U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Understanding the Regulations and Recommendations for Drug Development in Pediatrics and Older Adults with Cancer

Youwei Bi, PhD

Division of Pharmacometrics

Office of Clinical Pharmacology, OTS/CDER/FDA

Disclaimer: The content and views expressed in this presentation are that of the author and should not be interpreted as the position of the US FDA

Outline

- **Pediatric drug development regulations in USA**
  - **PREA**
  - **BPCA**
- **Points to consider in pediatric oncology**
  - **Importance of dose optimization in pediatric oncology**
  - **General PK consideration in pediatric patients**
  - **Application of model-informed drug development**
  - **Pediatric extrapolation**
- **Drug development regulations in older adults with cancer**
- **Points to consider in older adults with cancer**

Pediatric Drug Development Regulations in USA

For approval, pediatric product development is held to same evidentiary standard as adult product development

- Pediatric Research Equity Act (PREA)
  - **Requires** companies to assess safety and effectiveness of new drugs/biologics in pediatric patients (Pediatric Assessment)
- Best Pharmaceuticals for Children Act (BPCA)
  - **Provides** a financial incentive to companies to voluntarily conduct pediatric studies
- 2007 FDA Amendment Act (FDAAA)
- 2012 FDA Safety & Innovation Act (FDASIA) - Title V
- 2017 FDA Reauthorization Act
  - RACE Act for Children

PREA vs BPCA

	PREA	BPCA
Voluntary/ Mandatory	Mandatory	Voluntary
Indication	Requires studies only on indication(s) under review	Studies relate to entire moiety and may expand Indications
Orphan Designation	Orphan drug designations exempt from studies	Studies may be requested for orphan indications
Document	Pediatric Study Plan (PSP)	Written request (WR); Proposed Pediatric Study Request (PPSR)
Incentive	None	6-month patent extension + exclusivity

New Pediatric Labeling

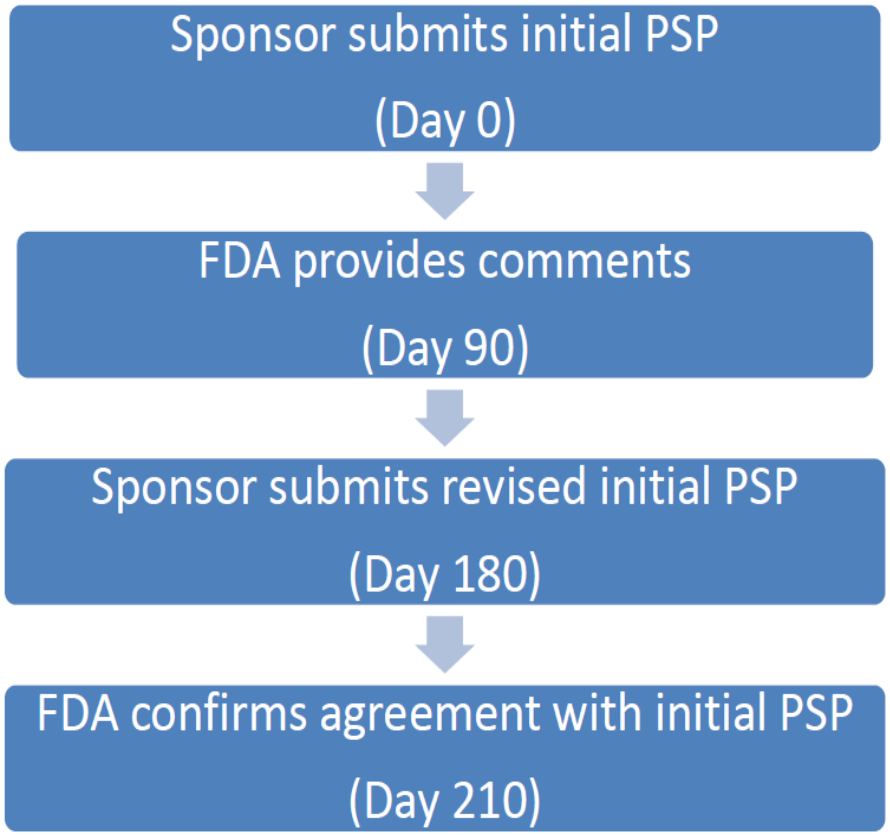
to encourage appropriate use of medications to treat pediatric patients

