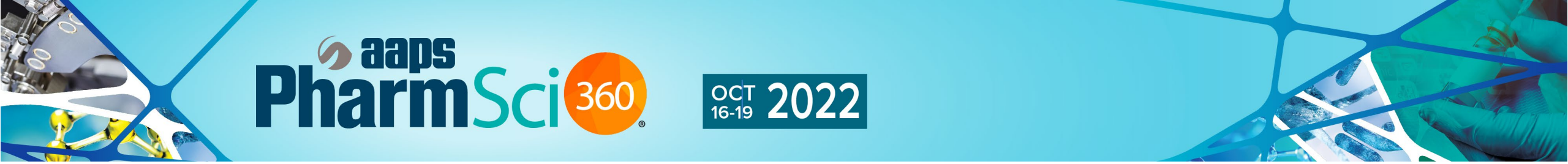

From Preclinical to Clinical Drug Product Development: A Path for Smooth Transition

October 18, 2022

Sandra Suarez Sharp

Vice President, Regulatory Affairs, Simulations Plus, Inc.

SimulationsPlus

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Session Description and Objectives

- It is challenging to establish a standard approach for moving from preclinical to clinical phases of development. Many hurdles exist during formulation selection and for extrapolation of doses from animals to humans; what may have worked well for one drug candidate may not be appropriate for others. This presentation will provide a general framework/strategy to follow when moving from preclinical to clinical studies (FIH) based on risk identification and mitigation focusing on the application of mechanistic modeling and simulation (PBPK)

- To emphasize the relevance of cross-functional multidisciplinary collaboration for successful transition from preclinical to clinical studies
- To describe data collection considerations on drug product quality, biopharmaceutics, preclinical and clinical testing strategies, as well as study design on the conduct of FIH studies (small molecules)
- To discuss the principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts
- To list strategies for risk assessment and mitigation
- To illustrate the relevance of PBPK models on streamlining the transition from preclinical to clinical phases and its contribution in accelerating the drug product development process

Biography and Contact Information

- Dr. Sandra Suarez-Sharp is currently the Vice President of Regulatory Affairs at Simulations Plus
- Prior to joining Simulations Plus, Dr. Suarez-Sharp was a master reviewer and scientific advisor to the Division of Biopharmaceutics, Office of Product Quality in areas such as in vitro in vivo correlations (IVIVCs), biowaivers, RTRT dissolution models, and physiologically based biopharmaceutics modeling (PBBM)
- She spent 10 years as a clinical pharmacology reviewer at OCP/FDA supporting several therapeutic areas
- She has many publications related to the areas of dissolution, IVIVCs, establishment of specifications with clinical relevance, and the use of PBBM in regulatory decision making

