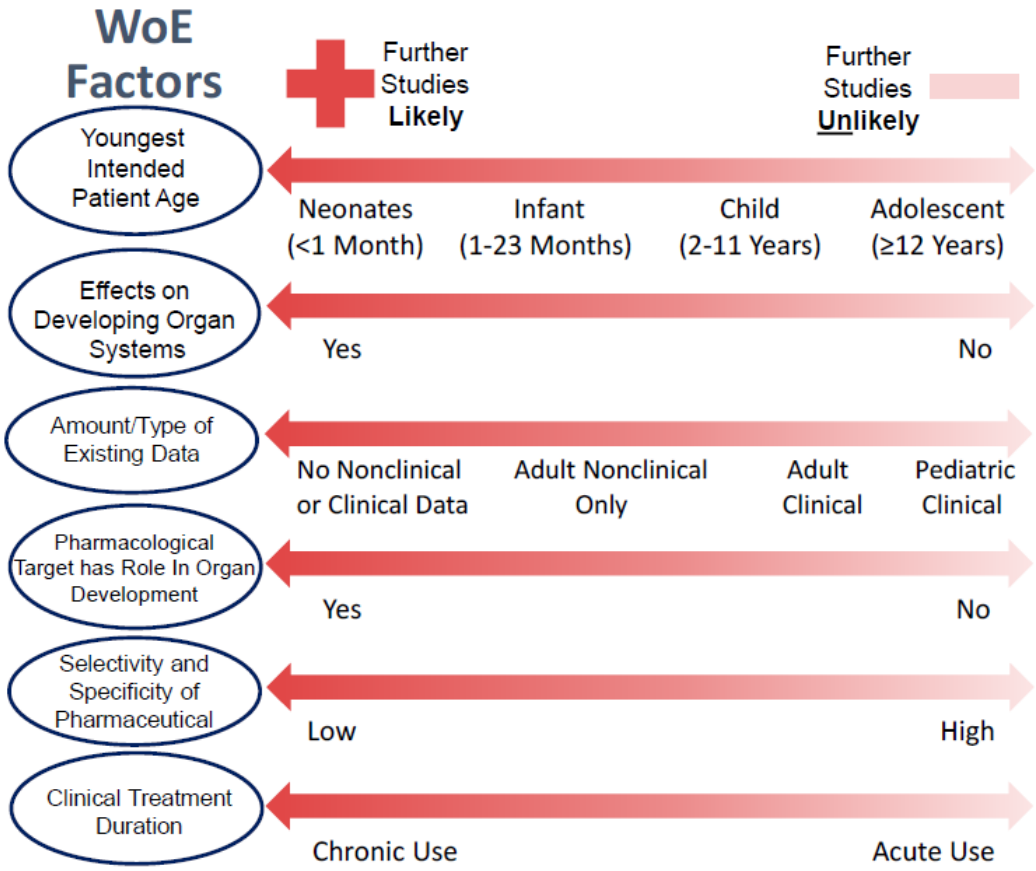
2.2 Weight of evidence approach

- The nonclinical development plan for a paediatric pharmaceutical depends on an **integrated assessment based on the totality of the evidence**, including the **clinical context** together with the **pharmacology, pharmacokinetic (ADME), and nonclinical in vitro and in vivo animal, and clinical safety data (adult and/or paediatric).**
- A WoE approach considers **multiple factors evaluated together** and, therefore, a single factor should not be considered in isolation.

2. Consideration for additional nonclinical safety investigations

- Key WoE factors to be considered for determination of nonclinical study

- The most important factors that should be highly weighted are the **youngest intended patient age** and whether there are **suspected adverse effects on developing organ systems** of the patients during the conduct of the paediatric trial.