Submission of Pediatric Study Plan (PSP)

- PREA Is triggered by an application for

– New indication /New dosage form/ New dosing regimen/ New route of administration/ New active ingredient

- Submission and Review of iPSP by FDA's internal Pediatric Review Committee (PERC)



Contents of iPSP

1) Overview - Disease Condition
2) Overview - Drug/Biologic Product
3) Plan for Extrapolation
4) Plan to Request Waiver(s)
5) Summary of Planned Nonclinical and Clinical Studies
6) Pediatric Formulation Development
7) Nonclinical Studies
8) Clinical Data to Support Design and/or Initiation of Studies
9) Planned Pediatric Clinical Studies
10) Timeline of the Pediatric Development Plan
11) Plan to Request Deferral
12) Agreements with Other Regulatory Authorities

FDA Guidance: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry (July 2020)

Best Pharmaceuticals for Children Act (BPCA)

- Provides for voluntary pediatric drug studies via a Written Request (WR)
- Reflects need for information that may produce health benefits in the pediatric population
- Authorizes FDA to request pediatric studies of approved and/or unapproved indications
- Incentive: Pediatric Exclusivity

  - If the terms of the WR have been met and studies were conducted using good scientific principles, the company is awarded an additional 6 months of exclusivity
    - Exclusivity attaches to all existing marketing exclusivities and patents for the drug moiety (initial WR)
    - Pediatric exclusivity does not require positive pediatric studies (initial WR)
    - Granting of exclusivity is reviewed by the FDA Pediatric Exclusivity Board

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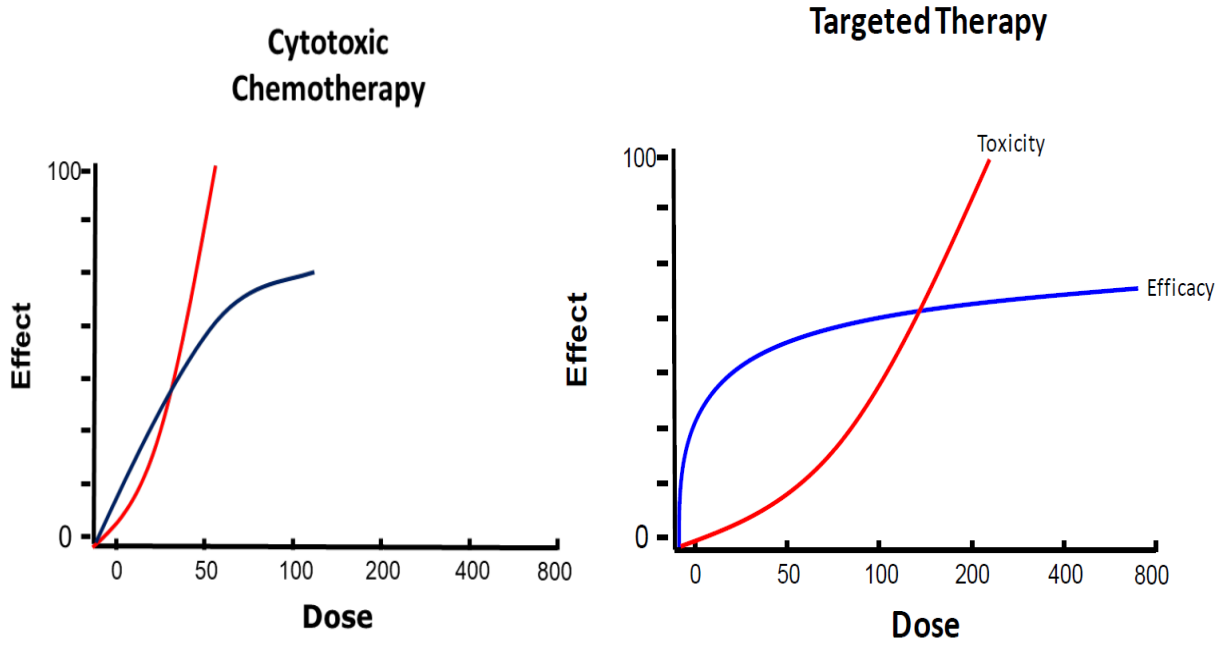
Importance of Dose Optimization in Pediatric Oncology