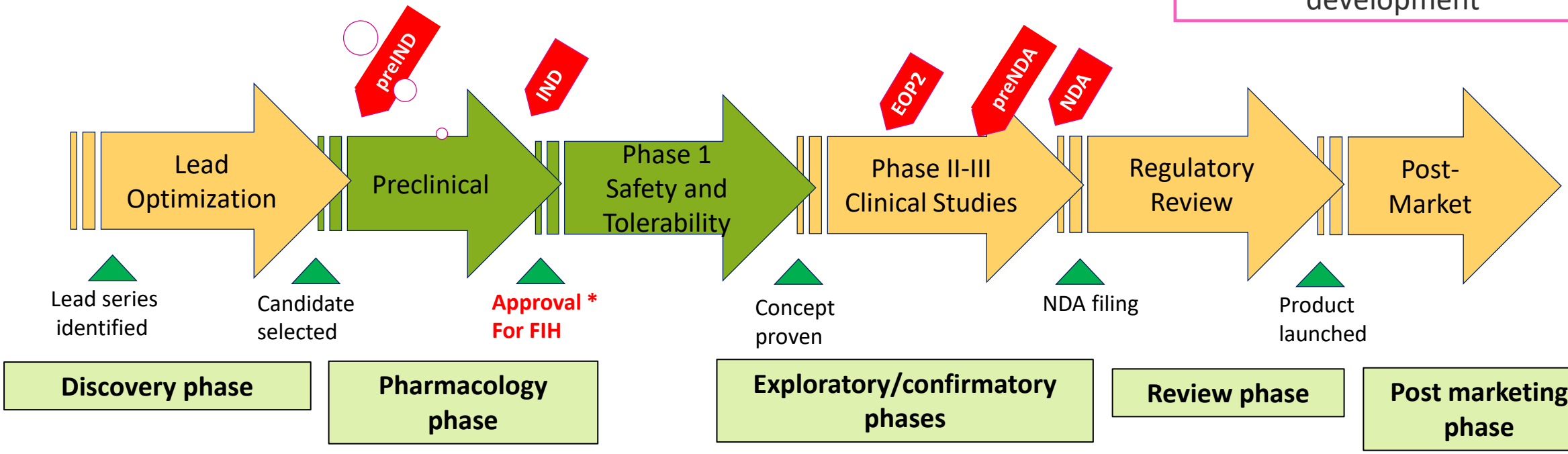
Contact Information

Sandra.Suarez@simulations-plus.com

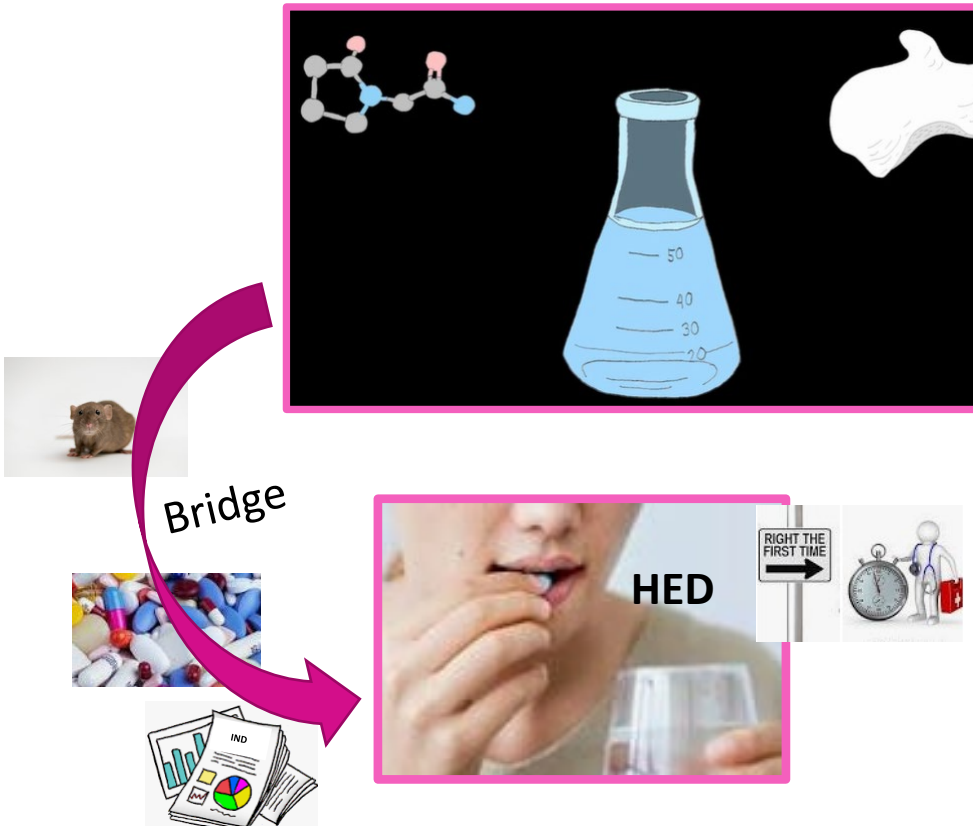
Phases of Drug Product Development – Milestones

How do we achieve smooth transition from preclinical to early clinical phases of development?

The motto "begin with the end in mind"* is particularly appropriate for preclinical development



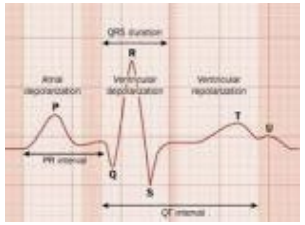
The Purpose of Preclinical Phase of Development