2. Consideration for additional nonclinical safety investigations

2.3 Considerations to Inform the Weight of Evidence Evaluation

- **Clinical Information** ←→ WoE Factors: Youngest Intended Patient Age; Amount/Type of Existing Data; Clinical Treatment Duration
- **Pharmacological Properties** ←→ WoE Factors: Effects on Developing Organ Systems; Pharmacological Target has Role in Organ Development; Selectivity and Specificity
- **Pharmacokinetic Data** ←→ WoE Factors: Amount/Type of Existing Data
- **Nonclinical Safety Data** ←→ WoE Factors: Effects on Developing Organ Systems; Amount/Type of Existing Data

2.4 Application and Outcome of the Weight of Evidence Evaluation

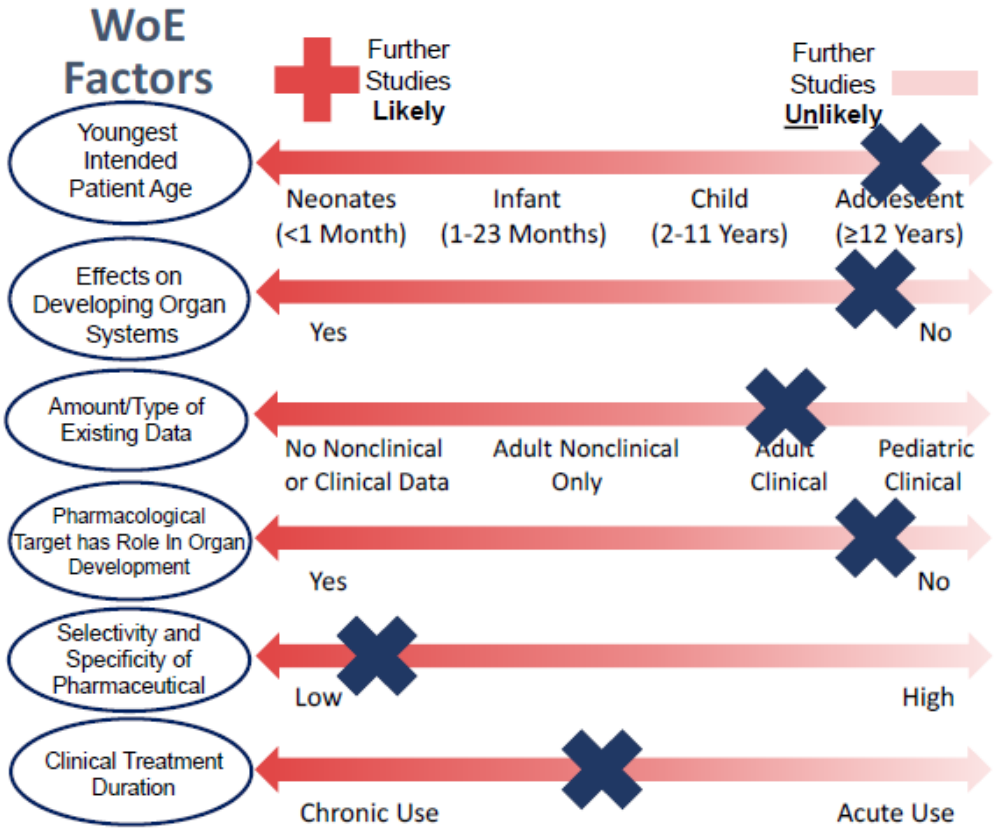
- The WoE approach should be applied to **determine whether additional nonclinical investigations are warranted**, with emphasis on the factors considered most important to inform the clinical risk assessment.
- **For a JAS, the study objectives should be aligned with the WoE outcome** and the intended paediatric use. This is essential to appropriately design and customize the JAS with regard to the treatment period and endpoints to be included.

2. Consideration for additional nonclinical safety investigations

Case Study #1. Applying The Weight of Evidence Approach

- Small molecule
- Known pharmacology
- Available adult clinical and nonclinical data including repeated-dose toxicity.
- None of these data suggest a safety concern in a developing organ for the intended paediatric population of adolescents (12 years and above) for a one-month duration of clinical treatment.

