EPTRI developmental pharmacology
TRP

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ePTRI
European Paediatric Translational Research Infrastructure

Erasmus MC
Universitair Medisch Centrum Rotterdam

KATHOLIEKE UNIVERSITEIT
LEUVEN

developmental pharmacokinetics and -dynamics

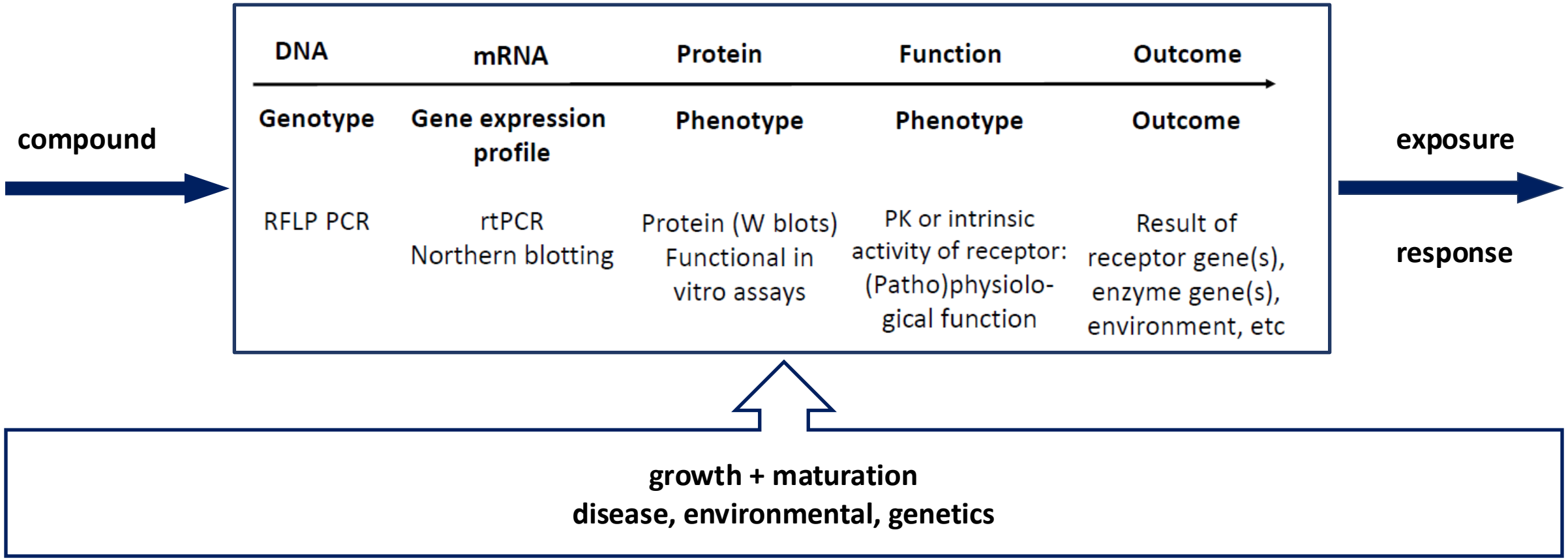

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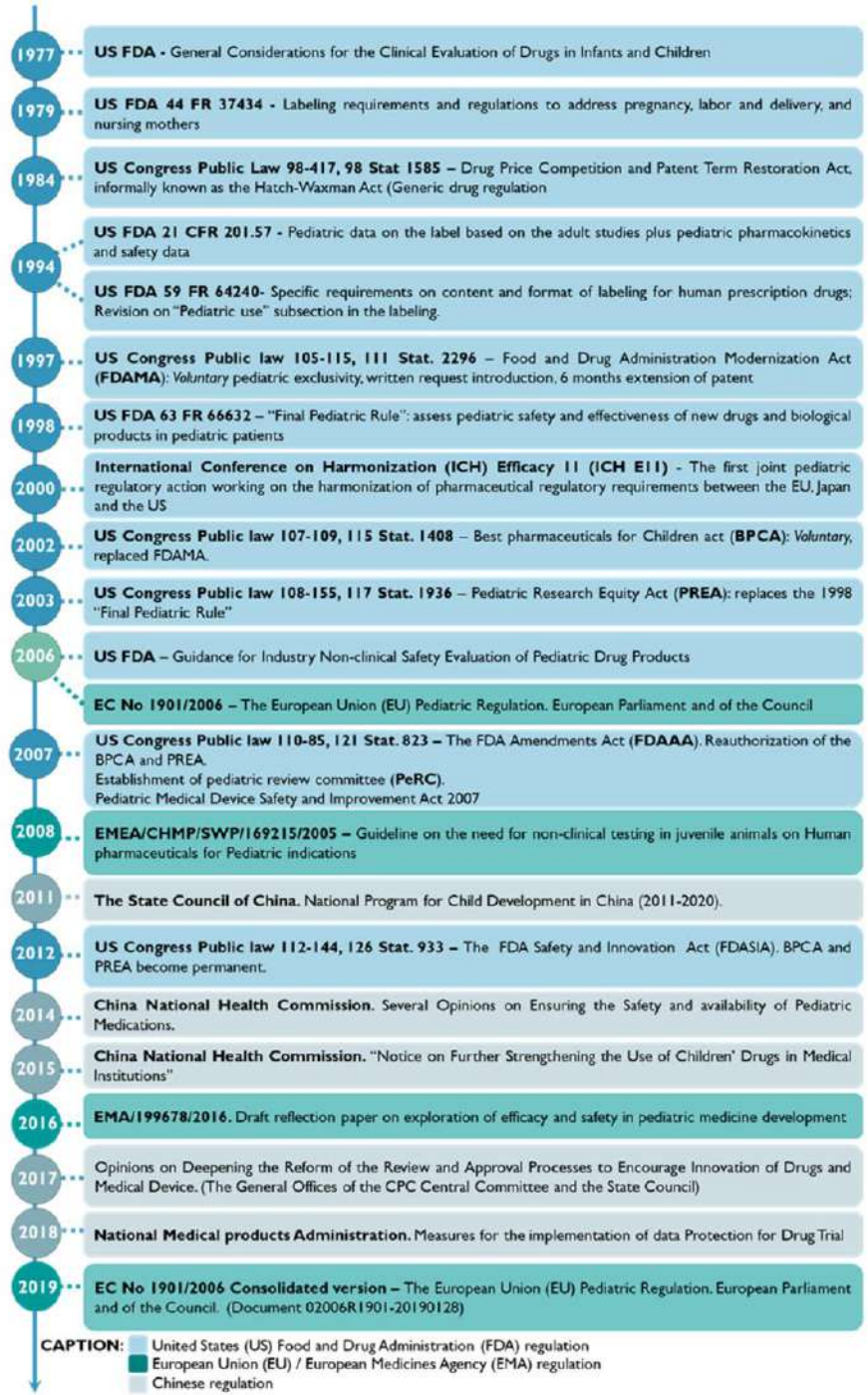
Figure 2. A summary of the factors impacting pharmacotherapy practice and the development of therapeutics aimed at pediatric patients.