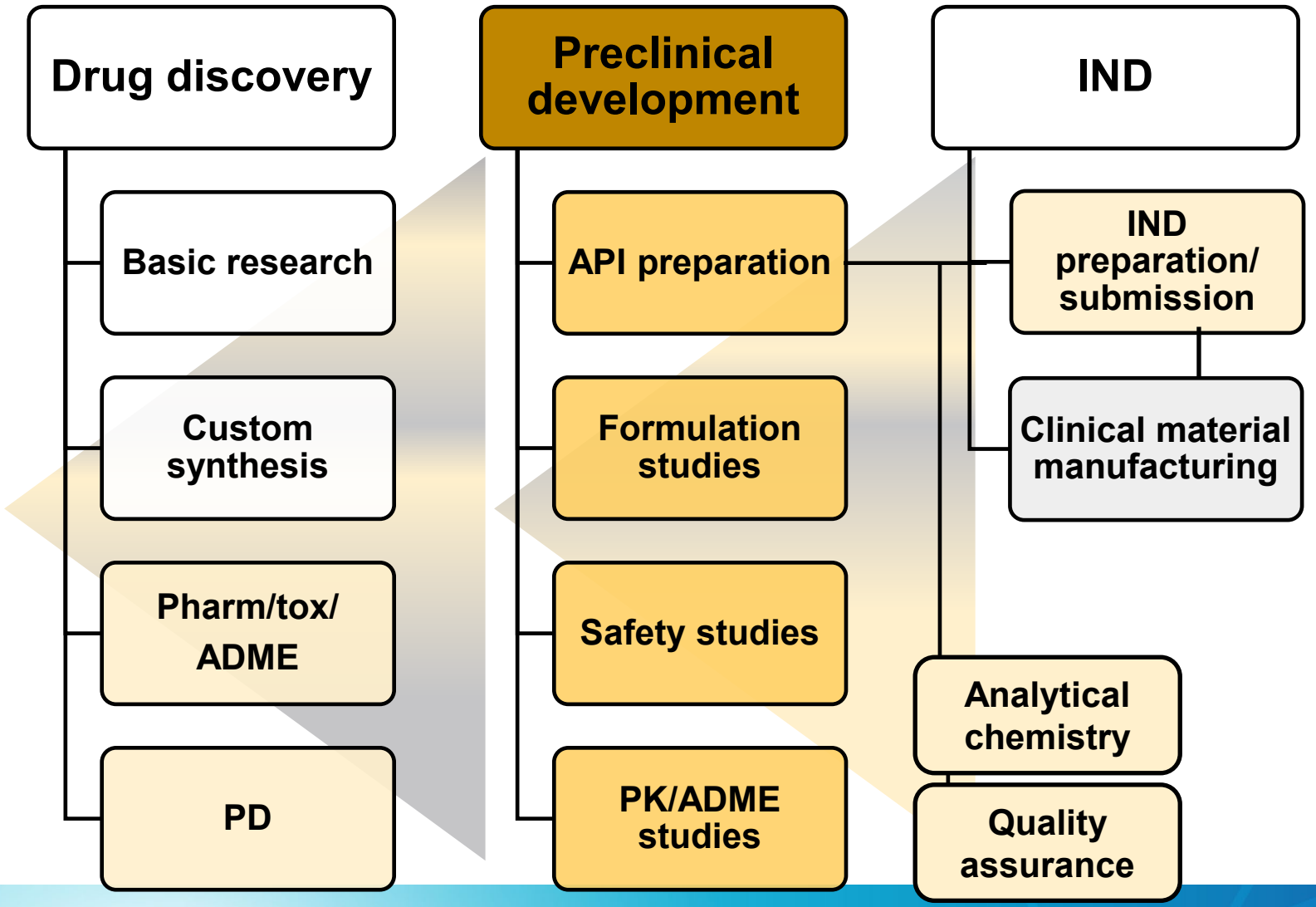
- Select an appropriate formulation (prototype)
- Identify an equivalent dose to be tested in humans (HED)
- Determine the dose range that should be studied prior to taking a new drug candidate into a FIH trial
- Determine the route, frequency, and duration of exposure
- Develop an appropriate procedure for new drug scale-up
- Compile associated documentation for e.g., IND filing to FDA or an Investigational Medicinal Product Dossier to EMA

