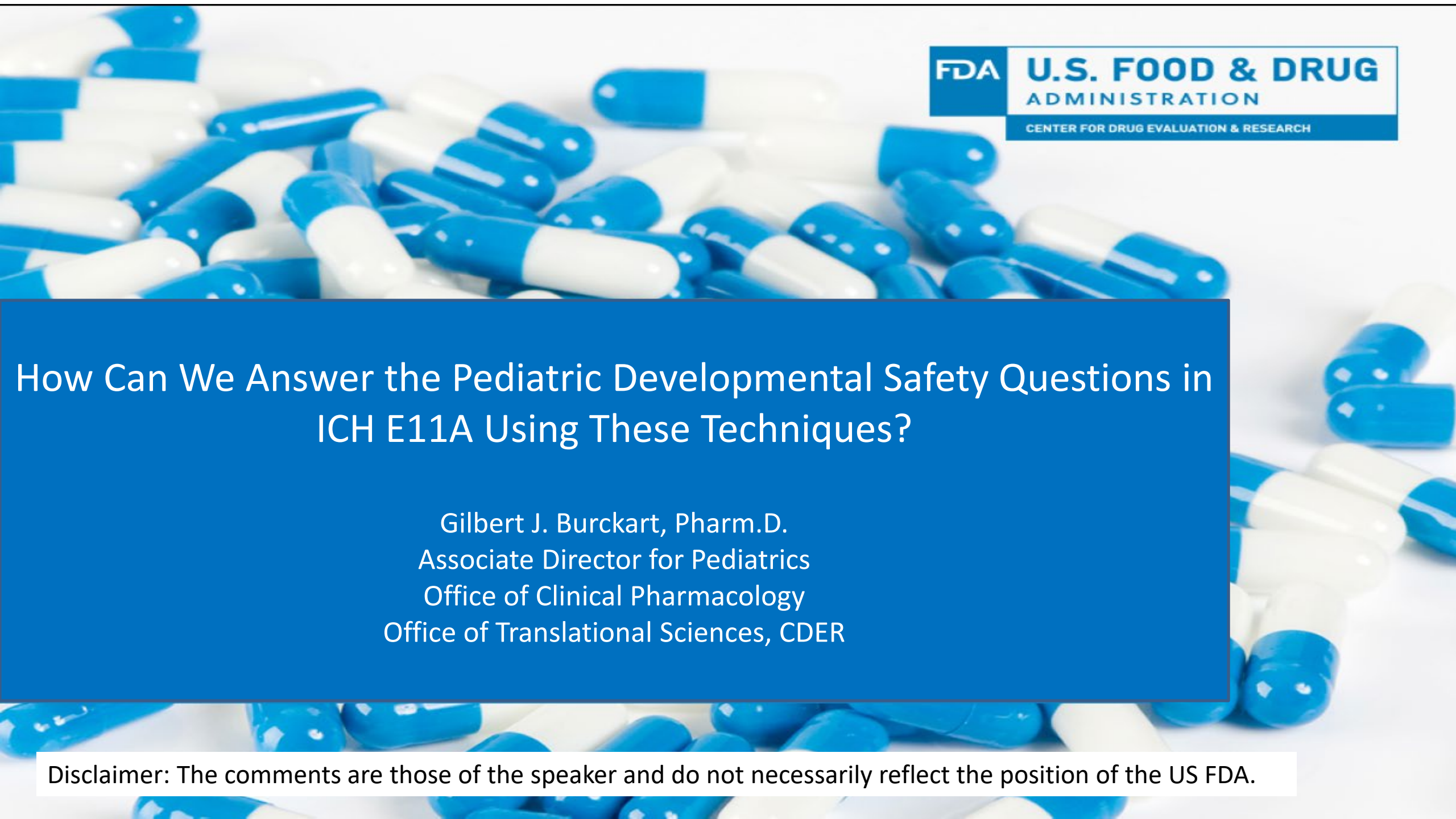

FDA U.S. FOOD & DRUG ADMINISTRATION
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How Can We Answer the Pediatric Developmental Safety Questions in ICH E11A Using These Techniques?

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

ICH E11A Extrapolation of Safety to Pediatric Patients

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COMMENTARY

Paediatric developmental safety and the ICH E11A extrapolation of safety

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- Major points:
  - ICH E11A is very clear that the Safety Extrapolation Plan (Section 4.1.7) should be considered separately from efficacy extrapolation;
  - Questions and additional considerations (Section 3.4.2) related to safety should be addressed.

