FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

Pediatric Developmental Safety Assessment and New Approach Methodologies

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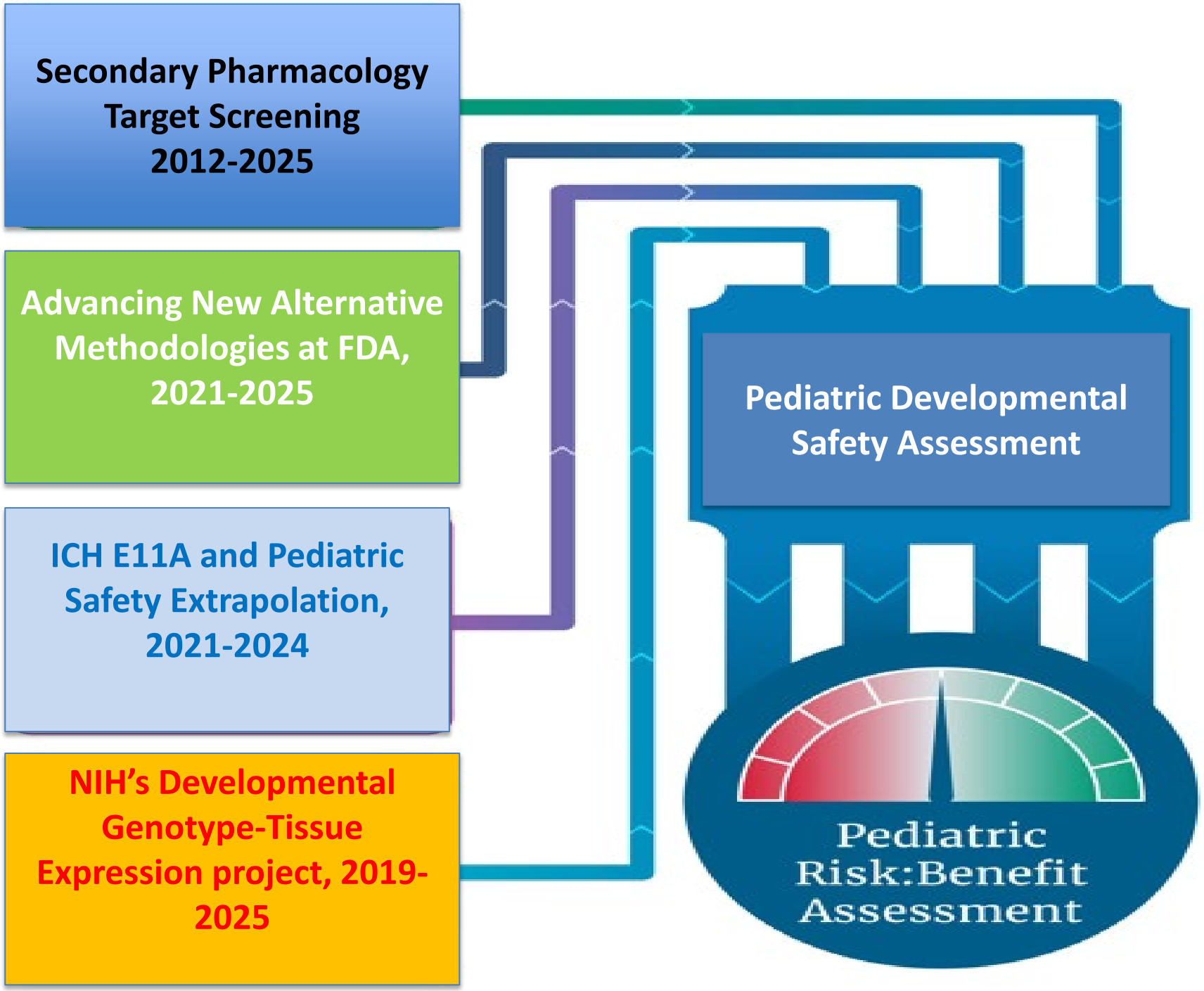
Disclaimer: The comments are those of the speaker and do not necessarily reflect the position of the US FDA.

Thank you Triangle CERSI!