The Purpose of First-in-Human (FIH) Trials

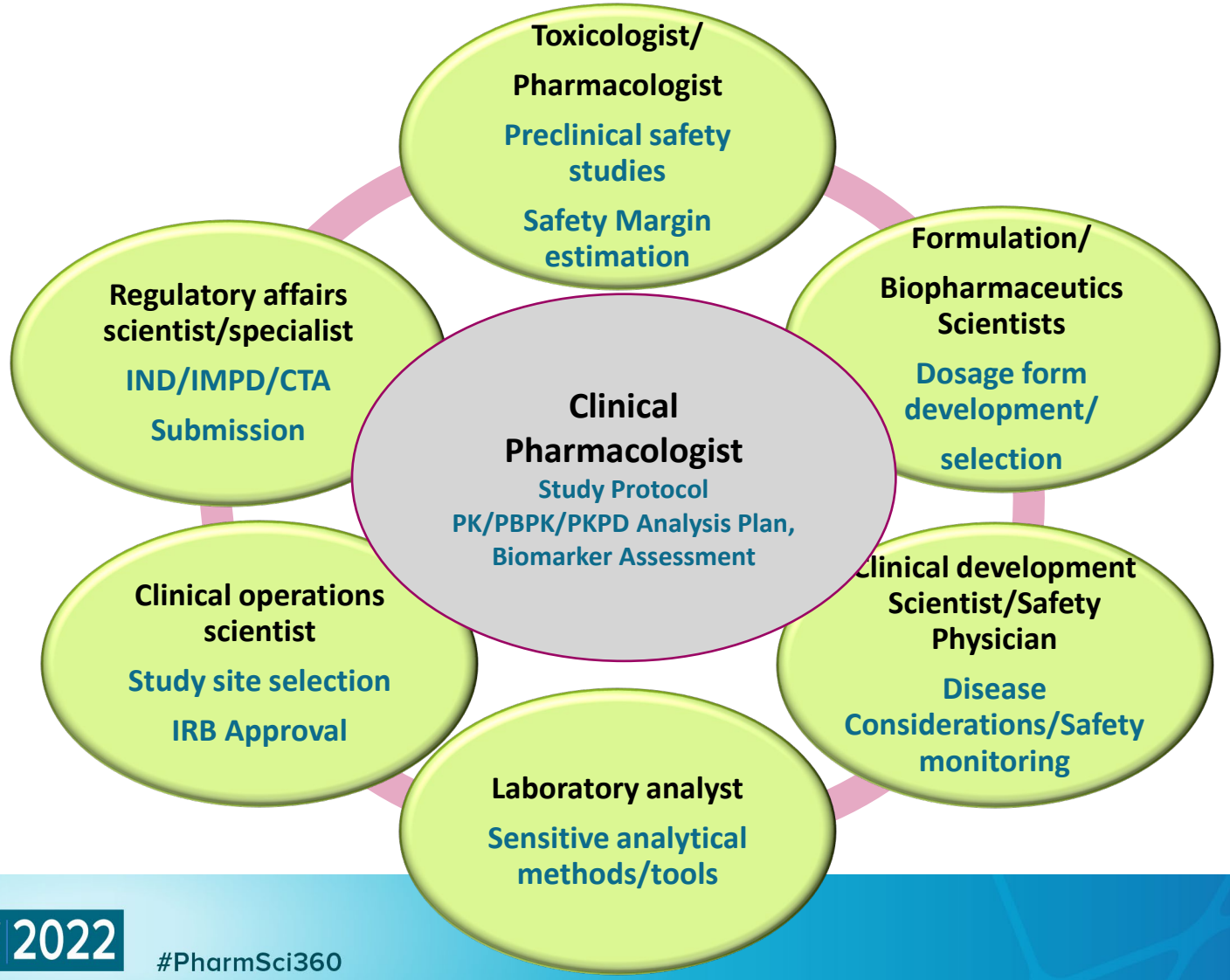
- To evaluate an investigational drug in humans for the first time
- To study the human clinical pharmacology, tolerability and safety of the investigational drug
  - Collection of additional data e.g., food effect, DDIs, different age groups or gender, proof of concept and relative BA of different formulations, QTc prolongation
- To understand how effects seen in preclinical studies translate into humans
- To inform the decision-making processes for the continuation of dosing and inform commercial formulation development



Preclinical Drug Development Stages



Multidisciplinary Integration – Key for Successful Transition to FIH



The Role of Preclinical Safety – Data Collection Considerations

- Identification of target expression/nature
- The relationship to drug exposure
  - Metabolism and other PK aspects
- Pharmacodynamics
  - Receptor binding occupancy
  - Dose-response relationships
- Determination of on-target and off-target effects
- Identification of organ toxicity
  - Toxicokinetic/safety pharmacology should be available in all species evaluated in the preclinical safety studies
- Identification/ qualification of safety biomarkers to monitor in the clinic

Data collection will depend on e.g., type of molecule and QTPP

The use of in vitro studies, including studies using human-derived materials, is encouraged whenever scientifically relevant and sufficiently validated.[1]

QTTP: Quality Target Product Profile

References 1,2,3,4

ICH recommended preclinical studies enabling FIH for small molecules – Example preclinical check list*