ICH E11A Safety Extrapolation

The ICH E11A Safety Extrapolation questions are quite comprehensive and should be addressed completely as part of the safety extrapolation plan.

The methods for addressing these questions are not detailed in the ICH E11A guidance, but many of the methods to answer these questions are a routine part of the drug development process.

The following slides address each question and suggest a potential way to answer the question.

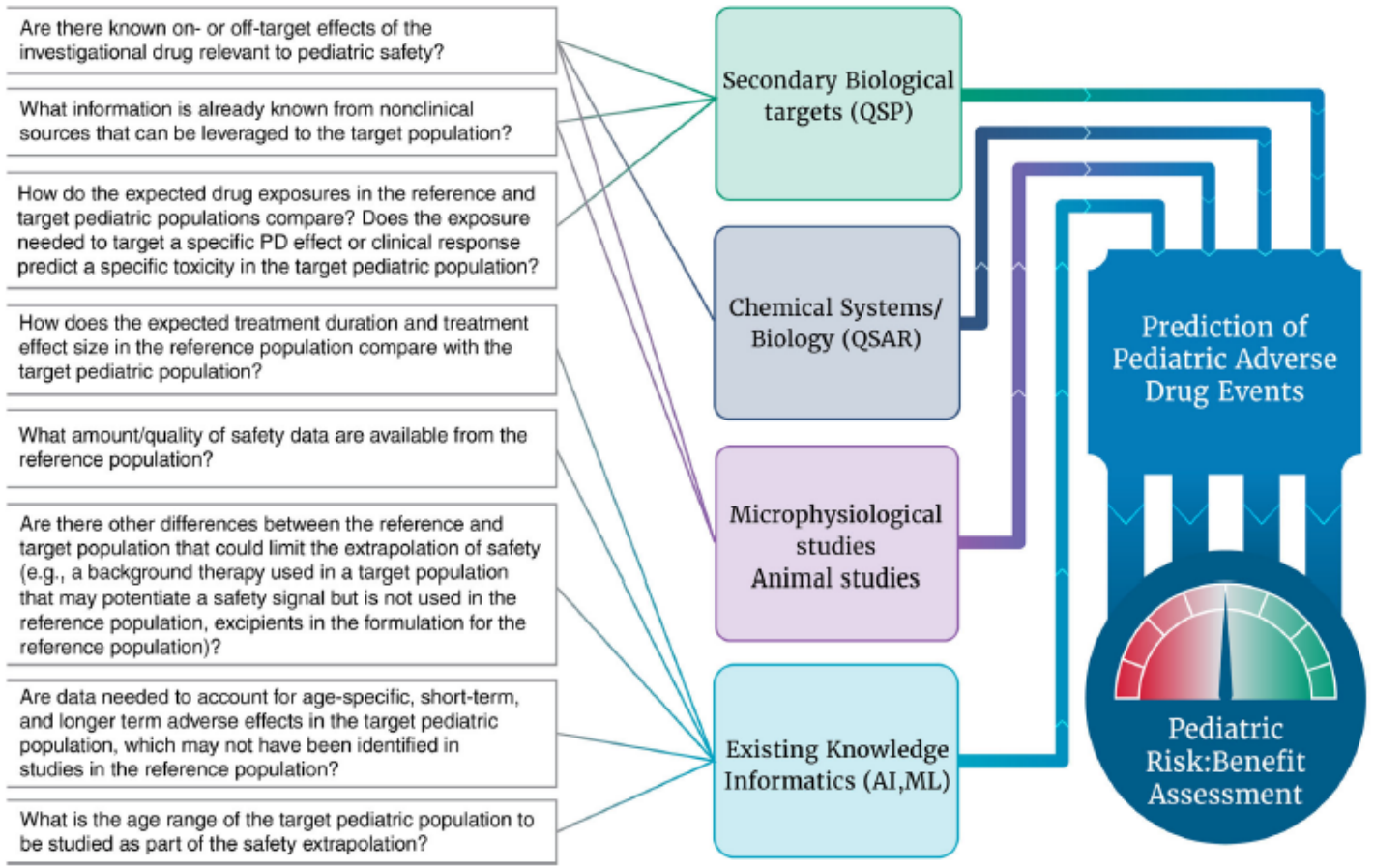


FIGURE 1 Graphical representation of the safety-related ICH E11A questions on the left, the available tools for answering those questions in the middle and the integrated prediction of paediatric adverse effects with a benefit–risk analysis on the right.