➔ The WoE analysis indicates that additional nonclinical investigations will **not contribute useful information.**

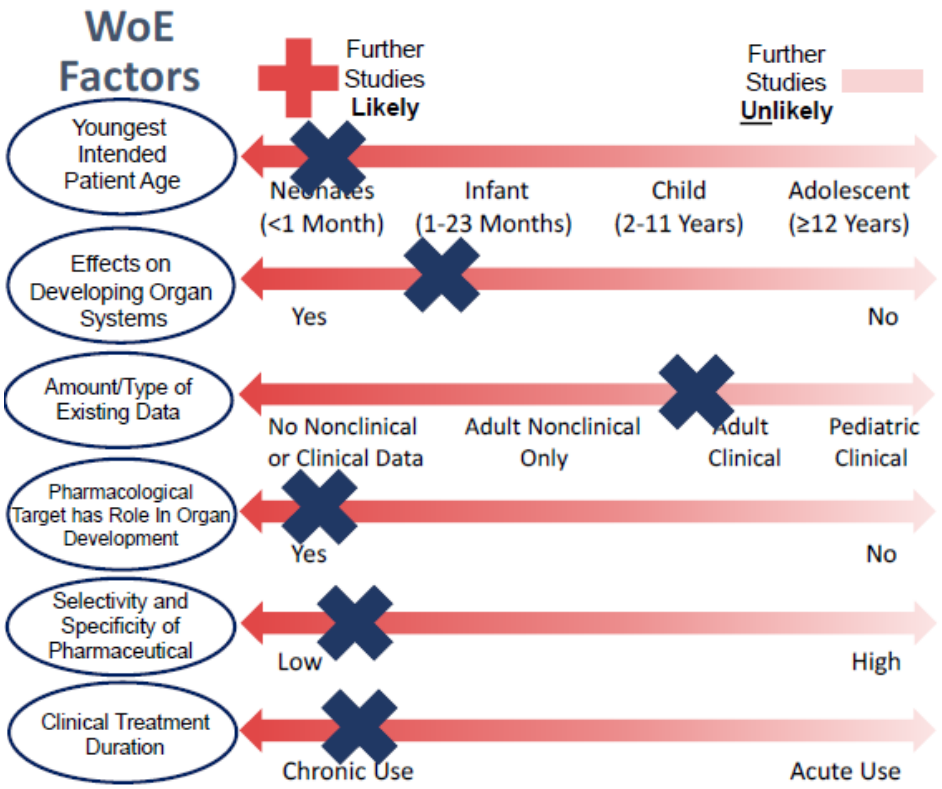


2. Consideration for additional nonclinical safety investigations

Case Study #2. Applying The Weight of Evidence Approach

- Small molecule
- Novel mode of action
- Intended for chronic use starting in neonates or infants
- Limited Phase 1 clinical and nonclinical safety data
- No significant safety concerns identified
- There are potential effects on developing organ systems based on the pharmacology

➔ The WoE analysis indicates **further nonclinical investigation**, such as a **JAS with additional endpoints based on the targeted developing organ systems**, would be useful.