- Workshop organizing committee, February 2024
- Plans for a February 2025 hybrid workshop
- Postponed until a December 2025 hybrid workshop
- Changed to a virtual December 2025 workshop

- BUT the critical need for pediatric drug development has not changed!

Convergence of Critical Concepts For Pediatric Developmental Safety Assessment



October 2025

Replacing and Reducing Animal Testing at CDER

CDER's primary focus is ensuring the safety and efficacy of human drugs. It has become increasingly clear that new approach methodologies (NAMs)—when combined with knowledge of the pathway, results of pharmacology studies, and other relevant data—may offer ways to achieve this goal more effectively and efficiently than traditional animal testing. Furthermore, NAMs support CDER's long-standing interest and investment in implementing the 3Rs (Replacement, Reduction, and Refinement) of animal testing in drug development, aligning with both FDA's priorities and those of the public. By embracing NAMs and other methods of replacing and reducing animal testing, CDER aims to enhance its ability to protect public health, improve the drug development process, and respond to evolving scientific advancements in the field of drug evaluation and safety assessment.

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/replacing-and-reducing-animal-testing-cder

Developmental and Reproductive Toxicity (DART)	General reduction of fertility, embryofetal development, and/or pre- and postnatal development studies	Studies may be submitted at the time of marketing application in certain circumstances. A number of alternative in vitro, ex vivo, and nonmammalian in vivo assays (alternative assays) have been developed to detect potential hazards to

Replacing and Reducing Aimal Testing at CDER

Category	Context of Use	Current Regulatory Expectations and Opportunities for Reduced Animal Use	Reference
Safety Pharmacology	General safety pharmacology testing	Safety pharmacology endpoints may be incorporated into general toxicity studies in order to reduce animal use. This practice is routine for biologics. May include non-animal methods. May be based on a risk assessment that includes information from biodistribution data for radiopharmaceuticals.	• ICH S7A: Safety Pharmacology Studies for Human Pharmaceuticals • ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals • ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals • Guidance for Industry: Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/replacing-and-reducing-animal-testing-cder