ICH E11A Safety Extrapolation Question - 1

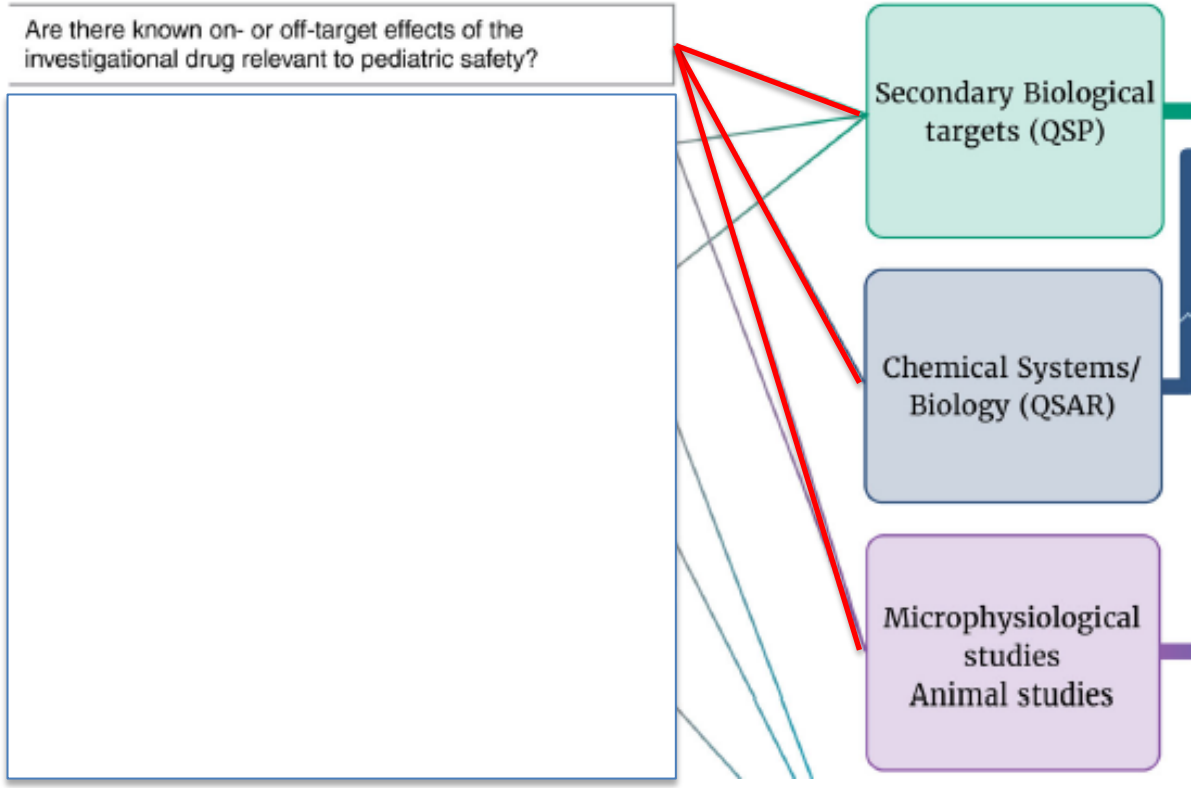
Are there known on- or off-target effects of the investigational drug relevant to pediatric safety?

Per the discussion today, “secondary pharmacology” fits this question quite well, and often has already been conducted during the IND phase of development.

Are there additional targets that should be added to the traditional panel that is used for secondary pharmacology?

“On target” effects also should be considered, and do extend the discussion beyond small molecules (i.e. effects of cytokines and growth factors targeted by MAbs).

Structure-activity relationships (SAR) and microphysiologic studies also can help to answer this question.