Study	Conducted	In vitro/ animal study	Risk assessment	Risk mitigation strategy
Pharmacodynamics *In vitro* (MOA) *In vivo* (MOA and therapeutic effect)	✓	Both	**HIGH:** Mode of action involves irreversible binding	Detailed characterization of PKPD relationship. Application of safety factors.
Safety pharmacology *In vitro* (concentration-effect relationship) *In vivo* (dose-response for e.g., CNS, CV, respiratory effects)				
Pharmacokinetics *In vitro* metabolism (across species microsomal metabolism) *In vitro* plasma protein binding Toxicokinetics from repeat dose GLP toxicity studies				
Genotoxicity battery				
Single-dose / dose range finding Rodent single-dose (could be MTD study) Nonrodent single-dose (could be MTD study)				
Repeat dose toxicity Rodent multidose Nonrodent multidose				
Other studies Immunotoxicity Photosafety Abuse liability				*Adapted from references 1, 2,3

MOA= mechanism of action; **CNS=** central nervous system**; CV**=cardiovascular; **MTD=** maximum tolerated dose

QTPP Relevance – FIH Studies

QTPP (clinical outcome metrics) could include:

- Intended use in clinical setting
  - Route of administration, dosage form
- Quality attributes of drug product
  - Appearance, identity, strength, assay, uniformity, purity/impurity, stability, and others
- Drug substance attributes affecting in vitro performance and PK characteristics (safety)

QST= Quantitative systems pharmacology; PBPK=physiologically based pharmacokinetics

The QTPP forms the basis of design for the development of the product (ICHQ8-R2)

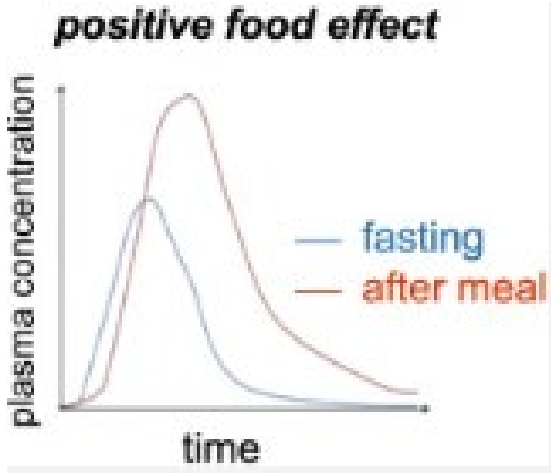
Could rely on:
Prior knowledge
Mechanistic understanding
Risk Assessment
Predictive tools (eg, QST/PBPK models)

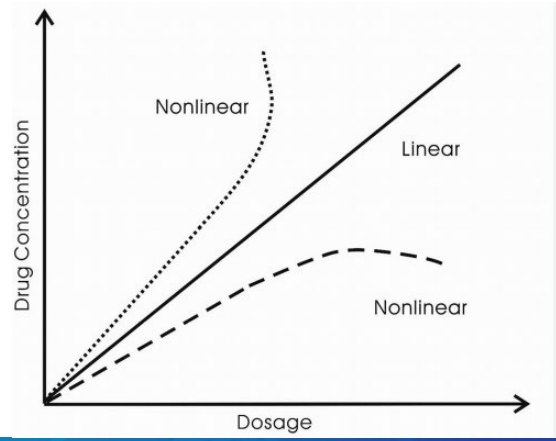
The Role of Drug Product Quality/Biopharmaceutics – Data Collection Considerations

- Determination of strength and potency
  - Use a defined reference material to ensure measurable biological activity and reduce uncertainty
- Qualification of materials to be used
  - Solubility-pH profile
    - Solubility in biorelevant media
    - Potential degradation profile
  - Product and process related impurities
  - Potential for disproportionation
  - Impact of formulation differences on in vitro performance (e.g., dissolution) and in vivo performance (exposure)
  - Impact of material attributes differences (e.g., PSD, morphic content) on in vitro/in vivo performance
  - Impact of food on BA
  - PK linearity/dose proportionality

Understanding what limits absorption in vivo is critical. The use of PBPK/PBBM in the preclinical stage can smooth the transition

