Accelerating Product Development for Pediatric Systemic Lupus Erythematosus (SLE)
July 30-31, 2026

Regulatory Framework for Drug Development and Pediatric Extrapolation

Lily Mulugeta
Division of Pediatrics and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
U.S. FDA

Disclosures

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Timely access to therapies for pediatric patients

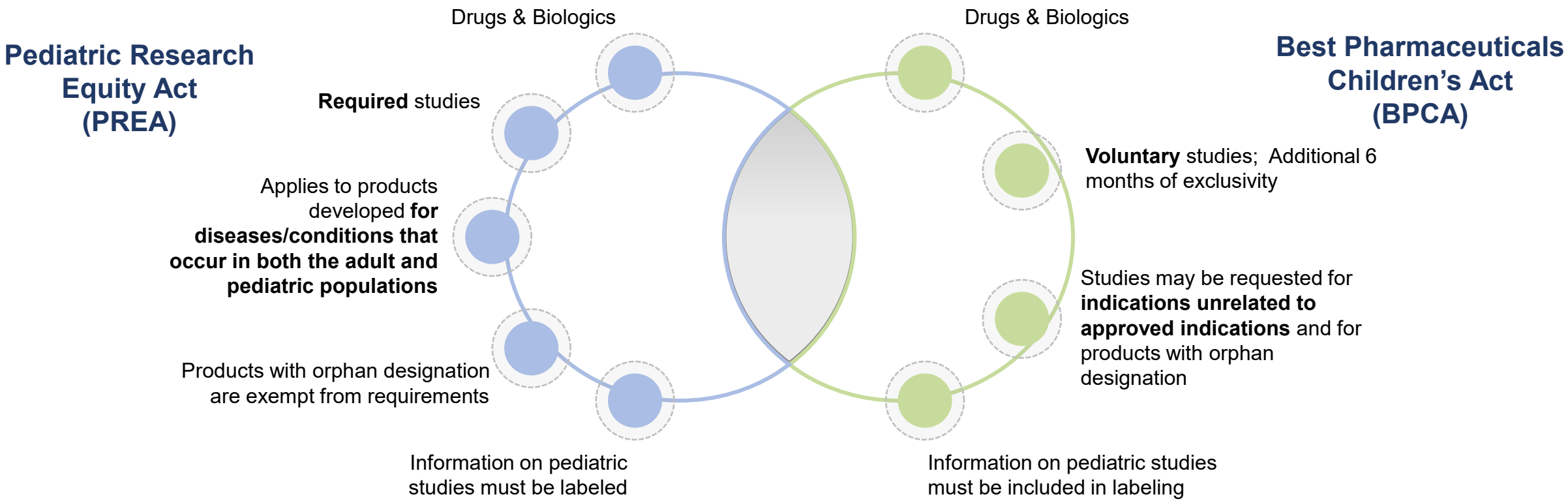
Pediatric development program should provide **timely access to**:

- **Clinical trials**:
  - The goal is to begin once prospect of direct benefit is determined and overall risk benefit has been considered to allow enrollment of children into a clinical trial
- **Approved therapies**:
  - Pediatric trials should complete enrollment before off-label use makes clinical trials difficult to complete (~2 to 3 years after approval in adults).

Extrapolation and innovative approaches are critical for expediting pediatric drug development

Pediatric Regulatory Framework

The context is a drug/biological product developed for **adult SLE, studied in adult patients** and then investigated for its potential use in children



Pediatric SLE studies are required down to 5 years under PREA

Global Pediatric Regulatory Framework

US FDA: Pediatric Study Plans (iPSP/PSP)

- Typically submitted after Phase 2 in adults
- Only when a relevant pediatric population exists (waiver may apply)
- Required for submissions with:
  - New active ingredient
  - New dosage form
  - New route of administration
  - New indication
  - New dosing regimen
- Orphan designated products: exempt

EU EMA: Pediatric Investigation Plan (PIP)

- Submitted early in development, typically end of Phase 1 in adults
- Required for **all new medicines**
- Orphan designated products: included
- Waiver may apply