Quantitative Structure-Activity Relationships (QSAR)

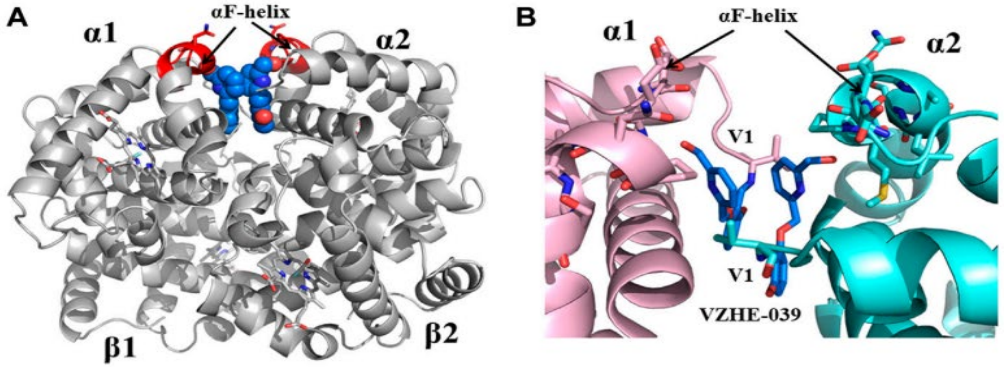


FIGURE 7
Crystal structure of liganded Hb (in the R2-state conformation) in complex with two molecules of VZHE-039 bound at the α-cleft. **(A)** A global view of VZHE-039 molecules (marine blue spheres) in complex with Hb (gray ribbon). The surface-located αF-helix is shown in red ribbon, and hemes shown in sticks. **(B)** A close-up view of Schiff-base interaction between VZHE-039 (marine blue sticks) and Hb αVal1 amine, as well as close interactions with the αF-helix residues (sticks). Other protein interactions are not shown for clarity. α1-subunit and α2-subunit are shown in pink and cyan, respectively.

Donkor AK et al. X-ray crystallography and sickle cell disease drug discovery—a tribute to Donald Abraham *Front Mol Biosci* 2023; https://doi.org/10.3389/fmolb.2023.1136970

Donald J. Abraham 1937-2021

-SARs can help to understand the interaction between a drug molecule and endogenous proteins/receptors.

-The “quantitative” aspect can determine whether such an interaction is likely to occur during the therapeutic use of the drug.

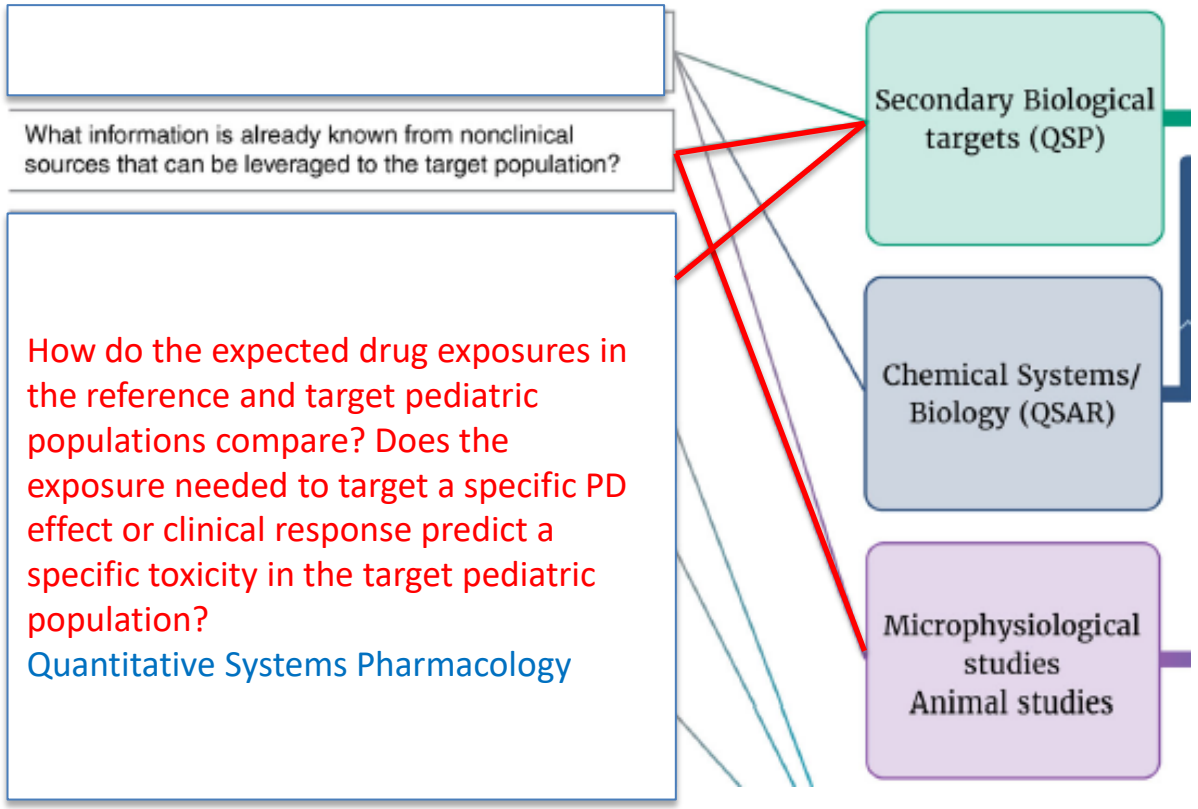
ICH E11A Safety Extrapolation Question – 2/3