- Maximization of benefit/risk balance
- Change in pediatric oncology drug landscape leads to more targeted therapies
- Difference in dose-response for oncology products

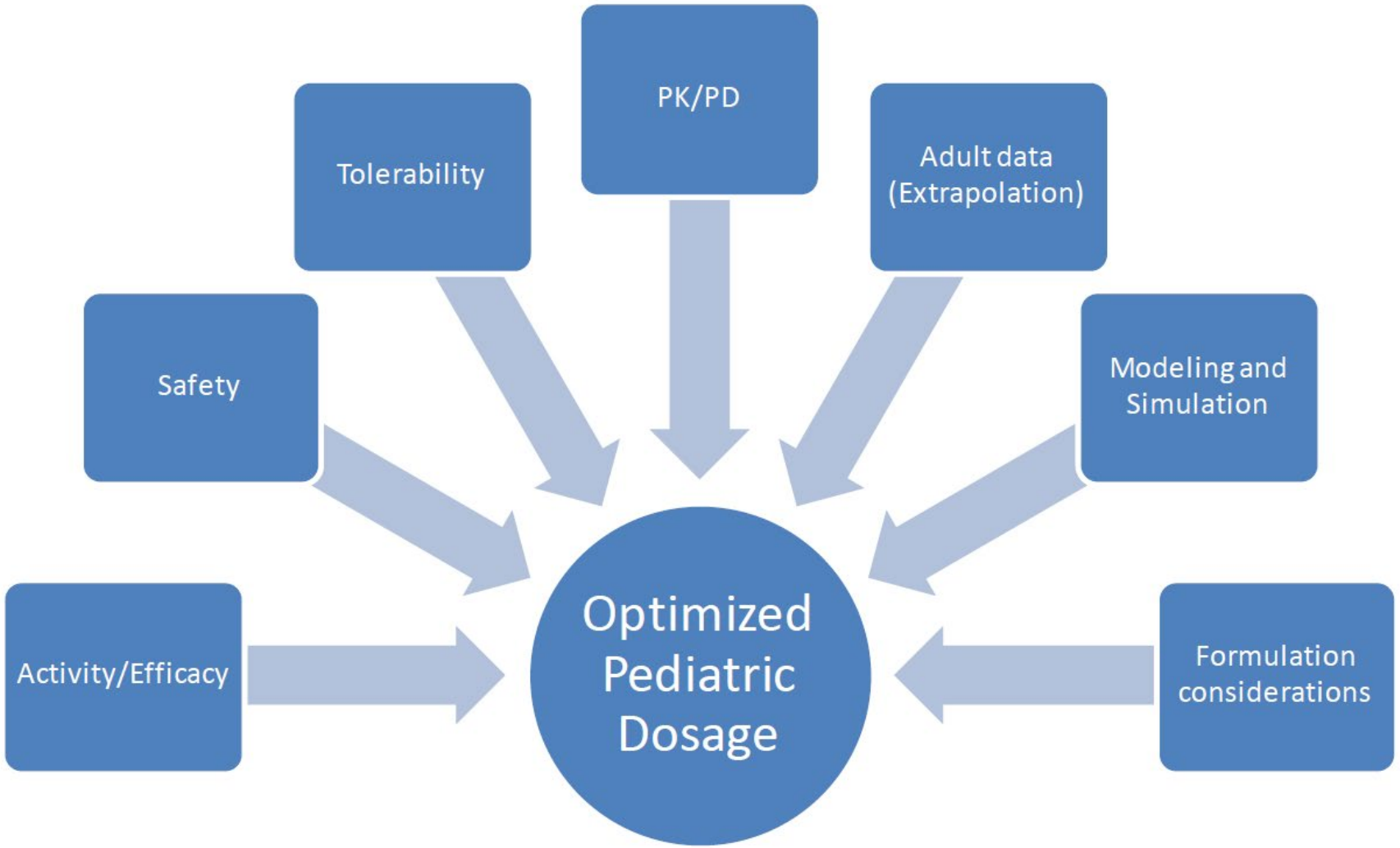


For targeted therapy

- MTD may not be needed
- Long time treatment (months or years)
- Long-term tolerability is important (consider management of grade 1 or 2 toxicities)