1977
US FDA - General Considerations for the Clinical Evaluation of Drugs in Infants and Children
1979
US FDA 44 FR 37434 - Labeling requirements and regulations to address pregnancy, labor and delivery, and nursing mothers
1984
US Congress Public Law 98-417, 98 Stat 1585 – Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act (Generic drug regulation
1994
US FDA 21 CFR 201.57 - Pediatric data on the label based on the adult studies plus pediatric pharmacokinetics and safety data
US FDA 59 FR 64240- Specific requirements on content and format of labeling for human prescription drugs; Revision on "Pediatric use" subsection in the labeling.
1997
US Congress Public law 105-115, 111 Stat. 2296 – Food and Drug Administration Modernization Act (FDAMA): Voluntary pediatric exclusivity, written request introduction, 6 months extension of patent
1998
US FDA 63 FR 66632 – "Final Pediatric Rule": assess pediatric safety and effectiveness of new drugs and biological products in pediatric patients
2000
International Conference on Harmonization (ICH) Efficacy 11 (ICH E11) - The first joint pediatric regulatory action working on the harmonization of pharmaceutical regulatory requirements between the EU, Japan and the US
2002
US Congress Public law 107-109, 115 Stat. 1408 – Best pharmaceuticals for Children act (BPCA): Voluntary, replaced FDAMA.
2003
US Congress Public law 108-155, 117 Stat. 1936 – Pediatric Research Equity Act (PREA): replaces the 1998 "Final Pediatric Rule"
2006
US FDA – Guidance for Industry Non-clinical Safety Evaluation of Pediatric Drug Products
EC No 1901/2006 – The European Union (EU) Pediatric Regulation. European Parliament and of the Council
2007
US Congress Public law 110-85, 121 Stat. 823 – The FDA Amendments Act (FDAAA). Reauthorization of the BPCA and PREA.
Establishment of pediatric review committee (PeRC).
Pediatric Medical Device Safety and Improvement Act 2007
2008
EMEA/CHMP/SWP/169215/2005 – Guideline on the need for non-clinical testing in juvenile animals on Human pharmaceuticals for Pediatric indications
2011
The State Council of China. National Program for Child Development in China (2011-2020).
2012
US Congress Public law 112-144, 126 Stat. 933 – The FDA Safety and Innovation Act (FDASIA). BPCA and PREA become permanent.
2014
China National Health Commission. Several Opinions on Ensuring the Safety and availability of Pediatric Medications.
2015
China National Health Commission. "Notice on Further Strengthening the Use of Children' Drugs in Medical Institutions"
2016
EMA/199678/2016. Draft reflection paper on exploration of efficacy and safety in pediatric medicine development
2017
Opinions on Deepening the Reform of the Review and Approval Processes to Encourage Innovation of Drugs and Medical Device. (The General Offices of the CPC Central Committee and the State Council)
2018
National Medical products Administration. Measures for the implementation of data Protection for Drug Trial
2019
EC No 1901/2006 Consolidated version – The European Union (EU) Pediatric Regulation. European Parliament and of the Council. (Document 02006R1901-20190128)
CAPTION:
United States (US) Food and Drug Administration (FDA) regulation
European Union (EU) / European Medicines Agency (EMA) regulation
Chinese regulation

Considerations for

Mechanism of Action / Molecular Target PIP

Art 75 EC proposal of legislation - Waivers

1. In accordance with the procedure set out in Article 78, the Agency may decide that the production of the information referred to in, Article 6(5), point (a), of [revised Directive 2001/83], shall be waived for products or for classes of medicinal products, if there is evidence showing any of the following:

(a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations, **unless when the product is directed at a molecular target that on the basis of existing scientific data**, is responsible for a different disease or condition in the same therapeutic area in children than the one for which the specific medicinal product or class of medicinal products is intended for in the adult population;

(c) that the specific medicinal product is likely to not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. The waiver provided for in paragraph 1 may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both.

3. On the basis of the **experience acquired as a result of the operation of this Article or of scientific knowledge the Commission is empowered to adopt delegated acts** in accordance with Article 175 to amend the grounds for granting a waiver detailed in paragraph 1.

Art 76 Validation of a paediatric investigation plan or of a waiver

1. A paediatric investigation plan or an application for waiver shall be submitted to the Agency with a request for agreement, except in duly justified cases, before the initiation of safety and efficacy clinical studies so as to ensure that a decision on use in the paediatric population of the medicinal product concerned can be given at the time of the marketing authorisation or other application concerned.