What information is already known from nonclinical sources (see Table 1) that can be leveraged to the target population?

Table 1: Examples of Sources and Types of Data to Evaluate Disease, Drug Pharmacology, and Response to Treatment

Sources of Data	Types of Data
Clinical trial data	PK, PD, E-R, and clinical data in the same disease for the drug or drugs in the same class
	PK, PD, E-R, and clinical data in other related diseases for the drug or drugs in the same class
	PK, PD, E-R, and clinical data in the same disease for drugs in a different class
Nonclinical data	ADME data from animal models
	In silico, in vitro, and in vivo animal data (e.g., animal disease models, PK, PK/PD, MOA)
	Adult and juvenile animal toxicology data
Real-world data	Including but not limited to disease registries (regional, national, and international), electronic health records, health claims databases
Other sources	Including but not limited to systematic reviews or meta-analyses, relevant published literature
	Professional organization guidelines/clinical practice guidelines/consensus documents
	Published models/simulations (e.g., PK/PD, mechanistic)
	Expert opinion
	Standard of care/practice of medicine

PK = pharmacokinetics/pharmacokinetic; PD = pharmacodynamics; E-R = exposure-response; ADME = absorption, distribution, metabolism, and excretion; MOA = mechanism of action.



ICH E11A Safety Extrapolation Question – 4-8

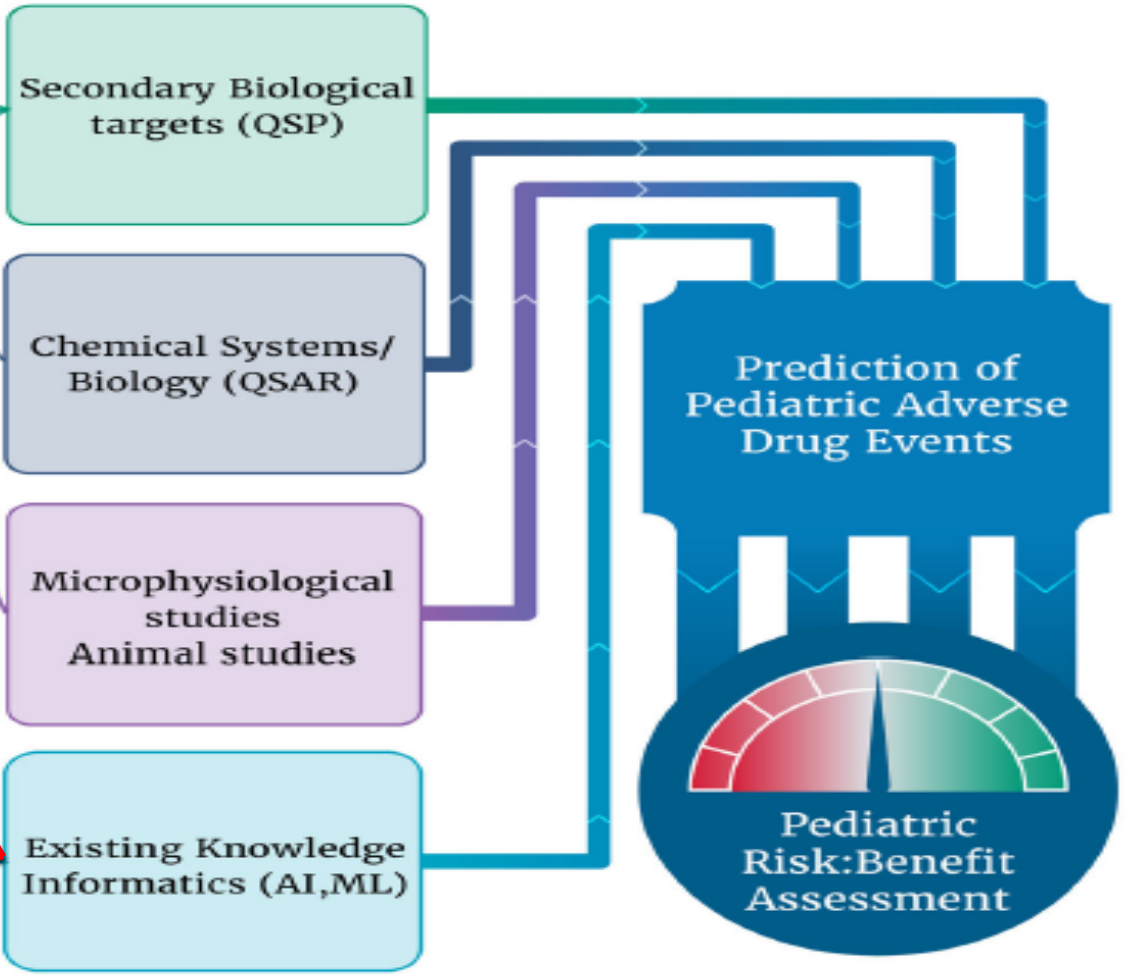
How does the expected treatment duration and treatment effect size in the reference population compare with the target pediatric population?