Juvenile Animal Studies

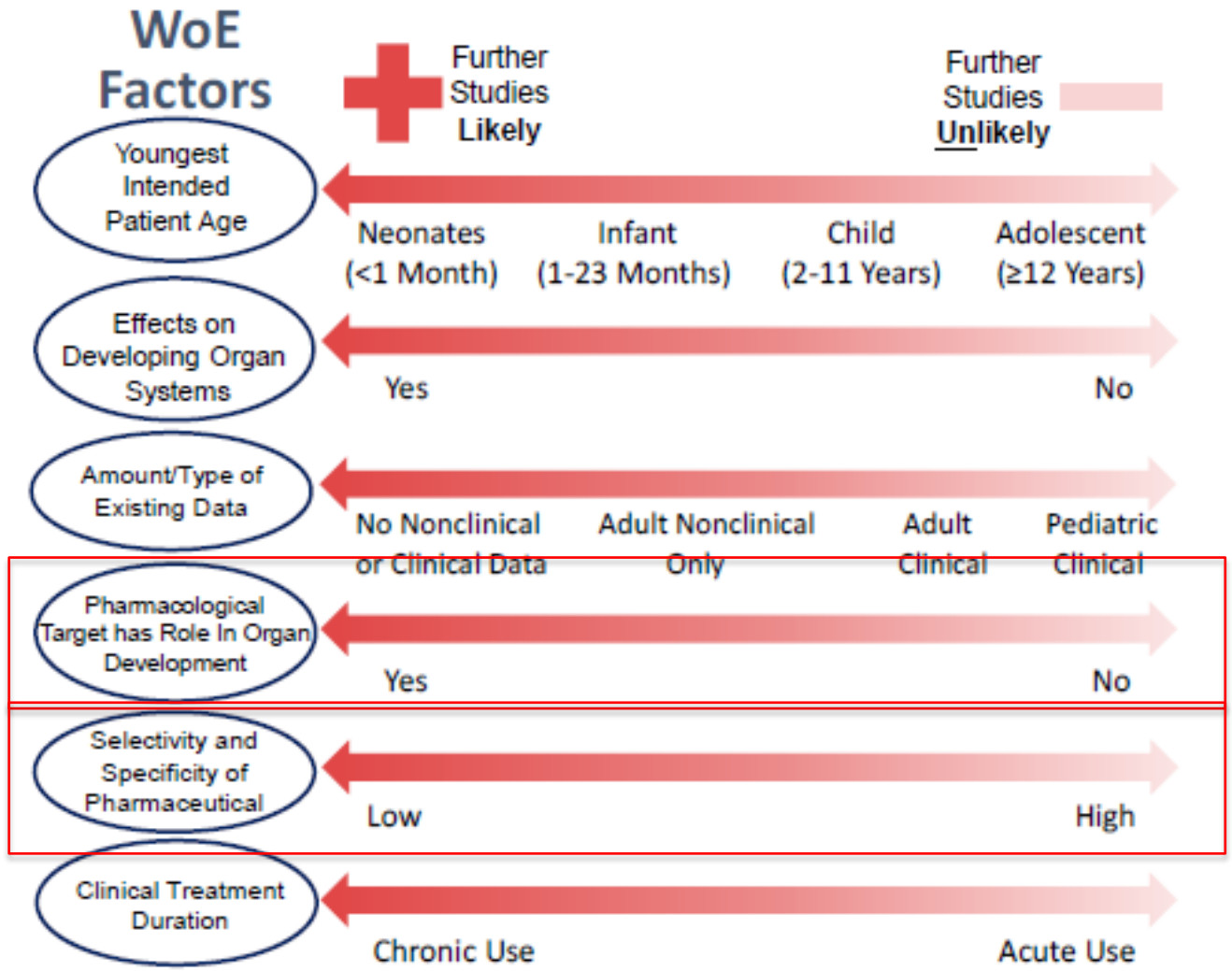
- Currently an essential part of pediatric developmental safety assessment, but criteria for performing a JAS are not optimal;
  - Only 8% of labeled JAS provide actionable information for pediatric drug use.
- **FDA commentary**: Leighton JK, Saber H, Reaman G, **Pazdur R**. An FDA oncology view of juvenile animal studies in support of initial pediatric trials for anticancer drugs. *Reg Tox Pharm*. 2016;79:142-143;
  - "When JAS is warranted, the design of the study should be based on the ability to address a **specific safety concern**. Unless there is a specific cause for concern, a JAS is not warranted, particularly if conduct of a study would delay the initiation of pediatric assessment."
  - Secondary pharmacology is one way of providing a **specific safety concern.**

Weight of Evidence Analysis

Guidance for Industry: S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals, May 2021

Analysis by Secondary Pharmacology and AI

Secondary Target Analysis



Should we be concerned about the adequacy of the current system of evaluating pediatric developmental toxicity?

Pediatric Developmental Safety Assessment: Are We Ready for the Next Thalidomide?