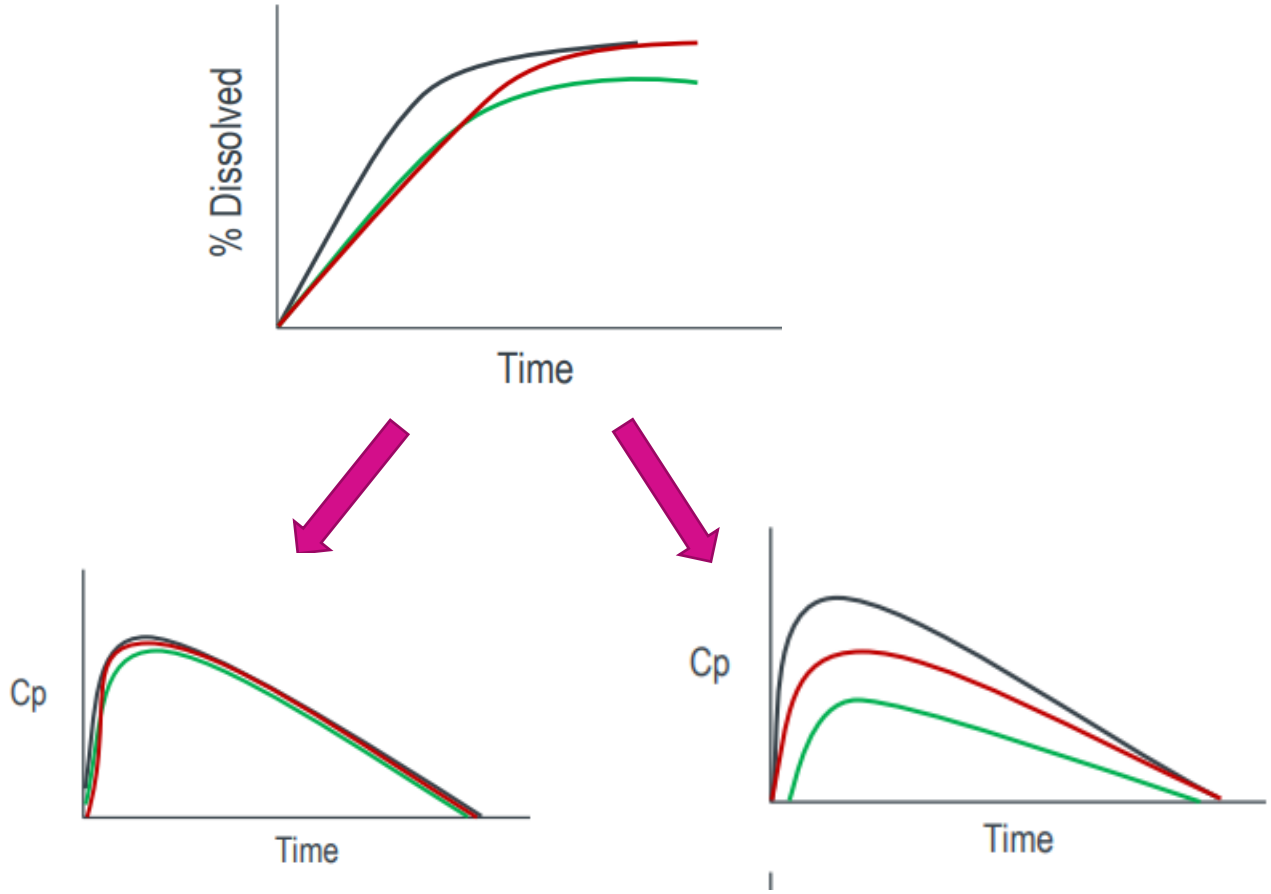
PSD= particle size distribution
PBBM=physiologically based biopharmaceutics models





Analytical Methodology/Biopharmaceutics – Data Collection Considerations

- Sponsors should provide a summary of the analytical assays used to characterize the preclinical PK and TK, including their accuracy, precision and limits of quantification
- Efforts should be undertaken to develop dissolution methods that are discriminating and if possible, biopredictive (fit-for-purpose) during the preclinical phase of development