What amount/quality of safety data are available from the reference population?

Are there other differences between the reference and target population that could limit the extrapolation of safety (e.g., a background therapy used in a target population that may potentiate a safety signal but is not used in the reference population, excipients in the formulation for the reference population)?

Are data needed to account for age-specific, short-term, and longer term adverse effects in the target pediatric population, which may not have been identified in studies in the reference population?

What is the age range of the target pediatric population to be studied as part of the safety extrapolation?



Additional ICH E11A Safety Considerations

Additional consideration as part of the pediatric extrapolation concept should be given to the collection of pediatric safety data in certain situations. Examples include:

- When the drug is a new molecular entity for a new class of drugs
- When there are known on- or off-target age-related safety concerns
- When there are significant safety findings noted in the reference population that would be of special importance in pediatrics (e.g. sedation, effects on motor skills)
- When the drug has a narrow therapeutic index (multiple examples, and especially those with a food effect)

Sedation in Pediatric Patients

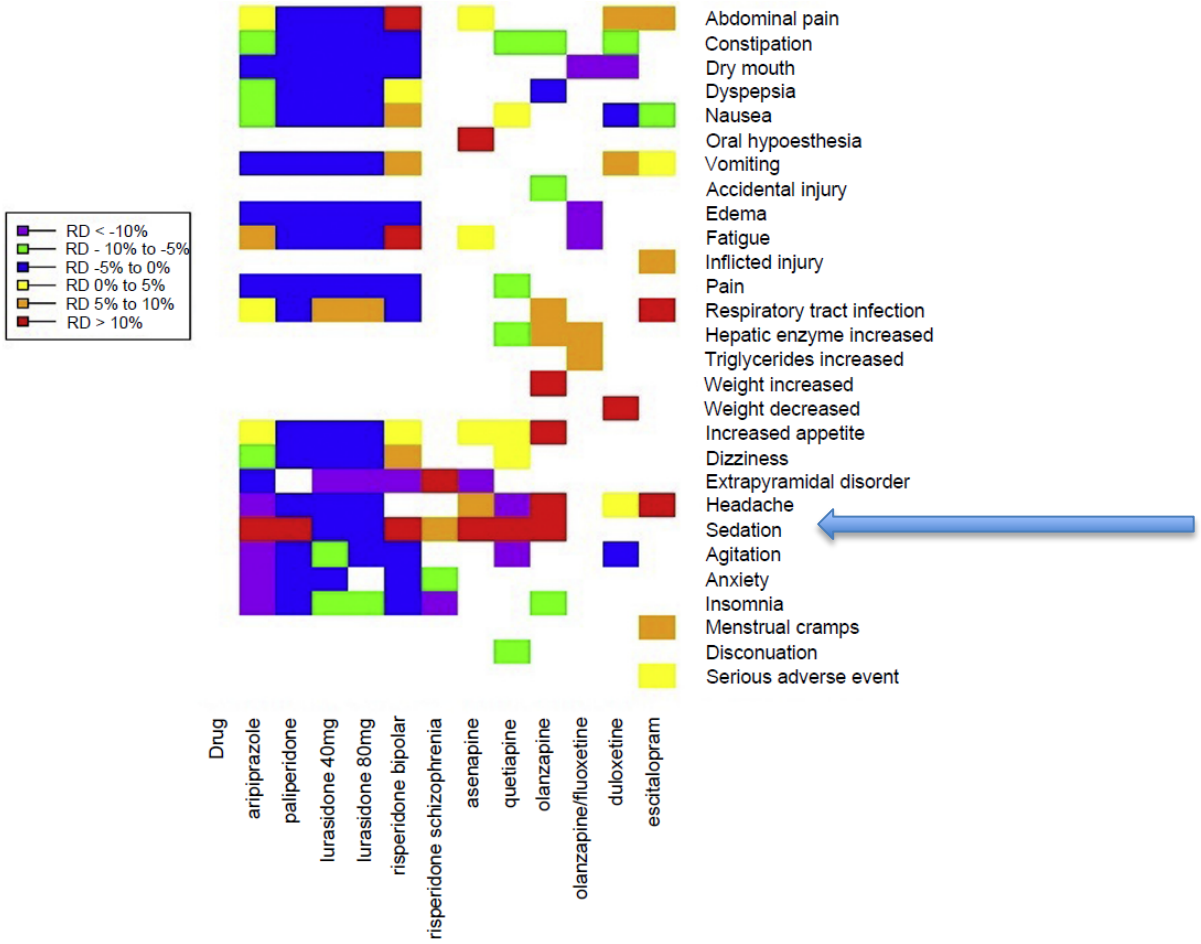


Figure 2. Summary of ADRs with significant RDs for all medications with any significant RD >5% or RD <−5%. RD = risk in pediatric patients minus risk in adult patients, so that positive RDs represent pediatrics > adults, and negative RDs represent adults > pediatrics. Classification of RD: RD >10% (*red*); RD 5%-10% (*orange*); RD 0%-5% (*yellow*); RD −5%-0% (*blue*); RD −10% to −5% (*green*); RD <−10% (*purple*).

Sedation was higher in 6 of 10 drugs and drug combinations with risk differences of 9.6 to 36.6% (red bars)