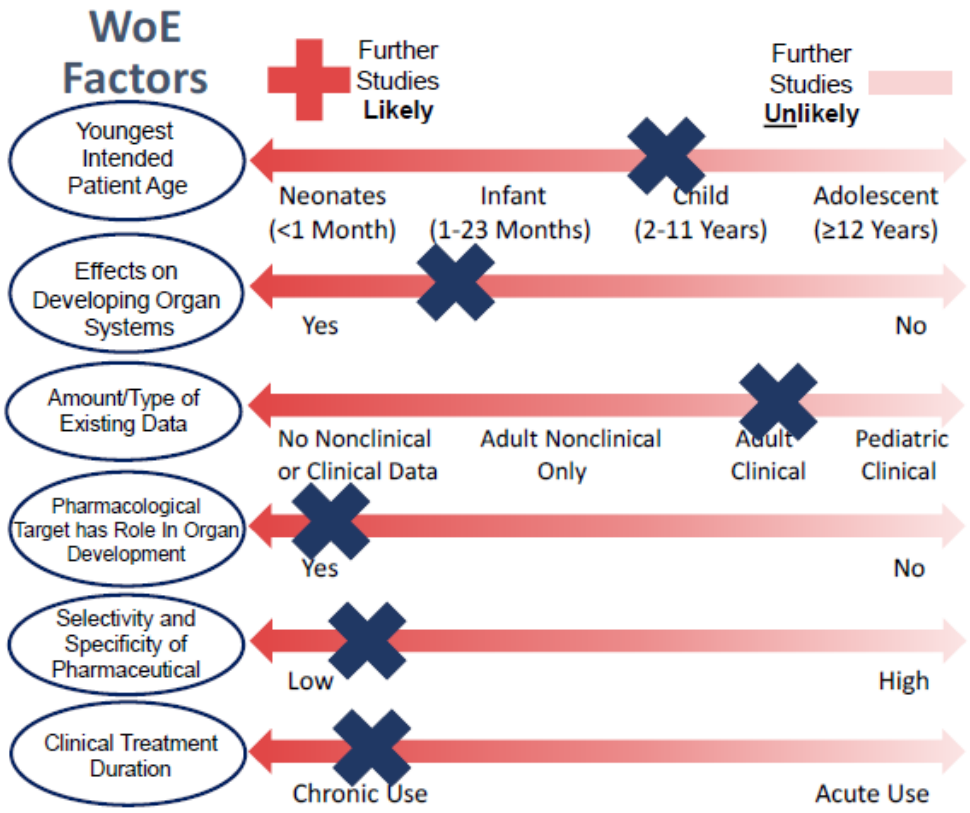


2. Consideration for additional nonclinical safety investigations

Case Study #3. Applying The Weight of Evidence Approach

- Small molecule
- Pharmacological target has a critical role in CNS development
- Intended for chronic use in children (6 years and above)
- Nonclinical and adult clinical data are available
- The concern for a potential effect on the developing CNS cannot be addressed clinically by monitoring and management

➔ The WoE analysis warrants a **postweaning JAS design that includes core endpoints and additional CNS endpoints** to address the specific concern.

