Industry Experience with Juvenile Animal Studies

Dr. Susan Laffan, Senior Director, Translational Safety and Risk Sciences, Amgen

Workshop: Pediatric Developmental Safety Assessment and New Approach Methodologies

05 Dec 2025

AMGEN

Agenda - Industry Experience with Juvenile Animal Studies

01	Industry Perspective of Regulatory Environment
02	ICH S11 Guidance for Juvenile Animal Studies
03	Industry Use of NAMs for Safety Assessment
04	Take Home Messages

Shared Goal: Efficient Global Pediatric Development

- **Industry Perspective : Deliver a single global pediatric development plan**
  - Not always possible to achieve a single program globally
  - Discussions should look to incorporate known needs for all regions
  - Can request FDA and EMA attend PSP or PIP discussions, respectively
  - Can submit any relevant meeting minutes/advise letters from other regulatory bodies

- **Key Legislation & Regulatory Guidance**
  - EU & US – Both require approval of pediatric development plans which include nonclinical and clinical elements and are binding agreements.
  - ICH (International Conference on Harmonisation)
    - ICH E11 & S11 Guidances
  - WHO (World Health Organisation)
    - "Make Medicines Child Size"

ICH harmonisation for better health

FDA U.S. Food and Drug Administration

World Health Organization

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Pmda JAPAN

Industry Approach to Deciding if Juvenile Animal Study is Warranted

The First Step: Defining the pediatric **clinical** plan

- Contrast the regulatory expectations on timing
- Waivers and deferrals for pediatric programs – age cut off
- ICH E11- implemented in 2000 and revised in 2018

Case-by-Case

The Second Step: Defining the pediatric **non**clinical plan

- ICH S11 – finalized in 2020
- Weight of evidence (WOE) approach for decision whether a JAS is warranted

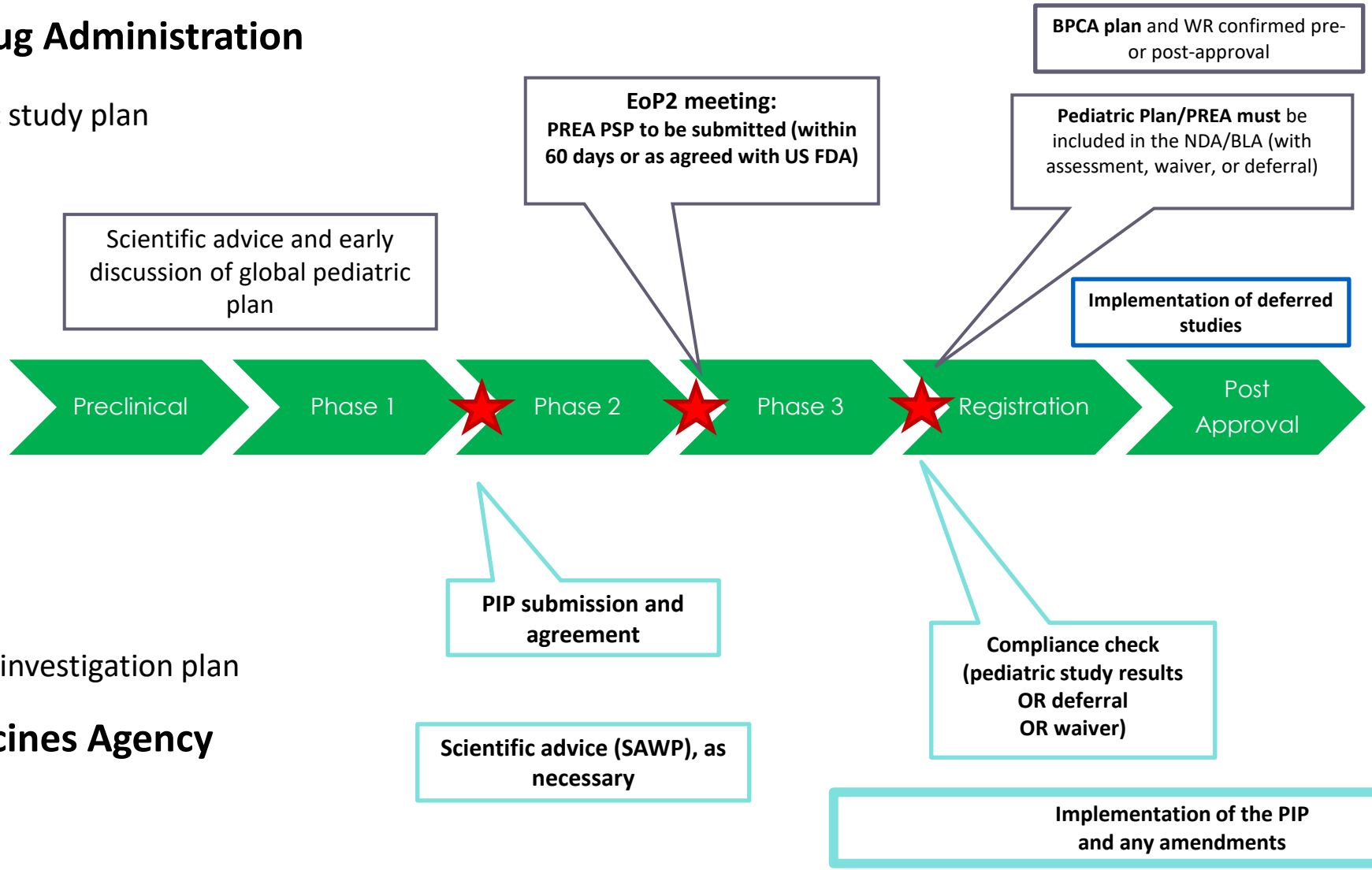
The Third Step: Obtain Global Heath Authority **Agreement** on Pediatric Plan