Slide adapted from Pediatric ODAC June 16, 2023 by Dr. Kristin Wessel;

Identifying Optimized Dose



Slide Courtesy: Kristin Wessel; Pediatric ODAC June 16, 2023

General PK Considerations for Pediatric Studies

- Well laid out in the regulatory guidance documents
  - General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (FDA Draft Guidance, 2022 Sep Revision 1)
  - Role of the Pharmacokinetics in the Development of Medical Products in the Paediatric Population (EMA, 2006)
  - Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11, 2000)
- PK/PD variability by patient age, organ function, developmental changes (maturation), body weight and body surface area (BSA)
- Pathophysiology (impaired organ function), pharmacogenetics, supportive treatment modalities (e.g., ECMO), age-specific formulation, administration modality (e.g., NJ feeding) can alter systemic exposure and lead to variability

Application of Model-Informed Drug Development (MIDD) in Pediatric Patients

FDA

Pediatric Dose Selection and Optimization

- Identify covariates (weight, BSA, age, etc.)
- Incorporate pediatric ontogeny
- Predict PK in various age groups

Leveraging Knowledge for Bridging Gaps

- Exposure-response for efficacy and safety
- Leveraging prior knowledge from adults or other drugs from the same class

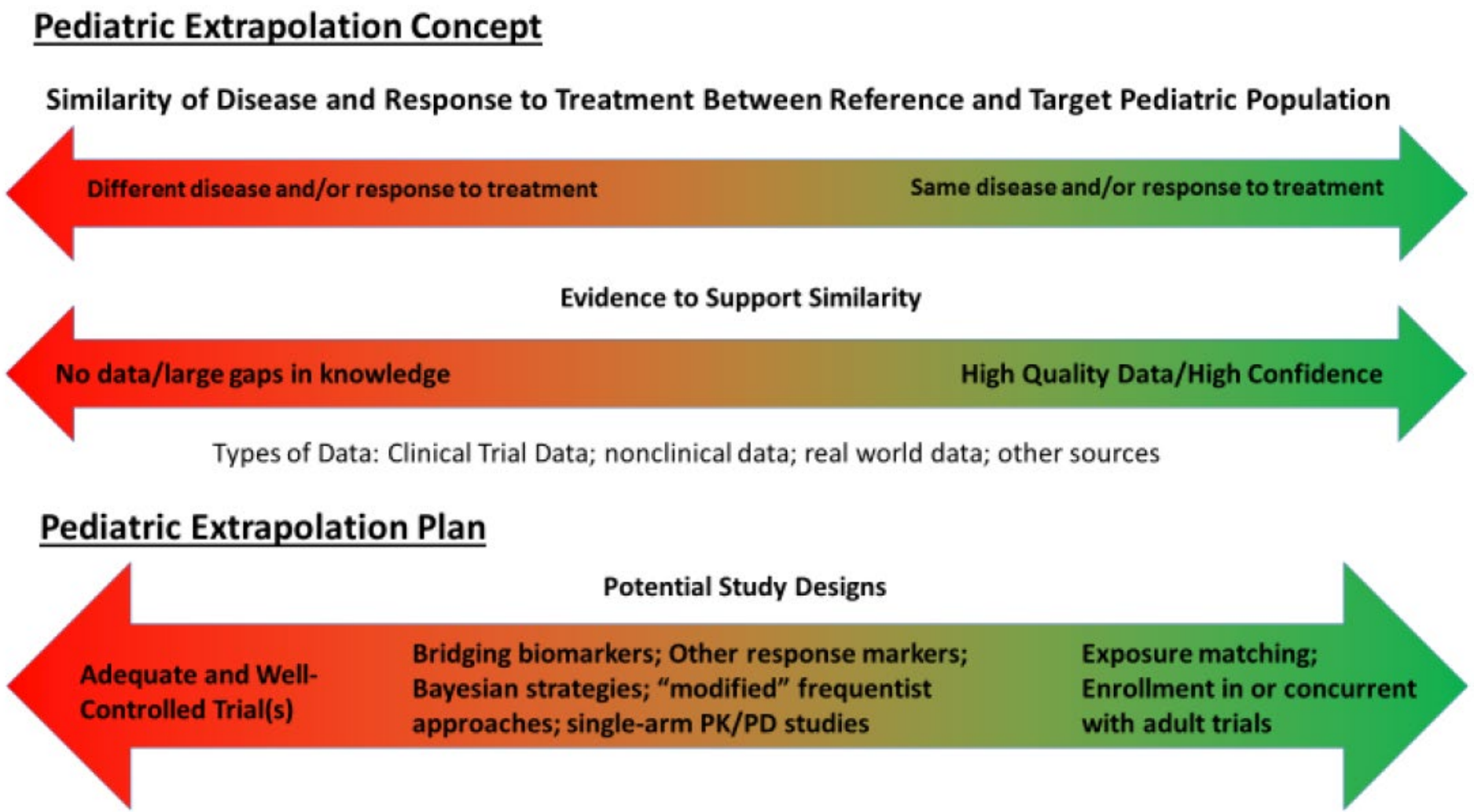
Informing Clinical Trial Design

- Determine appropriate dosages for evaluation across the pediatric age range, sample size, optimal PK sampling for pediatric patients

MIDD in Pediatric Patients: Case Examples

Drug	Indication	Brief Description
Recombinant asparaginase	Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older	Modeling and simulation provided primary evidence of efficacy for approval and recommendation for a dosing regimen not tested in the clinical trial.