Both require development of age-appropriate pediatric formulations

Pediatric Study Plan—Content

- Disease
- Drug mechanism of action (MOA); absorption, distribution, metabolism, and elimination (ADME)
- **Plan and justification for waiver for studies in one or more pediatric age groups**
  - e.g. for SLE, partial waiver under 5 years of age
- **Juvenile toxicology studies to inform safety** (typically for studies in patients less than 12 years of age)
- **Formulation and excipients;** Age-appropriate formulation required for relevant pediatric age groups
- **Available data** (adult data for the same drug, pediatric data for the same drug or related conditions, pediatric data for drugs in the same class)
- **Extrapolation plan**
- Planned clinical studies (Pharmacokinetics (PK), efficacy if not extrapolated, safety)
- Address potential inclusion of adolescents in adult trials
- **Timeline for studies** (timing of pediatric studies)
- **Agreement with other regulatory agencies** (typically European Medicines Agency—EMA)

Evidentiary Standard for Pediatric Drug Development

Same Rigorous Standard as Adult Product Development

Basis for Approval

Demonstrate substantial evidence of effectiveness/clinical benefit (21CFR 314.50).

Evidence of Effectiveness

Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports …[PHS Act, 505(d)]

Safety Assessment

Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)]

Clinical benefits to support drug approval

Clinical outcomes

- Direct measure of how a patient feels, functions, or survives
- Improvement or delay in progression of clinically meaningful aspects of the disease

Surrogate endpoints

- A substitute for how a patient feels, functions, or survives
- Established surrogates (e.g. blood pressure, low density lipoprotein (LDL) in adults, forced expiratory volume in 1 sec (FEV_1) in asthma)
- Surrogates reasonably likely to predict clinical benefit
  - Accelerated approval
  - Requires additional studies post-marketing to confirm clinical benefit
  - For serious conditions that filled an unmet medical need

Pediatric Extrapolation

"If the course of the disease and the effects of the drug are **sufficiently similar in adults and pediatric patients**, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well - controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." (21 CFR §314.55a)

Evolution of Pediatric Extrapolation

ICHE E11 (R1)
Clinical Investigation of Medicinal Products in the Pediatric Population (2018)

……an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult or other pediatric) population

ICH E11A Pediatric Extrapolation Guideline

…Final guidance published 2024
Recognition of the paradigm change in pediatric drug development
Consideration of pediatric extrapolation as a continuum, and
Identification of pediatric extrapolation as an iterative process
Certain element of using adult data in almost every pediatric development.