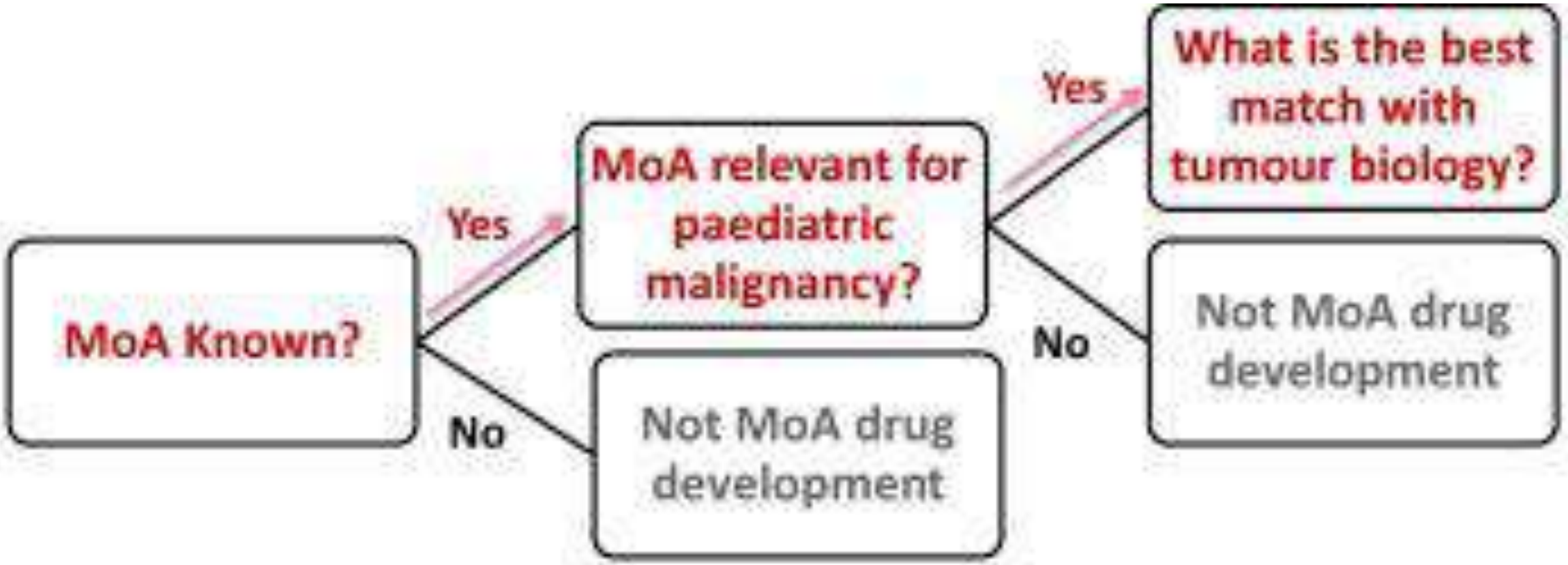
2. Within 30 days following receipt of the request referred to in paragraph 1, the Agency shall verify the validity of the request and communicate the result to the applicant.

3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until the supplementary information requested has been provided.

4. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Rationale

- The guidance will be a regulatory document with implications for the sponsors, the clinicians and the patients
- Therefore the „Mechanism of Action / Molecular Target PIP“ needs careful consideration preferably before any guidance will be discussed
- E.g. scientific questions, operational challenges, ethical considerations and patients’ views to be explored
- EFGCP is in our view an ideal convener for such multi-stakeholder discussions



- **Aggregated database of paediatric tumour targets** defines the information required to underpin selection of a paediatric MoA informed approach
- Drugs are selected based on the presence and prioritization of their molecular targets as key drivers of paediatric malignancies

Definition Molecular target vs Mechanism of Action (MoA)

- “how the product works” (its mechanism of action)
- “The term “target” is used most often in the scientific literature to describe the specific molecular target (protein, RNA molecule, etc.) that a drug interacts with to initiate a biological response”.
- MoA “is often used synonymously with “target,” but it is also used “to describe the drug's action at a higher level of biological complexity, referring to a cell signaling system or processes that are impacted by the drug through its interaction with a specific molecular target”

Davis RL. Mechanism of Action and Target Identification: A Matter of Timing in Drug Discovery. iScience 2020; 23(9):101487; https://doi.org/10.1016/j.isci.2020.101487

- **Scientifically and clinically meaningful, doable R&D** that benefits paediatric patients, e.g. preclinical models
- **Feasibility of clinical trials**, specifically in small geographically dispersed populations including rare diseases
- **Summary**: **Components of a robust framework** for the implementation of Art 75b underpinned by science and ethical principles of research in a vulnerable population

27 August 2024
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

ICH E11A Guideline on pediatric extrapolation

Step 5

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	06 April 2022
Deadline for comments	06 August 2022
Final adoption by CHMP	25 July 2024
Date for coming into effect	25 January 2025