- Long processes that are not harmonized for content, timing nor feedback
- Structure and contents of regulatory dossiers for
  - FDA's pediatric study plans (PSPs)
  - EMA's peadiatric investigative plans (PIPs)
- Recommend to project teams to delay initiation of any dose range JAS study until received regulatory feedback from EMA and/or FDA on timing & study design

Timing of Interactions with Heath Authorities for Pediatric Plans

US Food and Drug Administration

PSP pediatric study plan



PIP peadiatric investigation plan

European Medicines Agency

US FDA – Timeline for PSP: 4 milestones

End of Phase 2 meeting

Within 60 days*

1 Submission of Initial Pediatric Study Plan (iPSP)

Within 90 days

PeRC review

2 FDA Meeting or Comments received

Company responds to FDA's Comments

Within 90 days

3 Submission of Agreed Pediatric Study Plan (AIPSP)

Within 30 days

4 FDA acknowledges AIPSP

FDA or Company can request amendment to the plan at any time.

All significant changes to the AIPSP must go through the same process as the IPSP.

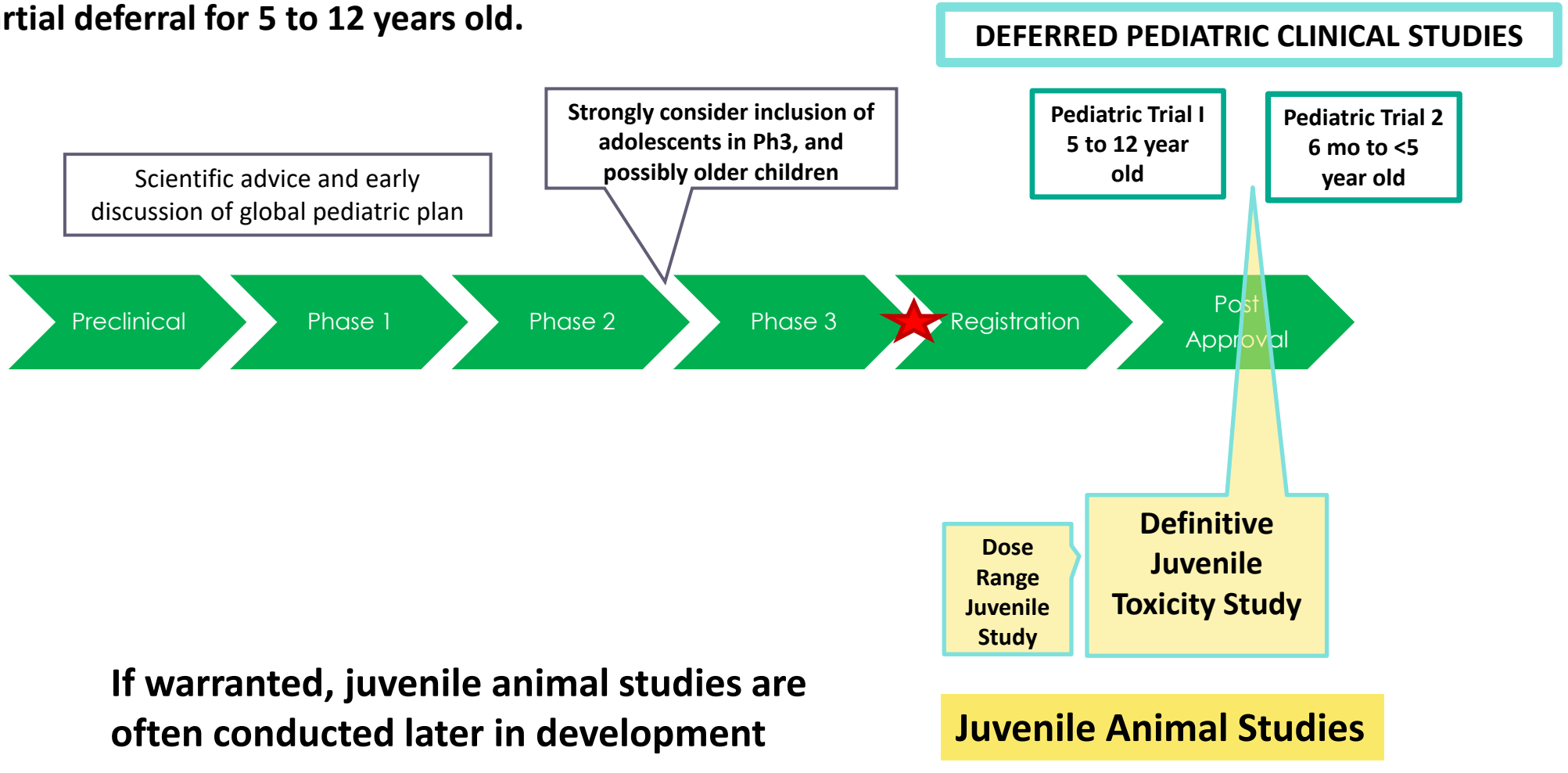
PeRC

** or as negotiated*

PSP Total Time from industry experience = ~ 9 months

An Example of Timing of Pediatric Plans Aligned with Adult Indication

This case has a waiver for under six months old, and partial deferral for 5 to 12 years old.



If warranted, juvenile animal studies are often conducted later in development

ICH S11 Guidance for Nonclinical Development for Safety

AMGEN

ICH E11: "Clinical Investigation of Medicinal Products in the Pediatric Population"

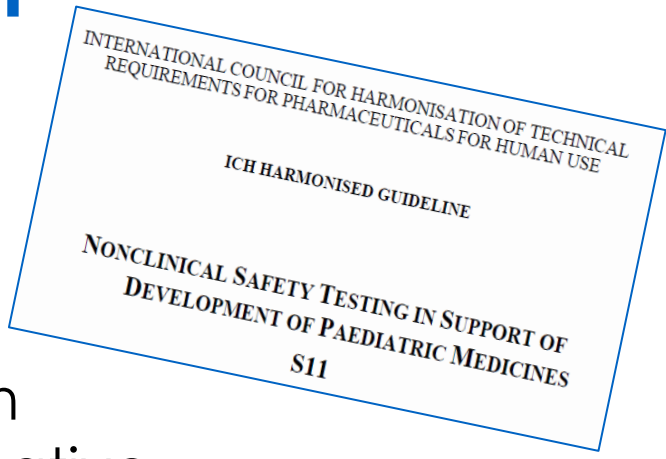
This key pediatric Guideline is important because it sets the age ranges that the majority of worldwide pediatric studies follow; it was implemented in 2000 and revised in 2018.