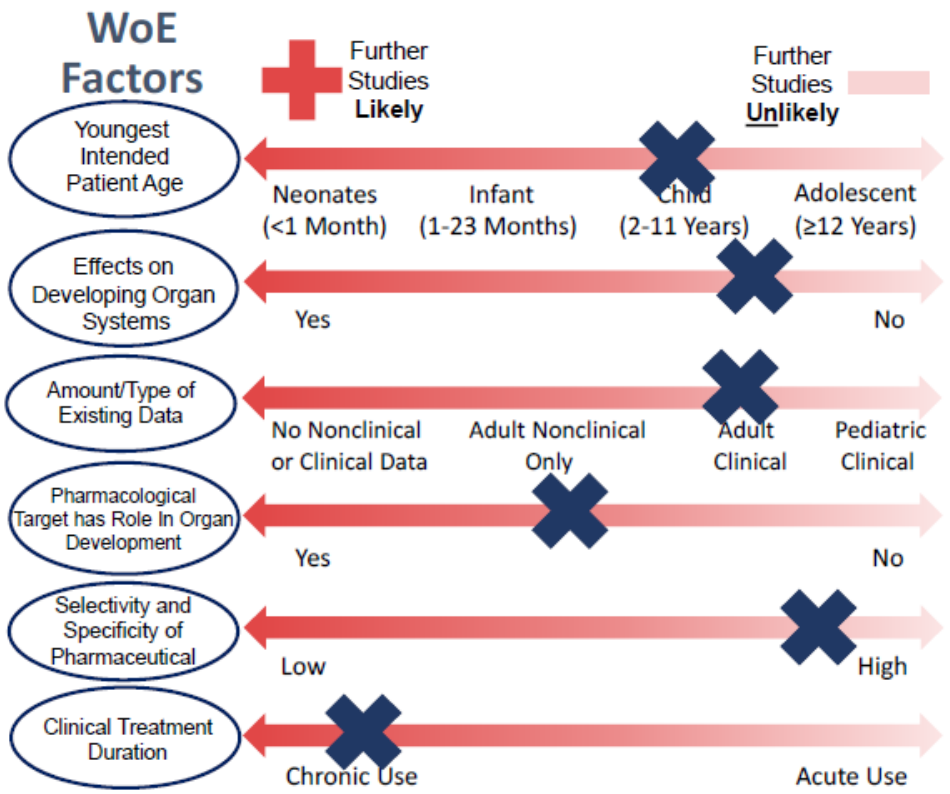


2. Consideration for additional nonclinical safety investigations

Case Study #4. Applying The Weight of Evidence Approach

- Monoclonal antibody
- Targets a soluble cytokine
- Intended for chronic paediatric use in rheumatologic and allergic diseases (>2 years old)
- Reversible decreased serum Ig and occasional injection site reactions in both animals and adult patients
- In a monkey ePPND study, offspring exposure was comparable to dams through PND28 and decreased thereafter.
- T-cell-dependent antibody response (TDAR) results were similar to controls (between 3-6 months postnatally).

➔ The WoE analysis **does not warrant a JAS**.



3. Design of Nonclinical Juvenile Animal Studies (JAS)

3.1 General Consideration

- **Understanding the relative level of maturity and function across species during development is needed** not only to design the appropriate JAS but also to aid the **translation of nonclinical toxicity findings to human age categories**
- **Comparison of development across species can be challenging** and is **not uniform across different organ systems**

[Overview of Age-Dependent Development of Organ Systems]

Human	Neonate	1st Solid Food	Weaning	Puberty	Adulthood
Rat	~ PND 1-10	~ PND 15	~ PND 21-25	Male: ~ PND 42 Female: ~PND 35	~ PND 70
Dog	< 3 weeks	~ 3 weeks	~ 8 weeks	Male: ~ 5-8 months Female: ~ 6-12 months	> 12 months
Minipig	< 2 weeks	~ 2-3 weeks	~4-6 weeks	~ 4-6 months	> ~ 6 months
Cynomolgus Monkey	< 1 month	~ 3 months	~ 6 months	~ 3-4 years	~ 4 years

3. Design of Nonclinical Juvenile Animal Studies (JAS)

3.2 Dose Range-Finding Studies

- A **DRF study with small group sizes of juvenile animals is recommended** to assess tolerability in relation to exposure and age.
- This is particularly valuable to design a definitive JAS when dosing starts prior to weaning **to avoid unexpected mortality or excessive toxicity**, often due to irrelevant exposures.

3.3 Animal test system selection

- When a JAS is warranted, in most cases a **single species is considered sufficient**.
- In principle, the **same species as used in adult repeated-dose studies** should initially be considered as the species for a JAS, **preferably a rodent**.
- The following factors should be considered when selecting a relevant species:
  - An **understanding of the ontogeny of the pharmacological or toxicological target** (e.g., the receptor) in animals
  - **Preference for a species and strain** for which adult repeated-dose toxicity data are available to facilitate a comparison of the toxicity and systemic exposure profiles
  - **Toxicological target organs**
  - **Similarity to human ADME** characteristics
  - The **technical/practical feasibility to conduct the study** in the selected species

3. Design of Nonclinical Juvenile Animal Studies (JAS)

3.4 Age of animals, dosing period, dosing regimen

- **Age**

  : Correspond to the youngest intended patient age, depend on **human-to animal comparison of developmental period of organ systems**

- **Dosing period**

  : **Not directly related to the clinical treatment duration**

  : **Consider the paediatric age range and the shorter developmental period of animals** compared to humans, the safety concern for the intended paediatric population, and the relevant period of organ development for the target organ of concern