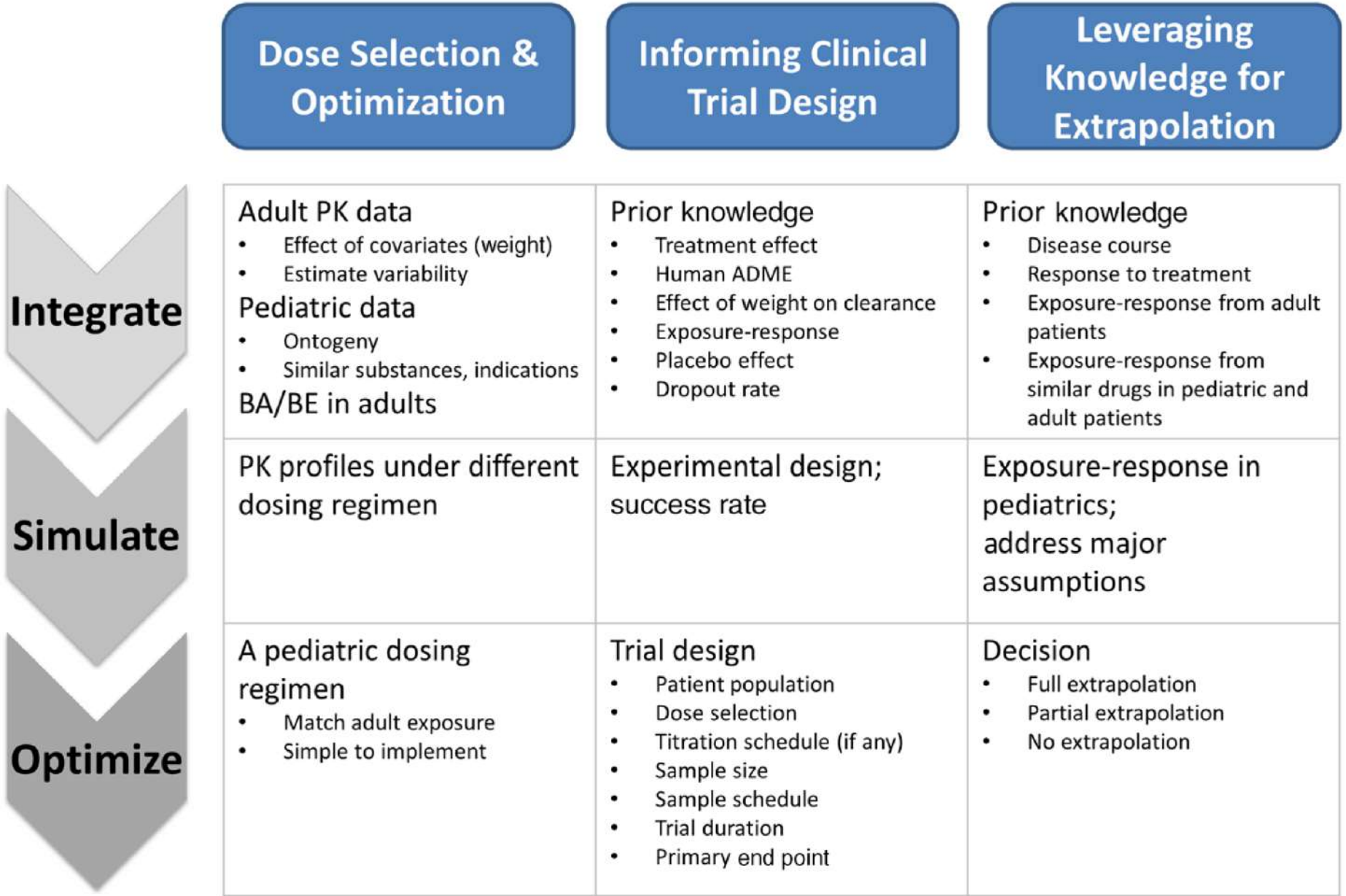
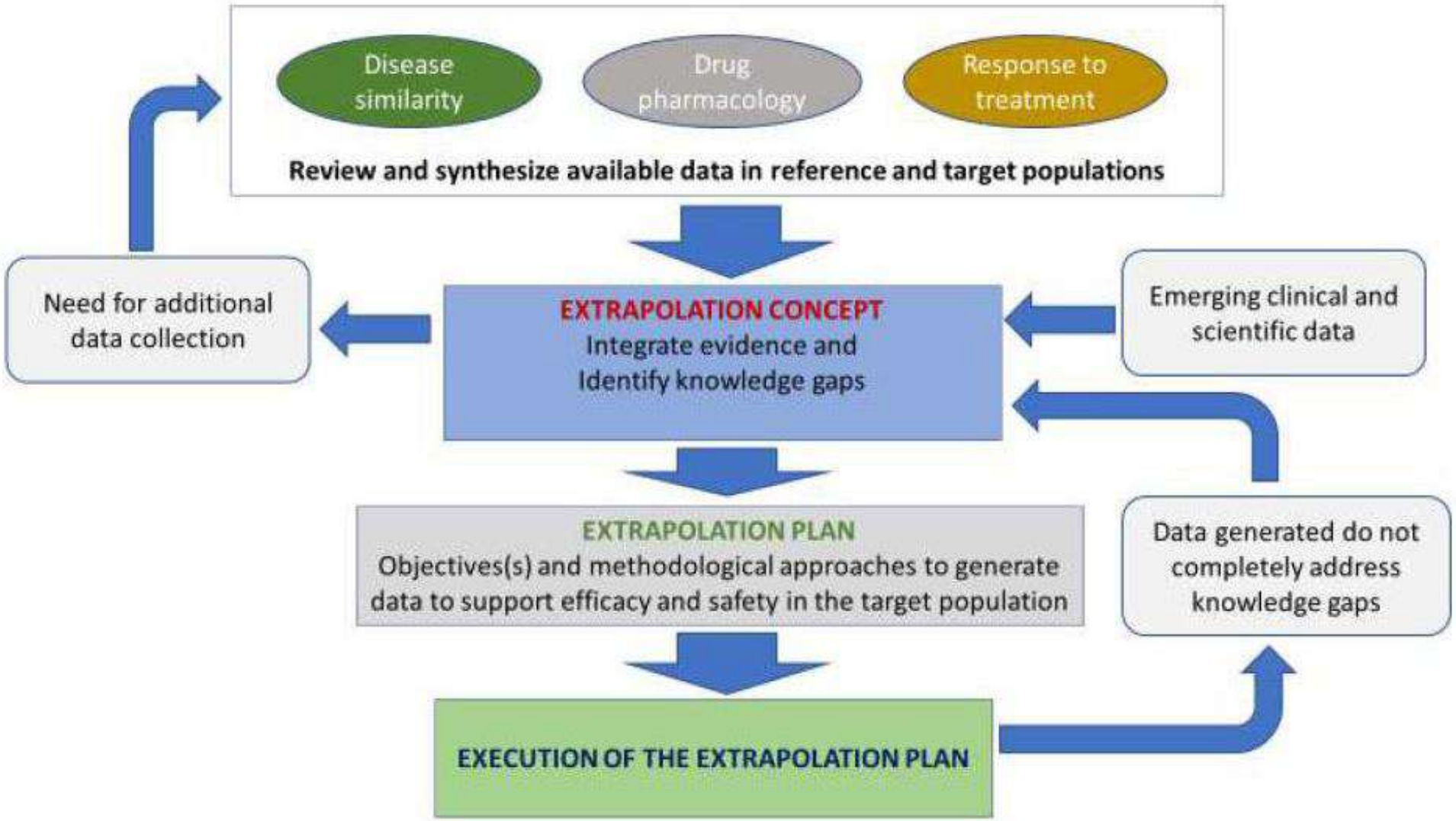