Evidence to Build Foundation for Extrapolation

01 Disease Etiology and Progression:
- Clinical presentation
- Phenotypic presentation
- Pathophysiology

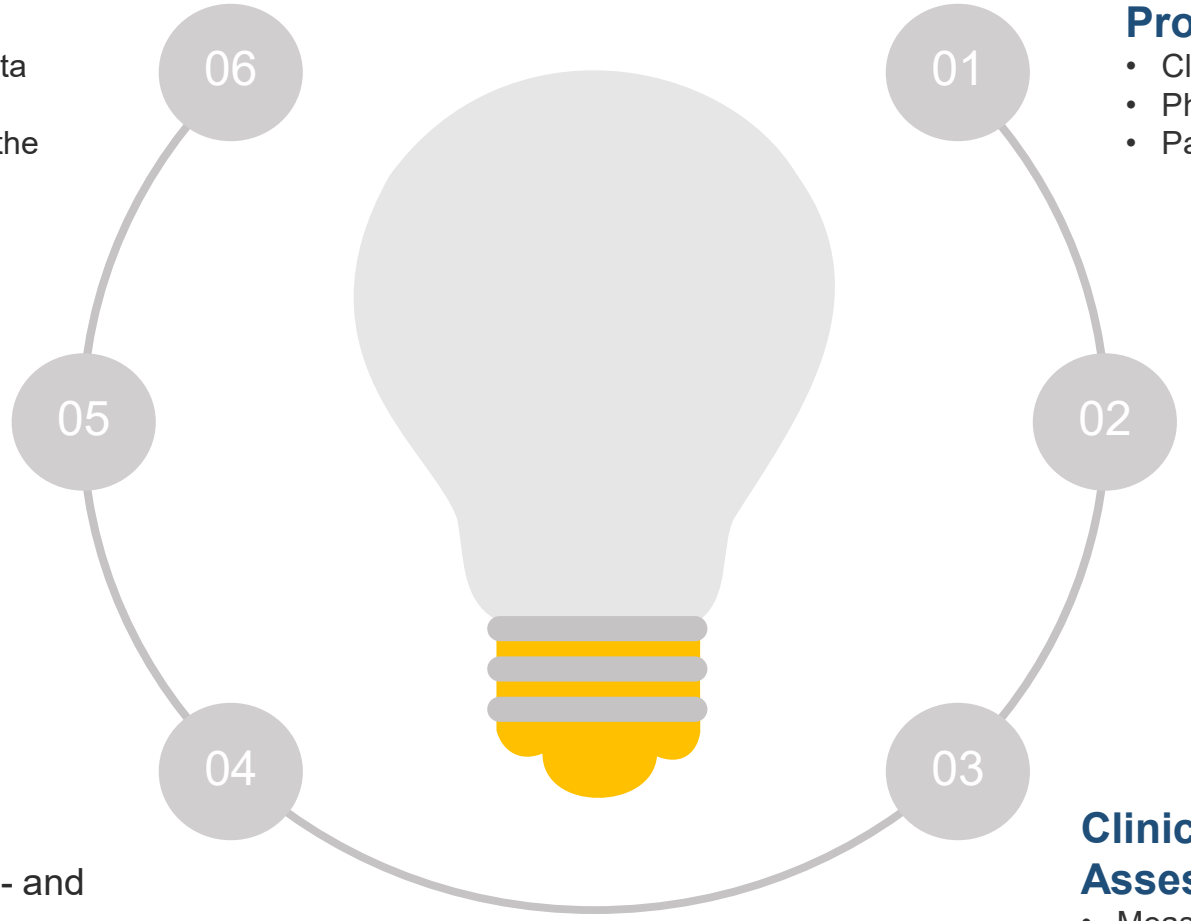
02 Diagnostic Criteria.
- Disease manifestation or diagnostic criteria that define disease
- Disease subtypes

03 Clinical Outcome Assessments
- Measurements used to assess clinical course
- Validation across age groups

04 Study Endpoints
- Accepted efficacy short- and long-term endpoints
- Study design and duration

05 Drug Pharmacology
- Mechanism of action
- ADME
- Target expression

06 Response to Treatment
- Similar endpoints, E-R data
- Placebo response
- Experience with drugs in the same therapeutic class



Knowledge Gap Identification

- What are the identified gaps in knowledge?
- Do these gaps in knowledge require additional data collection before going into pediatrics?
- What additional data should be collected in pediatric patients to address these gaps

Pediatric Dose Selection

Aim of pediatric dose selection **<u>often</u> is to target exposures known to be safe and efficacious** in a reference population, usually adults

PK data collection may be within efficacy studies or as a lead-in when justified

Evaluation of different dose/exposure levels (i.e. dose ranging data) when

- Insufficient dose exploration in adult program
- Uncertainty in the disease and/or response similarity
- Data from early phase trials or other programs indicate different E-R
- Potential age-related differences in target expression (efficacy/safety)

Modeling and simulation strategies to support the initial dose selection

Approaches for Extrapolation of Efficacy

- SAME DISEASE/RESPONSE:
  - No additional pediatric efficacy data needed (establish dose and safety: conduct PK/safety study)
- DIFFERENT DISEASE:
  - 1 or more controlled trial to establish efficacy in pediatric patients
- UNCERTAINTY IN THE DISEASE/RESPONSE SIMILARITY:
  - Design depends on the degree of uncertainty

Approaches range on a continuum

Similarity of Disease, Pharmacology, and Response to Treatment

Different disease and/or response to treatment ← → Same disease and/or response to treatment

Evidence to Support Similarity

No data/large gaps in knowledge ← → High Quality Data/High confidence

Types of Data: Clinical Trial Data; nonclinical data; real world data; other sources