  : **Dosing in a JAS should usually occur during the critical and active periods of growth and development** (ex. kidney target agent → focusing on the relevant period of renal development irrespective the clinical treatment duration)

- **Dosing regimen**

  : **May not be exactly the same as in the clinic**

  : For example, even though a clinical regimen is once a week, more frequent dosing in juvenile animals might be more appropriate

  : If drug accumulation is a concern in juvenile animals, dosing could be less frequent than in adult toxicity studies

3. Design of Nonclinical Juvenile Animal Studies (JAS)

3.5 Post-treatment period assessments

- Purpose 1. Whether any effects observed during treatment are reversible, persistent, or progressive
- Purpose 2. Whether any effects emerge later in development as a result of early life exposure (i.e., delayed onset).

3.6 Route of administration

- **Intended clinical route**, obtaining adequate systemic exposure

3.7 Dose selection

- To **establish a dose-response relationship** for adverse effects + to **determine a NOAEL**
- Dose levels should be selected to achieve some **overlap in the range of exposure in adult animals to enable comparison of effects between young and adult animals**
- High dose should not result in marked toxicity that can confound the growth and development endpoints and complicate the assessment
- **At least one dose** should result in **exposure levels similar to** the anticipated exposure in the **intended clinical population if tolerable**
- For small molecules, selection of the high dose in accordance with ICH M3 applies
- For biotechnology-derived products, the principles for dose selection described in ICH S6 apply

3. Design of Nonclinical Juvenile Animal Studies (JAS)

3.8 Endpoints

- **Core endpoints**
  - Mortality and clinical observation
  - Growth (BW and long bone length)
  - Food consumption
  - Sexual development
  - Clinical pathology
  - Anatomic pathology
  - Toxicokinetics
- **Additional endpoints**
  - Other growth endpoints (body length, withers height)
  - Bone assessment
  - Additional clinical pathology
  - Ophthalmology
  - CNS assessments
  - Reproductive assessments, immunologic assessments

4. Consideration for Paediatric-First/Only Development

- **Paediatric patients are treated without any prior adult patient or healthy volunteer data**
  - The FIH trial would be in paediatric patients
  - Conduct JAS both in a rodent and non-rodent species
  - Safety pharmacology and genotoxicity testing would be conducted for adult use
- **Pharmaceutical is intended to treat a chronic paediatric disease**
  - Chronic toxicity studies should be conducted in rodent and non-rodent species
  - In at least one of these studies, dosing should start at an age developmentally matched to the lowest age of the intended patient population
  - Reproductive toxicity and carcinogenic potential can be warranted
- **Biopharmaceuticals which are warranted juvenile animals studies**
  - As per ICH S6, limited to relevant species
  - Non-invasive safety pharmacology endpoints can be included in the juvenile or standard NHP repeated-dose studies
  - Genotoxic and carcinogenic potential should be addressed

5. Data Interpretation

5.1 Considerations for endpoint interpretation

- Many observations in a JAS are **age, sex and species/strain dependent**, **Age-matched concurrent control data** are critical for interpretation.
- Appropriate **historical control data or reference materials** (e.g., tissue database or atlas) can also be helpful to interpret results
- In necropsy, **evaluation of long bone length in conjunction with body weight, and food intake** if available. Differentiate between potential **direct effects on skeletal development** or **indirect effects** (secondary to toxicity causing malnutrition and body weight loss/decrease) on long bone length
- Assessment of **organ weight data and the onset of sexual development** should be performed in the context of growth. Organ weight changes are not always proportional to body weight changes because some organs grow at different rates throughout development. Additionally, organs have different sensitivity to growth effects

5. Data Interpretation

5.2 Overall Interpretation

- An **integrated assessment** should be made across all appropriate studies, **comparing available findings in juvenile and adult animals, and evaluating clinical relevance**
- **Relevant findings in juvenile animals not observed in adults should be discussed**, as well as any **marked differences in sensitivity compared to adults**
- The **overall interpretation** of relevant findings should consider **the type, severity and recovery of the effects, the age of the animals and the exposures** and/or doses at which any effects were observed