It covers:

- Ethical issues, pediatric formulations, timings of and types of studies
- Age classifications:
  - **Preterm newborn infants**
  - **Term newborn infants (0 to 27 days)**
  - **Infants and toddlers (28 days to 23 months)**
  - **Children (2 to 11 years)**
  - **Adolescents (12 to 17 years)**

S. Laffan

ICH S11: Nonclinical Safety Testing in Support of Development of Pediatric Medicines


INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

NONCLINICAL SAFETY TESTING IN SUPPORT OF DEVELOPMENT OF PAEDIATRIC MEDICINES

S11

- **Objectives**
  - Recommend standards for the conditions under which nonclinical juvenile animal testing is considered informative and necessary to support pediatric clinical trials
  - Provide guidance on the design of the studies

- **Scope**
  - The following products are out of scope: anticancer pharmaceuticals for serious and life-threatening malignancies as defined in ICH S9, cellular therapies, gene therapies, vaccines, and tissue-engineered products

10

Internal Use Only General and Administrative

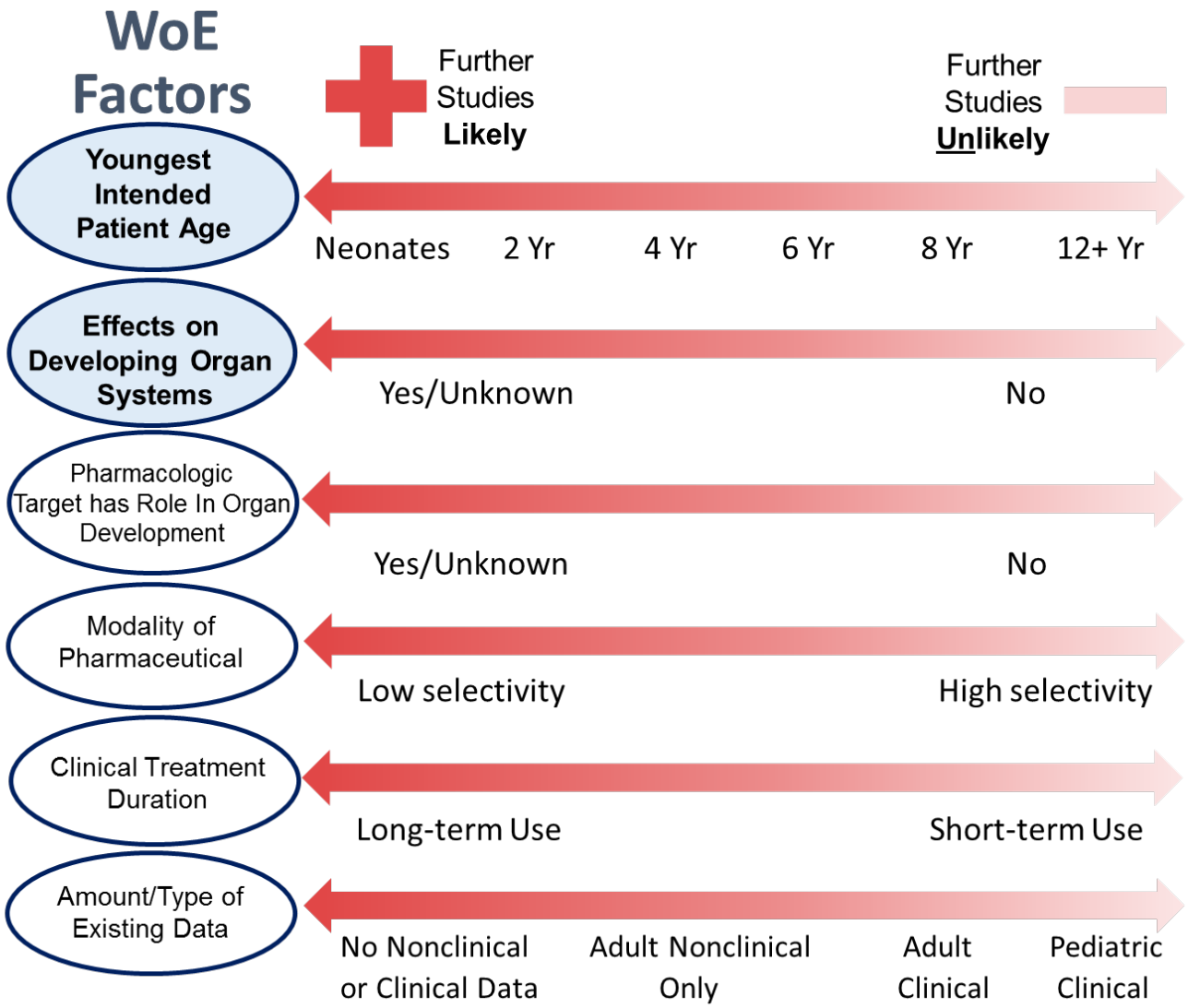
AMGEN

Figure 1 of the ICH S11: Weight of Evidence 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)



11

Internal Use Only General and Administrative

Recent Review of Juvenile Animal Studies by EMA

frontiers

From Guideline to Practice: Three Years of ICH S11 Insights and Recommendations

Diana Tavares[1†], Hsiao-Tzu Chien[2, 3†], Maria Elzbieta Sheean[1], Peter Theunissen[2, 3], Peter van Meer[2, 3, 4 ¤], Karen Van Malderen[5¤*].