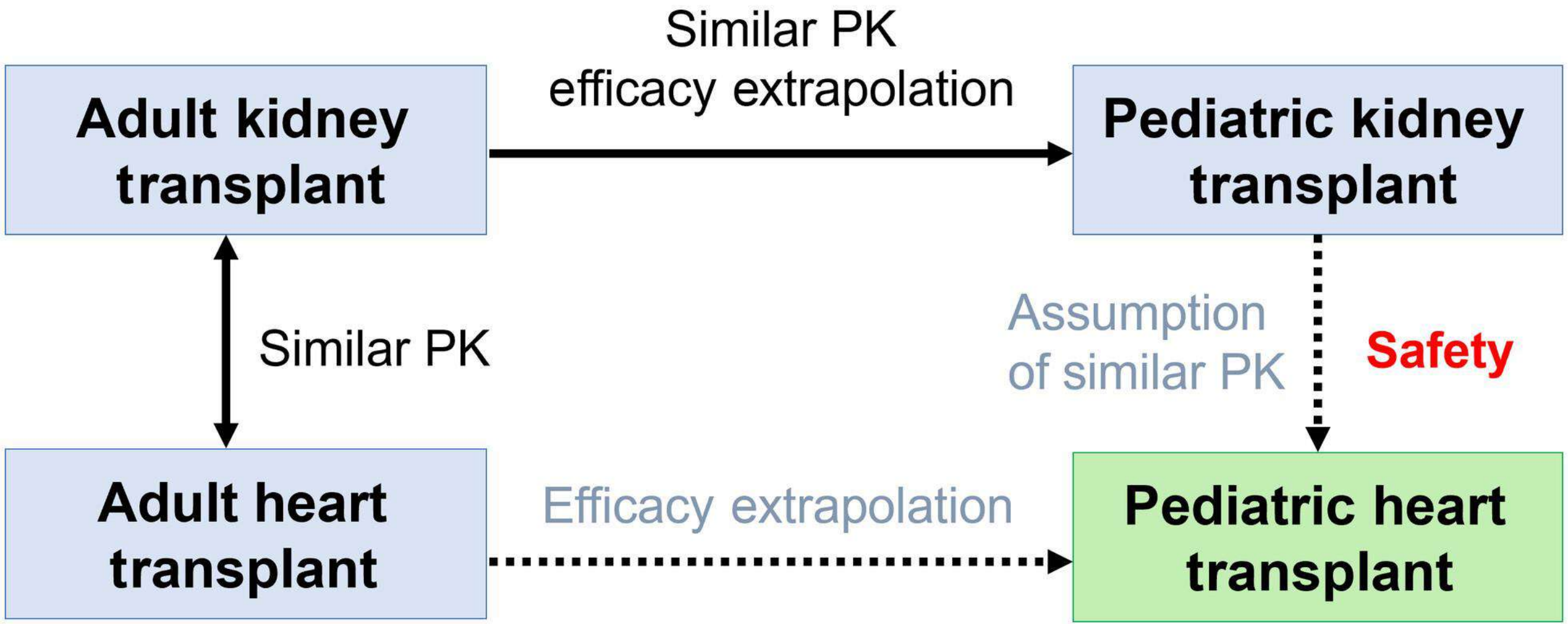
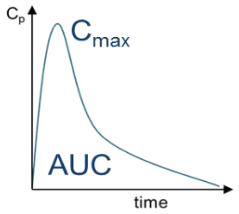
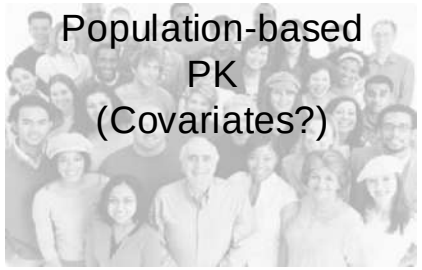
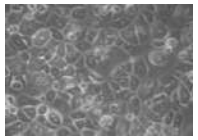
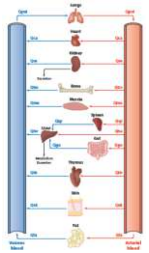