Pediatric Extrapolation Plan

Potential Study Designs

Adequate and Well-Controlled Trial(s) ← → Exposure matching; Enrollment in or concurrent with adult trials

Extrapolation Approaches

Increasing level of **evidence required from pediatric studies**

Increasing level of **confidence in similarity of disease/pharmacology/ response**

1 or more adequate-well controlled studies powered on a clinically meaningful endpoint
e.g. Major depressive disorders, migraine, prophylaxis of venous thromboembolism

1 or more adequate-well controlled studies powered on a surrogate endpoint
e.g. Type 2 diabetes, hypercholesterolemia

Controlled study without formal statistical power

Descriptive efficacy study without concurrent control
e.g. Neurogenic detrusor over-activity

Dose-ranging studies (randomization to multiple dose levels)
e.g. Inflammatory bowel disease

Small PK/PD studies (single dose level matching adult exposures)
e.g. Erosive esophagitis (infants), anesthetics, PAH

PK/safety only (single dose level matching adult exposures)
e.g. Acute pain (well known MOAs; over 2 y/o), hidradenitis suppurativa (adolescents), pJIA

List partially adapted from Dunne et al. *Pediatrics* 2011

Safety extrapolation (ICH E11A)

- Recognition that principles underlying use of data from a reference population(s) also apply to the generation of safety data
- Extrapolation of safety data based on *known* and/or *potential* safety issues in the reference population that are relevant to the target pediatric population
- Other information (e.g., nonclinical, mechanistic) should be considered as part of this analysis

Case Example: Drug X (TNF-inhibitor) in pJIA

	Disease	Drug Pharmacology	Response to Treatment	Safety
Identified gaps in knowledge	No	Yes (Dosing in pediatric patients)	No	Yes [Long-term safety concerns in class, e.g. malignancy, new autoimmune disease]
Do these gaps require additional data generation to finalize Extrapolation Concept	N/A	No	N/A	No
How will gaps be addressed in the Extrapolation Plan	N/A	PK data to support pediatric dosing	N/A	› Leverage existing data in TNF-α inhibitor class › Evaluate need for long-term safety data

No action required Action required Not applicable because no gaps were identified (may be applicable in other scenarios)

Examples of Advances in Use of Pediatric Extrapolation

Disease	Treatment	Evidence of Similarity	Innovation
Heart Failure (1 year and older)	Sacubitril/Valsartan (Entresto)	New MOA; Similar disease process in pediatric and adult subgroup	Use of a bridging biomarker
Schizophrenia (> 13 yrs) Bipolar (>7 yrs)	Atypical Antipsychotics	Similar disease; Similar E-R relationship across multiple drugs	PK/safety study (exposure-matching approach)
pJIA (2 years and older)	Drugs with established MOAs	Same disease Similar E-R relationship across multiple drugs	PK/safety study (exposure matching)
Hypertension (1 to < 6 years of age)	Valsartan	Different disease etiology but similar management Similar dose/exposure-response within drug class	Extrapolation from older pediatric age group (PK/safety study)

Enrolling Pediatric Patients in Adult Trials

- **Considered on case-by-case basis :**
  - Strong evidence of disease similarity between adults and pediatrics
  - Sufficient data to support dose selection including availability of a formulation
  - Evidence of preliminary clinical efficacy and safety data in adults
- **If enrolled in adult phase 3 trial:**
  - Include pediatric patients in the primary endpoint analysis
  - Subgroup analysis focused on direction rather than magnitude of effect
  - Adequate safety monitoring required
- **Additional considerations:**
  - Evaluation of the adult trial design
    - Ease and suitability of the endpoint in pediatric patients and the timing of the endpoint
    - Choice of the comparator
    - Frequency of blood draws and other invasive procedures; frequency of visits and assessments
- **Operational considerations including site selection**

Other Approaches to Expedite Pediatric Programs

- **PK lead-in instead of separate study**
- **Use of M&S to estimate dosing in pediatric patients**
  - Alleviates need to conduct a separate or lead-in PK study
- **Leveraging data from other relevant indications**

Challenges with Conducting Pediatric SLE trials

- Small pool of available patients for trials
- Large phenotypic variability
- More severe disease course
- Off-label use of therapies
- Feasibility and ethics of controlled trials
- Competing trials

Limited clinical trials

Focus for Today's Workshop Presentations/Discussions

Sessions

1 & 2 **What data exist?** What adult data, if any, can be leveraged?