[1] Paediatric Medicines Office, European Medicines Agency, The Netherlands.

[2] Medicines Evaluation Board, The Netherlands.

[3] Radboud University Medical Center, Nijmegen, the Netherlands.

[4] Department of Pharmaceutics, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands.

[5] Federal Agency for Medicines and Health Products, Belgium.

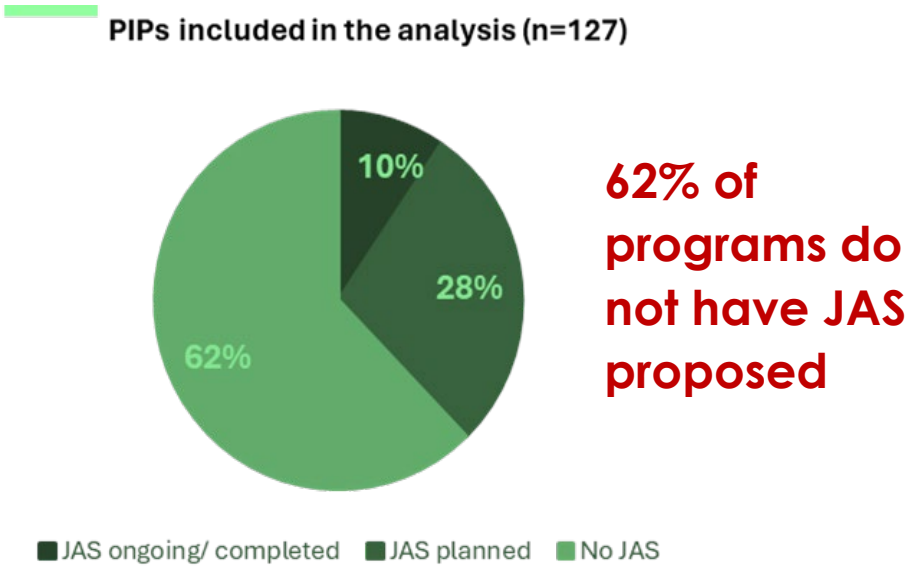
*** Correspondence:**
Karen Van Malderen,
karen.vanmalderen@fagg-afmps.be

Keywords: ICH S11, weight-of-evidence approach, juvenile animal study, paediatric investigations plans, 3Rs, EMA