Rituximab	Pediatric patients with mature B-cell NHL and mature B-cell acute leukemia (B-AL)	PK simulations as sensitivity analysis supported the recommended dosing regimen and approval in pediatric patients aged 6 months and older, with no PK data available < 3 years old.
Naxitamab-gqgk	Pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow	FDA recommends a dose cap for patients with a body weight (BW) > 50 kg, with a maximum naxitamab dose of 450 mg/cycle based on the pharmacokinetic characteristics of naxitamab and the relationships between naxitamab exposure and efficacy/safety.
Atezolizumab	For the treatment of pediatric patients 2 years of age and older with unresectable or metastatic ASPS	Provided support to treatment of pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma in the absence of efficacy data

Pediatric Extrapolation



ICH HARMONISED GUIDE E11A PEDIATRIC EXTRAPOLATION

Many Other Things to Consider

- Age-appropriate formulation
  - Ability to swallow, palatability, food effect
  - Consider it early
  - Relative bioavailability study of the pediatric and adult formulations should also be conducted (in adults) as early as feasible

- Inclusion of adolescents in adult trials
  - March 2019 - Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry

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Regulations for Drug Development in Older Adults with Cancer

- Need for more older adults in clinical trials
  - By 2030, it is estimated that 77 million people will be over 65 years of age
  - Often excluded due to perceived high risk associated with age, comorbidity, and polypharmacy
  - 'Geriatric gap' persists

- 2012 – ICH E7 studies in support of special populations: Geriatrics Questions and Answers guidance for industry
- September 2020 – FDA guidance: Labeling guidance for geriatric population
- Nov 2020 – Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry
- March 2022 – Inclusion of Older Adults in Cancer Clinical Trials Guidance for Industry