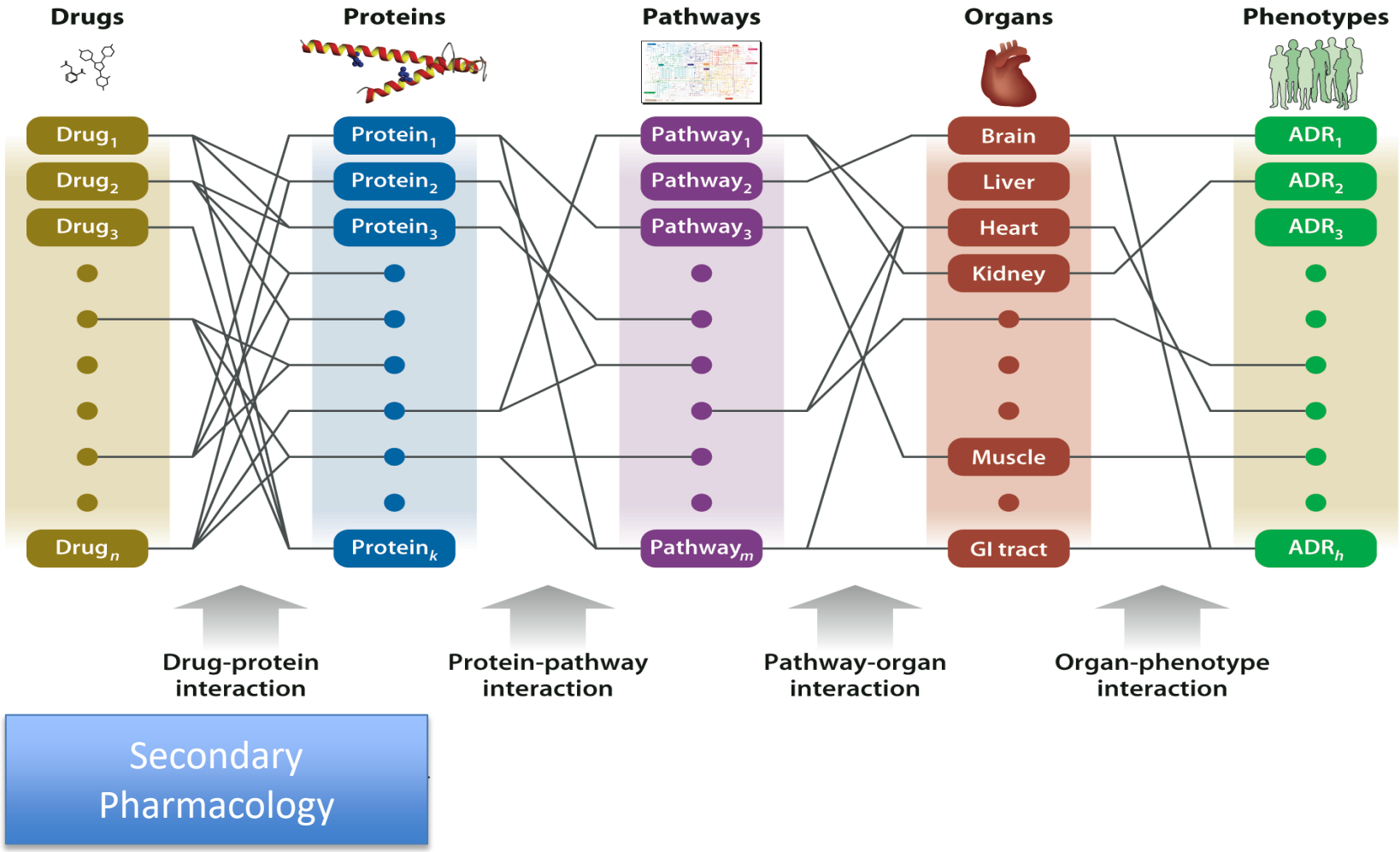
Gilbert J. Burckart[1,*], Susan M. Abdel-Rahman[1], Gelareh Abulwerdi[1], Sherbet Samuels[1], Rebecca Racz[1], Mohamed A. Mohamoud[2] and Nicholas P. Tatonetti[3]

Clinical Pharmacology and Therapeutics 2025;
doi:10.1002/cpt.70148

Major points:

- The current paradigm has major blind spots for assessing pediatric developmental safety;
- Adding NAMs increases the likelihood of identifying important risks;
- Secondary pharmacology targets are available today to assist in answering critical questions about pediatric developmental safety risks.

Systems Pharmacology and Predicting Drug Toxicity



Secondary Pharmacology

Darrell Abernethy, FDA
1949-2017

Bai and Abernethy: Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization. Annu. Rev. Pharmacol. Toxicol. 2013; 53:451-473

Summary

- Today we will be discussing NAMs such as secondary pharmacology, microphysiologic systems and in silico tools that can contribute to our understanding of pediatric developmental safety;
- We need a proactive approach that emphasizes the importance of integrating multiple methodologies to strengthen pediatric drug safety assessment.
- This information is immediately valuable in addressing the pediatric developmental safety questions posed by ICH E11A related to safety extrapolation.

Workshop Details

- Please ask questions using the Q&A button; we will answer all questions even if a post-workshop response is necessary;
- We have 2 long panel sessions for discussion, so only clarifying questions will be taken at the end of each talk if time allows;
- Speaker and moderator biographical sketches are available on the workshop website; please refer to those so that we do not have to take extra time with speaker introductions;
- Please enjoy the workshop, and more importantly consider how we can use these ideas to improve the safety of our pediatric patients.