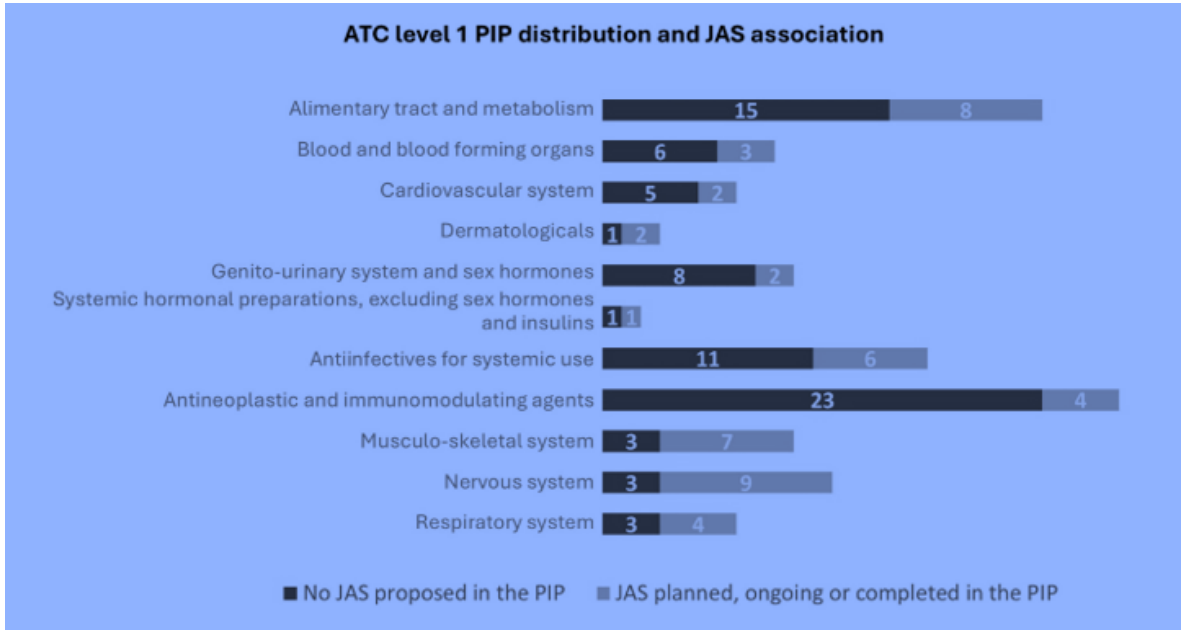
2025

Called for further alignment in **regulatory harmonization** between ICH regions

https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.1537001/full



62% of programs do not have JAS proposed



"Typical" Juvenile Animal Study Designs

customized to the medicine

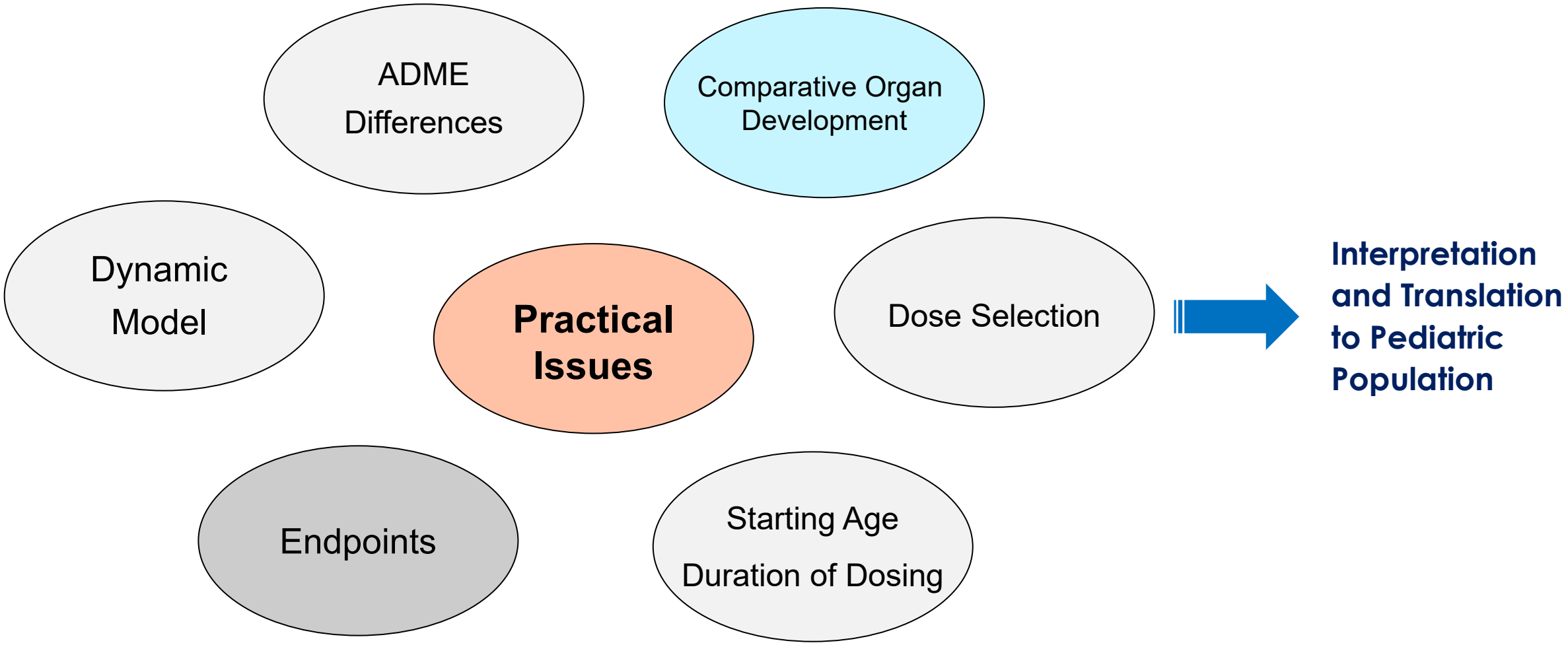
There is NO default design.