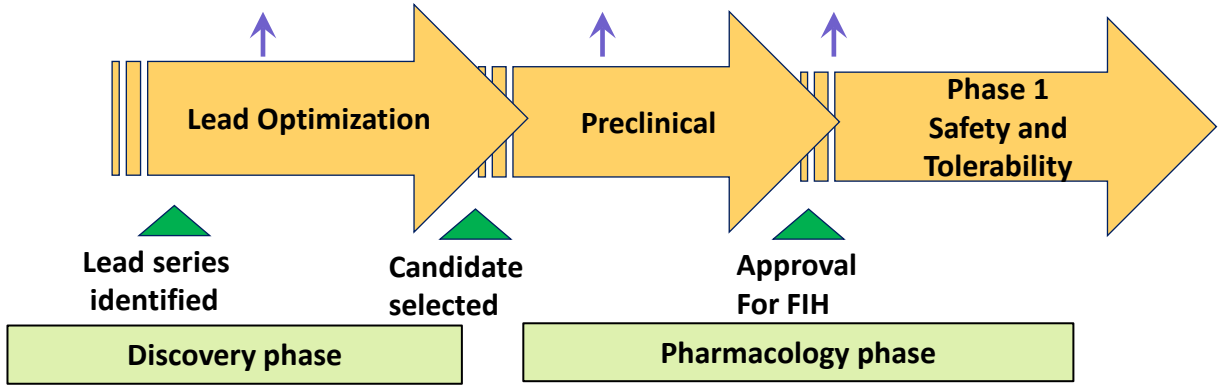
Example of Quality/Biopharmaceutics Risk Evaluation

PRODUCT PROPERTY/ IMPACT OF CHANGE/ CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	Risk	Comment
Physical stability (solid state)	3	1	4	**Low**	One API supplier is proposed. Crystalline Supplier A: Polymorphic form synthesized is 'Form-1'; hygroscopic (used to manufacture three submission lots); Freely soluble in water
Chemical stability	2	3	4	**Low**	No trending is observed in stability data. Formulation does not include stabilization agent.
Assay	2	3	3	**Low**	No overage of API Exhibit batches are of commercial scale
Content uniformity	2	2	4	**Low**	API loading is 85% Dry blend Capsule fill weight: 200 mg
Microbial limits	3	3	3	**Moderate**	API is hygroscopic Stability controls do NOT include tests for microbial content or water content
Dissolution	4	4	5	**High**	Immediate release drug product. Low solubility API. Dissolution medium contains surfactant. Method discrimination not well understood

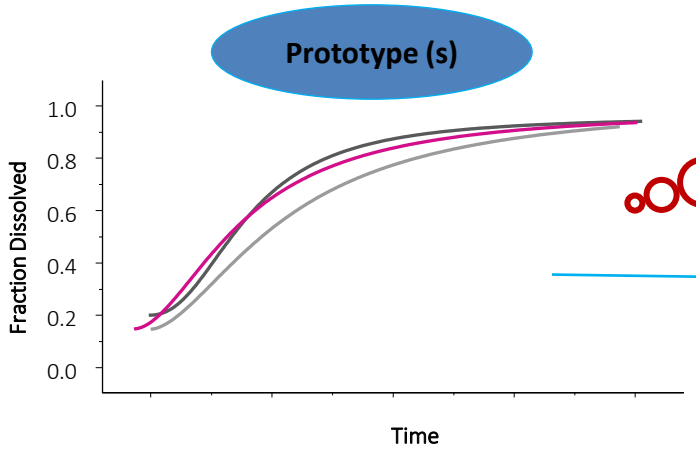
Biopharmaceutics Applications of PBPK in Early Phases of Development

Risk assessment, drugability and FIH formulation development

- Type of formulation/route
- Can we reach target exposure with the intended formulation?
- Source of variability
- Dose linearity/proportionality
- Effect of food on BA
- Dissolution method over/under discriminatory



The Use of PBPK on Risk Assessment Evaluation: Formulation Selection/Development of Biopredictive Dissolution Method

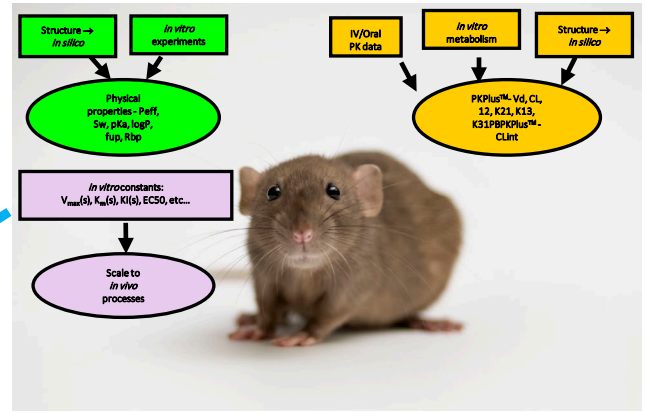


Biorelevant and discriminating dissolution method(s)

Gastroplus (GP)