Sedation is an ADE of special importance to pediatric patients (i.e. learning etc) and therefore requires an analysis with pediatric safety data.

Liu XI, Schuette P, Burckart GJ, et al. A Comparison of Pediatric and Adult Safety Studies for Anti-Psychotic and Antidepressant Drugs Submitted to the United States Food and Drug Administration. *Journal of Pediatrics* 2019; 208:236-242.

Narrow Therapeutic Index Drugs

Multiple factors can produce differences between the reference and the pediatric target populations, which adds to the safety risk with a NTI drug.

Tunehag KR, George B, Samuels S…… Burckart GJ. Food-Drug Effects and Pediatric Drug Development Studies Submitted to the US Food and Drug Administration 2012-2022. *J Clin Pharmacology* 2024; 64(6): 697-703.

Table 2. Examples of Food Effects and Labeled Instructions for Narrow Therapeutic Index Oral Drug Products[a] Listed Under BPCA/PREA Between 2012 and 2022, and Approved in Pediatric Patients Aged <6 Years or Weighing <20 kg

Drug	Formulation	Labeled food instructions	Food effect according to FDA guidance
Dasatinib	Tablet	With or without food	No effect on AUC_{inf} or C_{max}
Everolimus	Tablet for oral suspension	Consistently with or without food	↓ AUC_{inf} with light-fat meal but not with high-fat meal ↓ C_{max} for both light-fat and high-fat meals
Levothyroxine	Oral solution	Without food	↓ AUC_{inf} and C_{max}
Nilotinib	Capsule	Without food	↑ AUC_{inf} and C_{max}
Tacrolimus	Capsule	Without food	↓ AUCinf and C_{max}

[a] As identified in DRUGBANK (https://go.drugbank.com/categories/DBCAT003972).

Summary

- ICH E11A has provided a reasonable structure for pediatric safety extrapolation, but it requires a separate assessment from efficacy extrapolation;
- There are clear approaches to answering the ICH E11A safety extrapolation questions which are generally intrinsic to most drug development programs;
- A proactive approach that emphasizes the importance of integrating multiple methodologies strengthens the pediatric drug safety assessment and protects our pediatric patients.