- **One species** (rat is most common by far)
- **Age of animals at dosing:** Should developmentally correspond to youngest patient age and will depend on a human-to-animal comparison of developmental periods of organ system(s) of concern
  - Dosing typically starts during preweaning period
- **Dosing duration:** Consider safety concern and relevant period of organ development, dosing during critical and active periods of growth/development. In contrast to ICH M3, not always directly related to clinical treatment duration.
- **Endpoints:** Core battery, plus those with scientific justification
- **Dose-range finding:** Highly recommended, may inform on the need for dose adjustment during the course of a the definitive study
- **Toxicokinetics** assessments included

Internal Use Only General and Administrative

AMGEN

Juvenile Animal Study Design Considerations

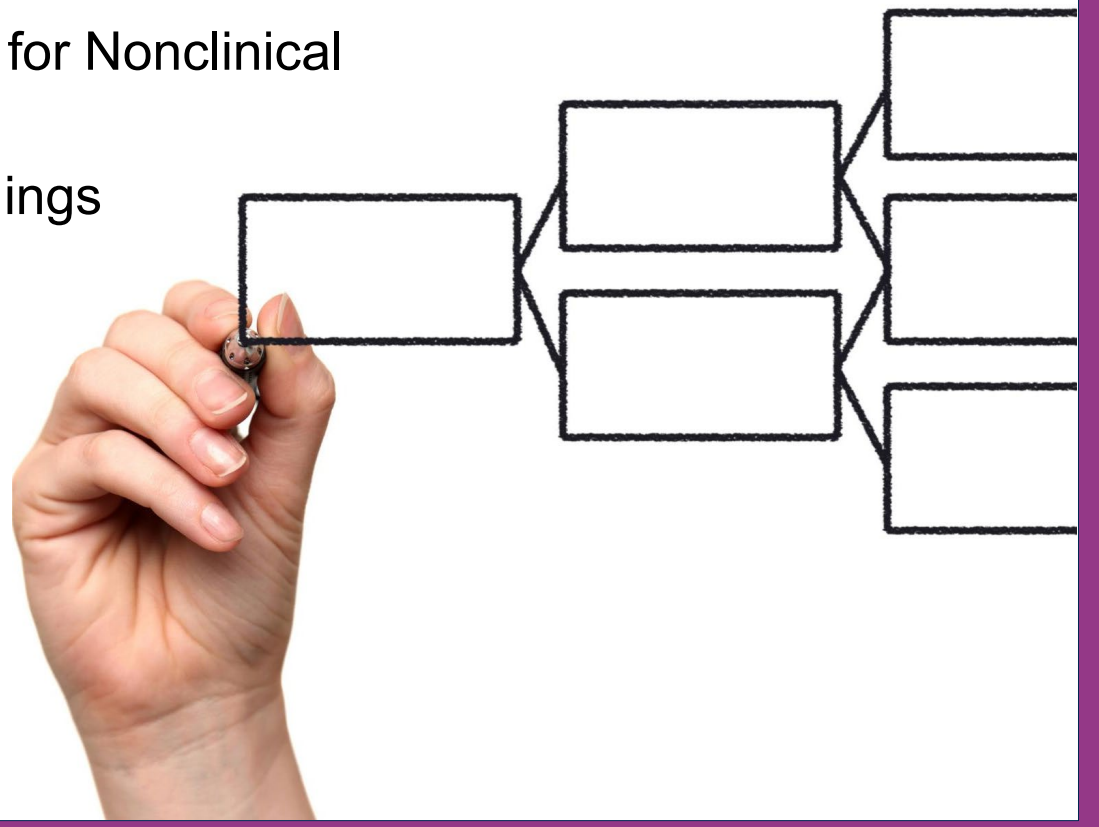


If we need to conduct a juvenile animal study, in rodents they typically involve a high number of animals due to litter effects although we continually look for ways to conduct the studies to gain the most information while using the fewest animals.