6. Other Considerations

6.1 Excipients

- Pharmaceutical formulations occasionally contain excipients for which only limited experience exists in paediatric populations.
- To assess the safety of the excipients in a paediatric clinical formulation, available information on the excipients should be evaluated (WoE).
- If there are **insufficient data to support the use of the excipient in the intended paediatric population**, further safety evaluation can be warranted, for example, an **additional group evaluating the excipient alone in a JAS**.

6.2 Combination Pharmaceuticals

- The development of combination pharmaceuticals for paediatric use should have a nonclinical evaluation consistent with the principles outlined in ICH M3 for combination products in general, together with the WoE principles.
- Consequently, a **JAS of a combination pharmaceutical should be considered only if previous human and animal data are determined to be insufficient to support paediatric development, and the WoE evaluation** suggests that a JAS would address identified concerns.

Appendices

3. Design of Nonclinical Juvenile Animal Studies (JAS)

[Advantages and disadvantages of various mammalian species for use in JAS]

Species	Advantages	Disadvantages
Rat	• **Well-studied species, extensive historical control data** • Several **consistent developmental milestones** (general growth, preputial separation/vaginal opening, puberty) • Compressed development (~10 weeks) • Easy to obtain many pups with the same postnatal stage • Passive immunity present at birth	• Small body size, high metabolic rate and rapid growth • **Several organ systems are less developed at birth relative to man** (particularly CNS, lung, kidney, GI tract and immune system) • ADME characteristics of oral pharmaceuticals given in the preweaning phase often translate poorly to humans due to immaturity of the GI tract • Potential impact of immunogenicity
Mouse	• Similar to those of the rat, but **postnatal development occurs faster** • Broad CYP enzymes; metabolism can be more relevant • Mice have a gall bladder (unlike rats) • **Many genetic modification models available (targeted therapy)**	• Similar to rat, additionally: • Small pup size allows fewer manipulations /administrations than rat from early on • **Less historical background information than the rat**

3. Design of Nonclinical Juvenile Animal Studies (JAS)

[Advantages and disadvantages of various mammalian species for use in JAS]

Species	Advantages	Disadvantages
Dog	• Relatively large at birth / Relatively easy to handle • **Postnatal development of several organ systems reasonably comparable to that of human infants** (cardiovascular, pulmonary, immune system) • CNS maturation relatively well characterised, with defined critical window for learning/cognitive development	• **Protracted development** (~5-12 months to sexual maturity, 12-18 months to skeletal maturity) with interindividual variability in growth and developmental milestones • Variable litter sizes and sex distribution can make it difficult to populate study with minimal bias (genetic/litter, sex distribution) across groups • Limited historical background data, especially for nonstandard endpoints
NHP	• **Many similar developmental milestones as humans** • Neonates/infants similar to human for GI tract, immune system, cardiovascular, renal and special sense (eye, ear) development • Extensive reference and historical background data from birth available • Maternal transfer of immunoglobulin is similar to humans, so infants are born with passive immunity (serum IgG) • Often the most pharmacologically relevant animal model for highly targeted therapies	• **Protracted development** (~3-6 years for sexual maturity, ~5-8 years for skeletal maturity in macaques) makes an extensive juvenile study to cover all developmental phases impractical • Offspring highly dependent on maternal care over first month (minimal procedural intervention recommended; preweaning manipulation & dosing feasible with risk of maternal rejection), and are cohoused with dam for first 3-6 months; with shipping and quarantine requirements it is rarely feasible to initiate studies in juvenile monkeys < 9 months of age • Cannot synchronise breeding (supply & study start over weeks or months for seasonal breeders such as rhesus) • **Ethical reservations (strong rationale to justify use of juvenile NHP)**

3. Design of Nonclinical Juvenile Animal Studies (JAS)