Knowledge Gap in Older Adults

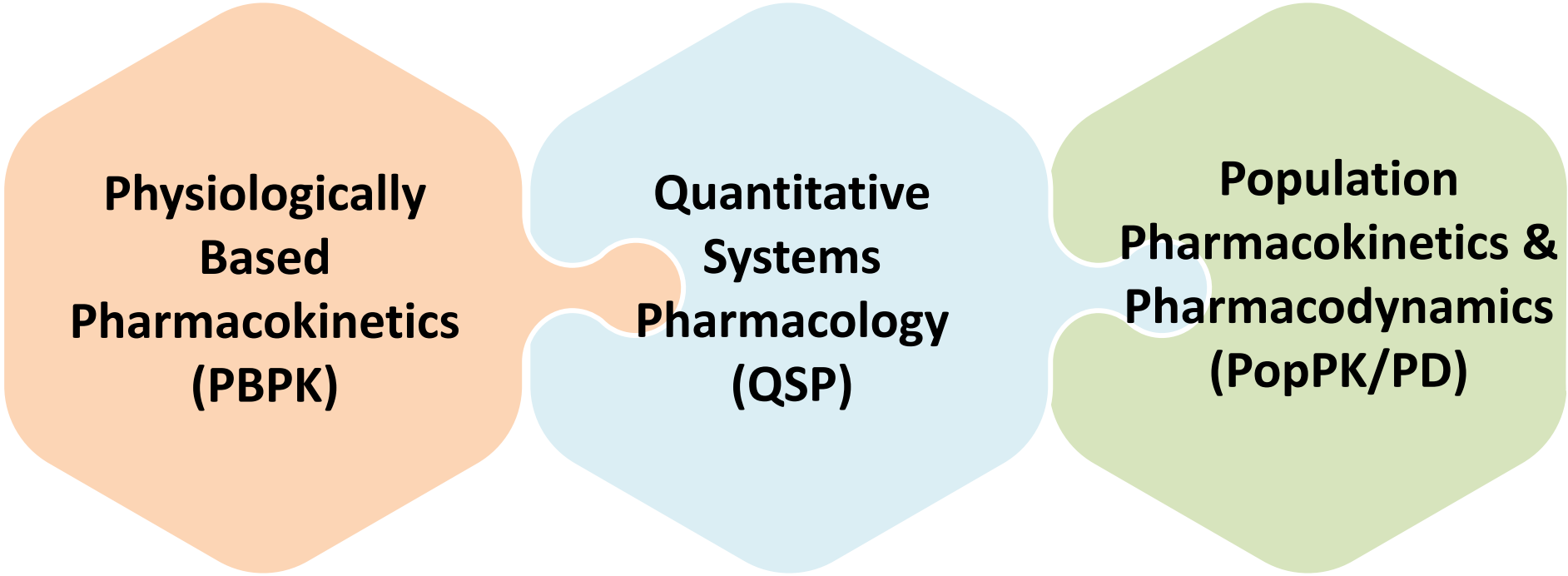
- Age effect on PK:
  - General more frequent organ impairment
  - General change in blood flow, liver size or transporter action
  - Liver enzyme (e.g. CYP3A) and DDI effect

Most demographic factors (age, weight) can be addressed by clinical pharmacology studies or tools (e.g. modeling)

- But age itself is not completely reflecting intrinsic factors (organ impairment) and external factors (compliance, comedication)

- The real GAP: PD, effectiveness, safety similarity (more harmful AEs), comedications, etc.

MIDD Tools to Inform Dose Selection in Older Adults



- Provide understanding of absorption and disposition in older adults
- Anticipate impact of polypharmacy on PK

- Integrate mechanisms of aging and comorbidities
- Anticipate PD response and clinical outcomes

- Integrate clinical data from early clinical studies
- Provide an estimate of drug variability

Slide Courtesy: R Madabushi

Interaction with FDA is Recommended

- Early discussions with FDA are recommended for input on dose optimization strategies/inclusion plan
  - Pre-Investigational New Drug (IND) meeting
  - End of Phase 1/2 meeting
  - Type D meeting –intended to focus on a narrow set of issues
  - **MIDD meeting**

- Resources
  - FDA guidance
  - ICH E11A guideline include updates on several topics including extrapolation, modeling and simulation, ethics, formulations
  - Public Meetings/Workshops
  - Publications

Summary

Ped-iatrics	• Children are protected through research, not from it • Established pediatric regulations (PREA, BPCA) increased the availability of pediatric-specific information in prescription product labeling. • Early and reliable characterization of PK and **dose optimization** is critical in pediatric drug development • **MIDD** approaches are very useful to integrate knowledge and inform dose • Improved framework for pediatric extrapolation (ICH E11A)
Older Adults	• Obtain PK and activity data early • Include older adults and collect additional relevant data in efficacy and safety trials • Evaluate differences/similarity in PK, PD, effectiveness and safety (**MIDD** can help)
Working Together	• FDA is committed to working with external stakeholders and to increase availability of safe and effective treatments for pediatric patients and older adults. Early communication is highly recommended

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