3 **What new data are needed?** What additional data are needed in the target pediatric SLE population?

4 **What trial design?** What is the optimal trial design to obtain the necessary data?

Drug Development in pSLE

	Disease	Drug Pharmacology	Response to Treatment	Safety
Identified gaps in knowledge				
Do these gaps require additional data generation ?				
How will gaps be addressed ?				

No action required

Action required

Not applicable because no gaps were identified (may be applicable in other scenarios)

Acknowledgments

Workshop planning committee

All speakers and panelists

DPMH project manager: Meshaun Payne, Kerri-Ann Jennings

UMD CERSI

FDA Office of External Affairs

Back-up slides

The foundation of pediatric extrapolation is degree of similarity: Disease, pharmacology, and response to treatment

Goal: To predict how a drug/biologic will behave in children on the basis of data generated in adults

What evidence supports disease and response similarity?

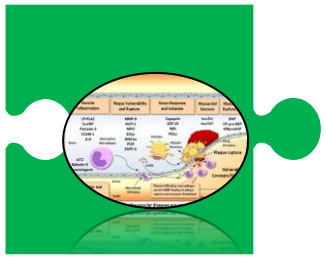
Disease similarity

pathophysiology, disease manifestations or etiology, disease progression

Pharmacology/Response similarity

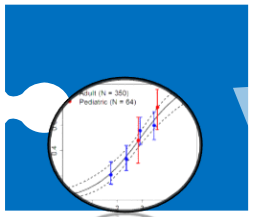
e.g. similar endpoints, mode of action,, ontogeny of receptor expressions, **experience with drugs in the same therapeutic class, exposure-response data, etc**.

What data are needed to support approval?



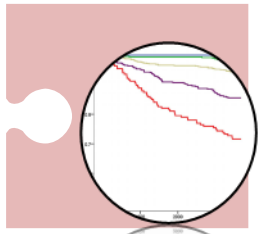
PK/safety

Availability of a PD endpoint/biomarker that can be used to predict efficacy in children?



PK/biomarker/safety

Evidence of similar concentration or concentration-response relationship in each population



Efficacy/safety

Single arm efficacy trial
Concurrently controlled
Externally controlled
Bayesian vs. frequentist analysis