Current Industry Use of NAMs for Safety

NAMs-Based Global Regulatory Filings in Pharmaceutical Nonclinical Safety Assessments

- **Industry Survey:** Initiated by BIO (BioSafe and RASC) NAMs Task Force
  - Survey on NAMs Use in Pharmaceutical Industry for Nonclinical Safety *(for Adults)*
  - Case study request for NAMs-based regulatory filings
- **Outcome:** 2025 publication[1]
  - Responses from 27 companies
  - Promote adoption, where scientifically justified
  - **Advocate for updates to ICH guidance**



BIO = Biotechnology Innovation Organization

RASC = Regulatory Affairs Steering Committee

[1]J Shenton, I Bousnina, M Oropallo, *et al* (2025) Opportunities and insights from pharmaceutical companies on the current use of new approach methodologies in nonclinical safety assessment, Drug Discovery Today, 30(4)

Despite Successes, NAMs Use Still Faces Key Concerns for Adult Indications

- NAMs are widely applied across drug modalities and disease types
- Regulatory interactions are common and often multinational
- Nine companies reported regulatory acceptance of NAMs as animal test replacements, with two-thirds achieving multi-regional approval
- Despite NAM use amongst respondents, concerns for usage of NAMs persist

Concerns for Usage of NAMs

Most Common Concerns

- **Regulatory** acceptance by FDA
- Lack of harmonized global **regulatory** acceptance

Other Common Concerns

- Lack of translatability
- Concern about false positives/negatives
- Added time for qualification process

NAMs Suite Strategy

- Suite of NAMs used to address each safety concern(s) was of greater interest than an individual NAM
- Acknowledge that it will likely be a collection of NAMs with each one fit for particular context of use

CONTEXT OF USE

Opportunities

- Recent industry and health authority publications have called for more harmonization across health authorities which would decrease animal use
- Increased clarity on acceptability of NAMs-based filings would help a lot
- In terms of using NAMs to support safety in pediatrics, could not identify use of a specific in vitro model as a substitute for in vivo testing
- Future looking, “juvenile” NAMs for areas in which our in vivo systems may not be optimal to predict effects in human neonates and infants:
  - GI: organoid models to help better understand potential ADME differences as transporters and efflux mechanisms come onboard developmentally
  - Liver: hepatocytes models for CYP maturation
  - CNS: neuronal apoptosis due to prolonged exposure to inhaled anesthetics in neonates
  - bespoke “NAMS” on primary pharmacology in the juvenile tissues/systems

Take Home Messages
Juvenile Animal Studies (JAS) in Pediatric Development

- Pediatric plans (PIPs and PSPs) are binding agreements with multiple health authorities
  - Plans include clinical and non-clinical development studies or plans
  - Global harmonization is a challenge, “only as strong as weakest link”
  - ICH S11 provides a weight of evidence framework to decide if JAS is warranted
  - Already have a framework to include NAMs in weight of evidence

- Juvenile Animal Studies
  - Conducted for less than half of new medicines
  - Study designs are customized to the pediatric use and safety concerns
  - Typically conducted later in development compared to adult indication

- NAMs are only at infant stage of being used for safety assessment generally
  - Few case studies of NAMs-based submissions for first in human studies **in adults**
  - Low industry confidence to obtain regulatory acceptance globally, requires risking time and money
  - Plea for harmonized framework on when and how to incorporate NAMs in submissions
  - Future is bright, explosion of interest and energy

Thank You!

Shared Goal:

Efficient Global Pediatric Development to get medicines to kids safer and sooner

Disclaimer

- Susan Laffan is an employee of Amgen
- Susan Laffan also served as the PhRMA representative on the International Council for Harmonisation (ICH) S11 Working Group
- The views and opinions expressed are those of the presenter and should not be attributed to the American College of Toxicology, PhRMA, ICH, Amgen, or any other organization with which the presenter was/is employed or affiliated
- All photos without attribution were taken by Susan Laffan

Abbreviations

- ADME = adsorption, distribution, metabolism, elimination
- BW = body weight
- EoP2 = end of Phase 2 clinical trial
- EMA = European Medicine Agency
- FC = food consumption
- ICH = International Council for Harmonisation
- IM = intramuscular injection
- IV = intravenous injection
- PIP = paediatric investigative plan
- PND = postnatal day
- PPN = pre- and postnatal
- PREA = Pediatric Research Equity Act (US FDA)
- PSP = pediatric study plan
- SubQ = subcutaneous injection
- TK = toxicokinetics
- WHO = World Health Organization
- 3Rs = Replacement, Reduction and Refinement framework for performing more humane animal research.