Figure 3. Suggested workflow of applying MIDD in pediatric drug development. The figure illustrates the suggested workflow for drug developers to consider when applying MIDD methods in pediatric dug development. The bullets cover some common considerations at each "Integrate-Simulate-Optimize" procedure. BA, bioavailability; BE, bioequivalence; PK, pharmacokinetic.

Figure 2: Pediatric Extrapolation Framework

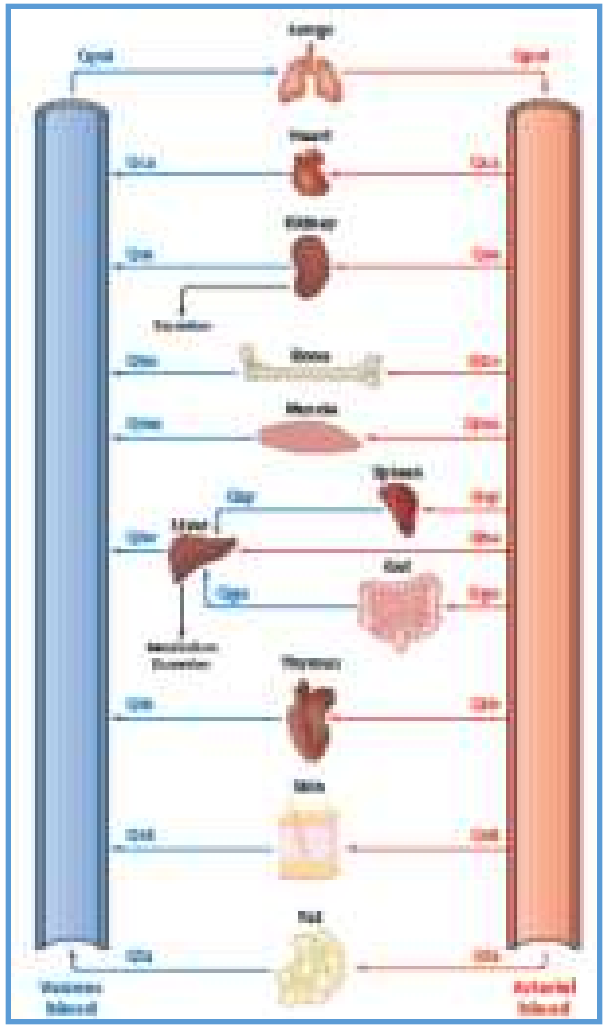


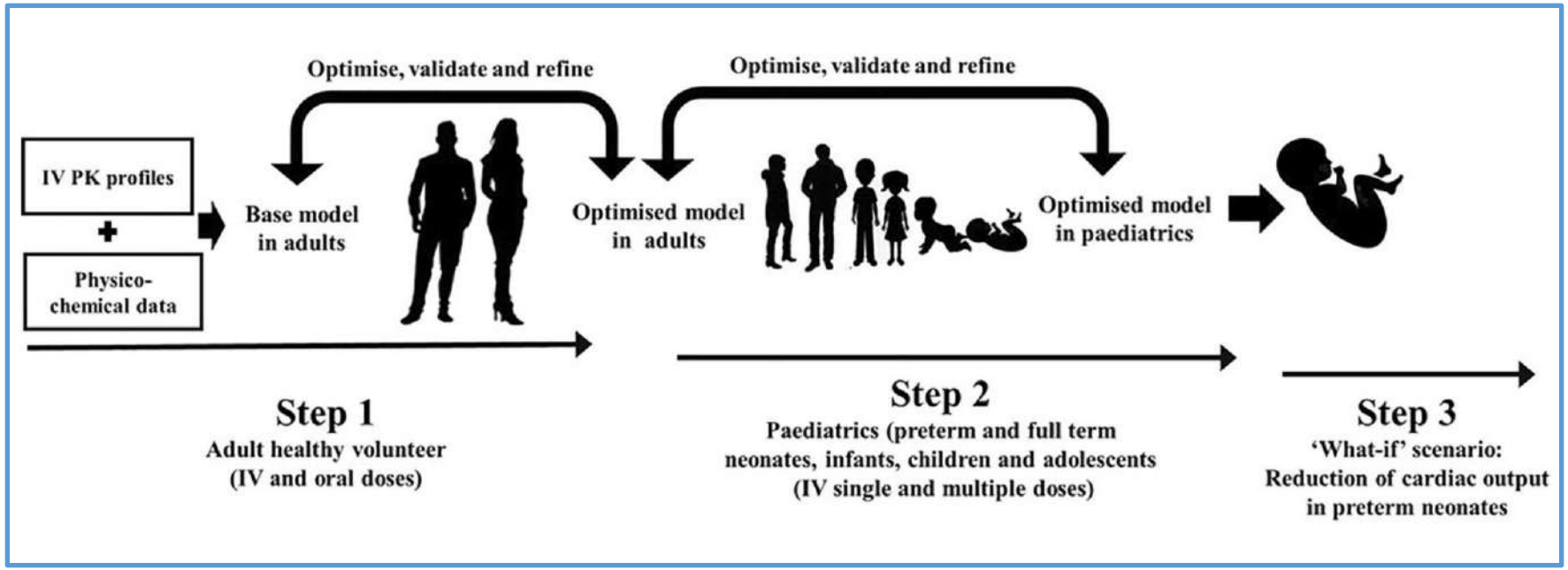

Similar PK
efficacy extrapolation
Adult kidney transplant
Pediatric kidney transplant
Similar PK
Assumption of similar PK
Safety
Adult heart transplant
Efficacy extrapolation
Pediatric heart transplant

	Data gathering	Modelling	Clinical implications
"TOP DOWN" **Clinic to mechanistic (population-based)**	Plasma Data 	Population-based PK (Covariates?) 	Confirming 
"BOTTOM UP" ***In vitro* to *In vivo* (IVIVE)**	 Demography Physiology Genetics *In vitro* data  	PBPK/IVIVE 	Learning 

how to integrate PK/PD, and safety

we can use what we already know, bottom up (‘*in silico*’, PBPK)





Olusola et al, Biopharm Drug Dispos 2021; Allegaert et al, Pharmaceutics 2022

Pharmacokinetics, -dynamics and dosing considerations in children

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