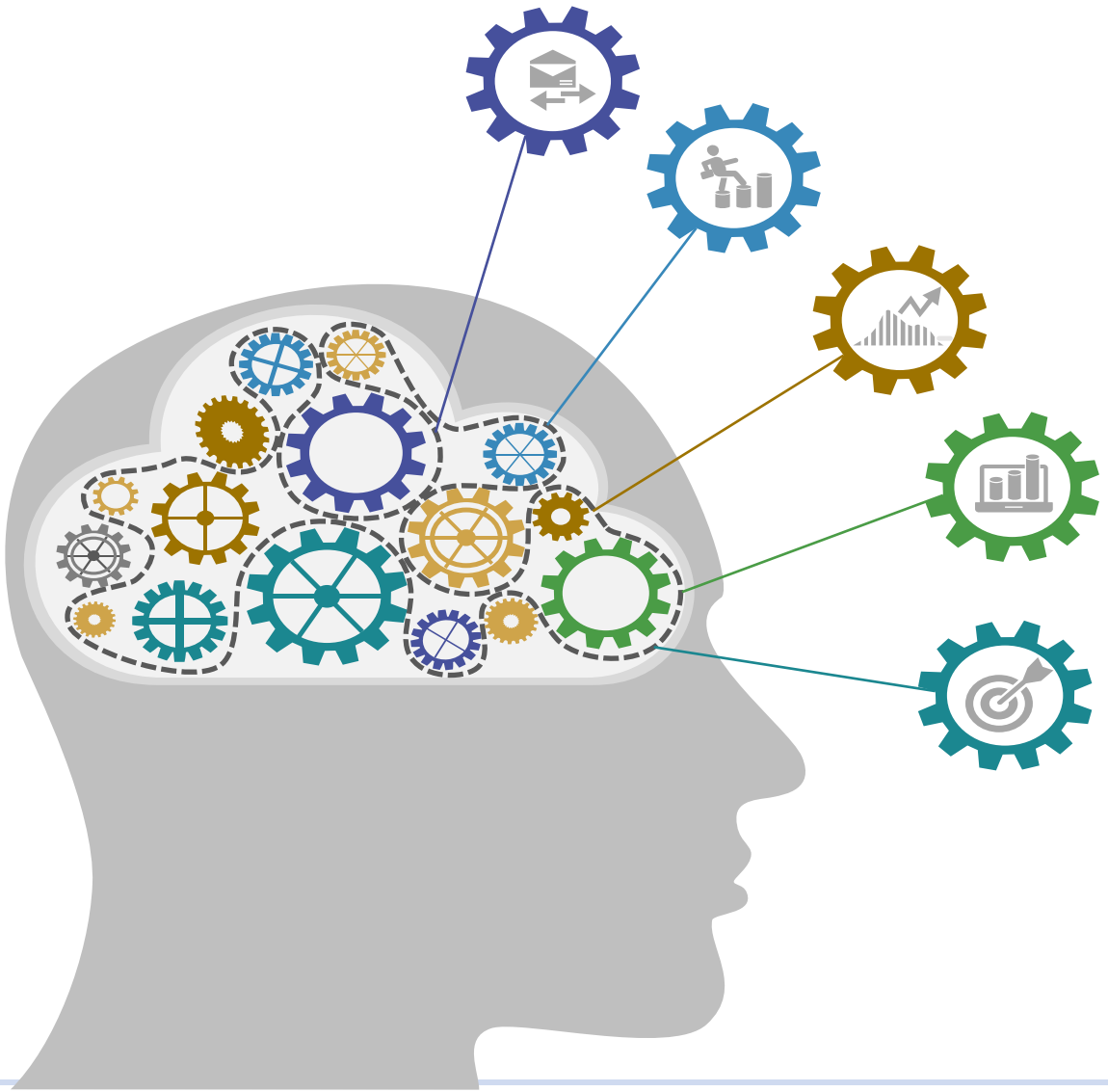
Techniques to make optimal use of available data: M&S, adaptive designs, Bayesian statistics, meta-analytic approaches, external controls, etc.

Evolution of Pediatric Drug Development and Extrapolation

- **Pediatric Heart failure (FDA Workshop: Oct 2017)**
  - Pre-workshop: Full waiver under PREA
  - Pediatric subpopulation similar to adults, use of bridging biomarkers (e.g. NT-proBNP), innovative trial designs in patients with congenital heart disease
- **Pediatric Inflammatory Bowel Disease (FDA Workshop: Nov 2018)**
  - Challenges with trial design, extrapolation, dose selection
  - Move away from placebo-controlled trials, inclusion of adolescents in adult trials, confidence in adult dose finding, PK lead-in versus separate study, totality of evidence approach
- **Polyarticular Juvenile Idiopathic Arthritis (FDA Workshop: Oct 2019)**
  - Similar disease to rheumatoid arthritis in adults
  - PK/safety study sufficient for drugs with well-established MOA; For 1st in class: PK/PD/safety studies may be needed to confirm response
- **Acute pain in patients less than 2 years (Oct 2021)**
  - Drug class specific considerations for extrapolation of efficacy
  - Neonates are different, objective endpoint measures, appropriate pain models and trial design considerations including adaptive trials

Advancing drug development in pediatric SLE

Focus for workshop presentations/discussions



1. What are the similarities and differences between adult and pediatric SLE: disease, pharmacology and response to treatment?
2. What evidence is needed to enable extrapolation of adult efficacy data? What data should be collected in adults to expedite pediatric programs?
3. What innovative trial design can be used expedite development of therapies in pediatric patients with SLE?
4. What are additional considerations for assessing safety of products in pediatric patients with SLE?