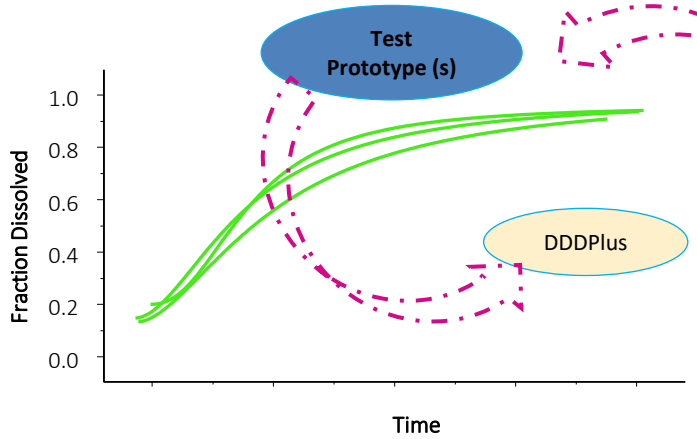
GP

Species specific PBPK Absorption Model



Obtain in vivo dissolution profiles

Predict Cp time profiles and select the dissolution method using virtual BE



Guided by DDDPlus, 1) select target formulation 2) develop/refine in vitro dissolution method that matches target in vivo release profile

Considerations for FIH Studies – Dose Selection

- Should include determination/justification of the starting dose, dose range/dose escalation steps and maximum exposure
- Should rely on the totality of data generated in previous phases of development
- Should consider risk mitigation for toxicity while balancing the need to elicit pharmacologic activity
- Should consider both preclinical and clinical data for molecules having a similar mode of action
- If an investigational drug has been administered to humans under the paradigm of microdose trials, any subsequent study using a non-microdose should follow guidance recommendations

References 1, 3, 4

General Consideration for Estimating a Starting Dose in FIH Clinical Trials

- As per regulatory guidance, the NOAEL should serve as the starting point for determining a reasonably safe starting dose
- NOAEL, in the most relevant animal species should be used for estimation of an equivalent exposure for humans (HED) (as per FDA guidance)[4]
- Measurements of exposure cannot be employed for setting a safe starting dose in humans; it is critical to rely on dose and observed toxic response data from toxicology studies[4]
  - When available, preclinical data on BA, metabolite profile, and plasma drug levels associated with toxicity may influence the choice of the NOAEL
    - E.g., when saturation of drug absorption occurs at a dose that produces no toxicity, use the lowest saturating dose
    - Estimation should be based on modelling (e.g., PK/PD and PBPK)

Methods for Estimating a Starting Dose in FIH Clinical Trials

Study	Description	Advantages	Disadvantages
Maximum recommended safe starting dose (MRSD)[4]	Based on administered doses, observed toxicities, and an algorithmic approach	Most widely used by FDA (good safety record); easy to calculate	Empirical, neglects pharmacological activity, and dose escalation. Use of arbitrary safety factors
Minimum anticipated biologic effect level (MABEL)[1]	Exposure and PD data are used to calculate the pharmacologically active dose (PAD) and anticipated therapeutic range in humans. Considers target binding and receptor occupancy studies	Safest approach for high-risk drug candidates with high degree of species-specificity	Requires the collection of more data. Use of arbitrary safety factors.
PBPK model	Mechanistic approach to determine drug exposure considering inter-species physiological and anatomical differences.	Accounts for species differences in PK parameters, physiology, organ/tissue size etc., rather than empirical scaling of dose; ability to calculate safety margins;	Requires experienced modelers and the collection of extensive amount of data
PKPD model	Preclinical PK/PD modeling is widely used, enabling the selection and optimization of human doses and/or dose regimens, including prediction of human efficacious doses	Accounts for species differences in both PK and PD; accounts for pharmacologic activity and can support dose escalation	Requires experienced modelers and the collection of extensive amount of data. Their utility in translating biological effects between species and their ability to rigorously assess the mechanism of action of novel drugs is limited

Maximum Recommended Starting Dose (MRSD) Approach-Allometric Scaling

- Identify the NOAEL for each species tested
- Convert the NOAEL to the human equivalent dose (HED) based on normalization of dose to body surface area (BSA)
  - BSA is the standard to approximate equivalent exposure if no further information is available[4]

$$\textbf{HED (mg/kg)}_{\text{j animal specie}} = \frac{\text{Animal NOAEL (mg/kg)}}{\text{BSA conversion factor}}$$

The species that generates the lowest HED is called the most sensitive species

When data are available suggesting a more relevant species (most appropriate species), apply the HED for that species for subsequent calculations

NOAEL=the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group

Maximum Recommended Starting Dose (MRSD) Approach-Allometric Scaling, cont.

Apply safety factor (10) to calculate MRSD

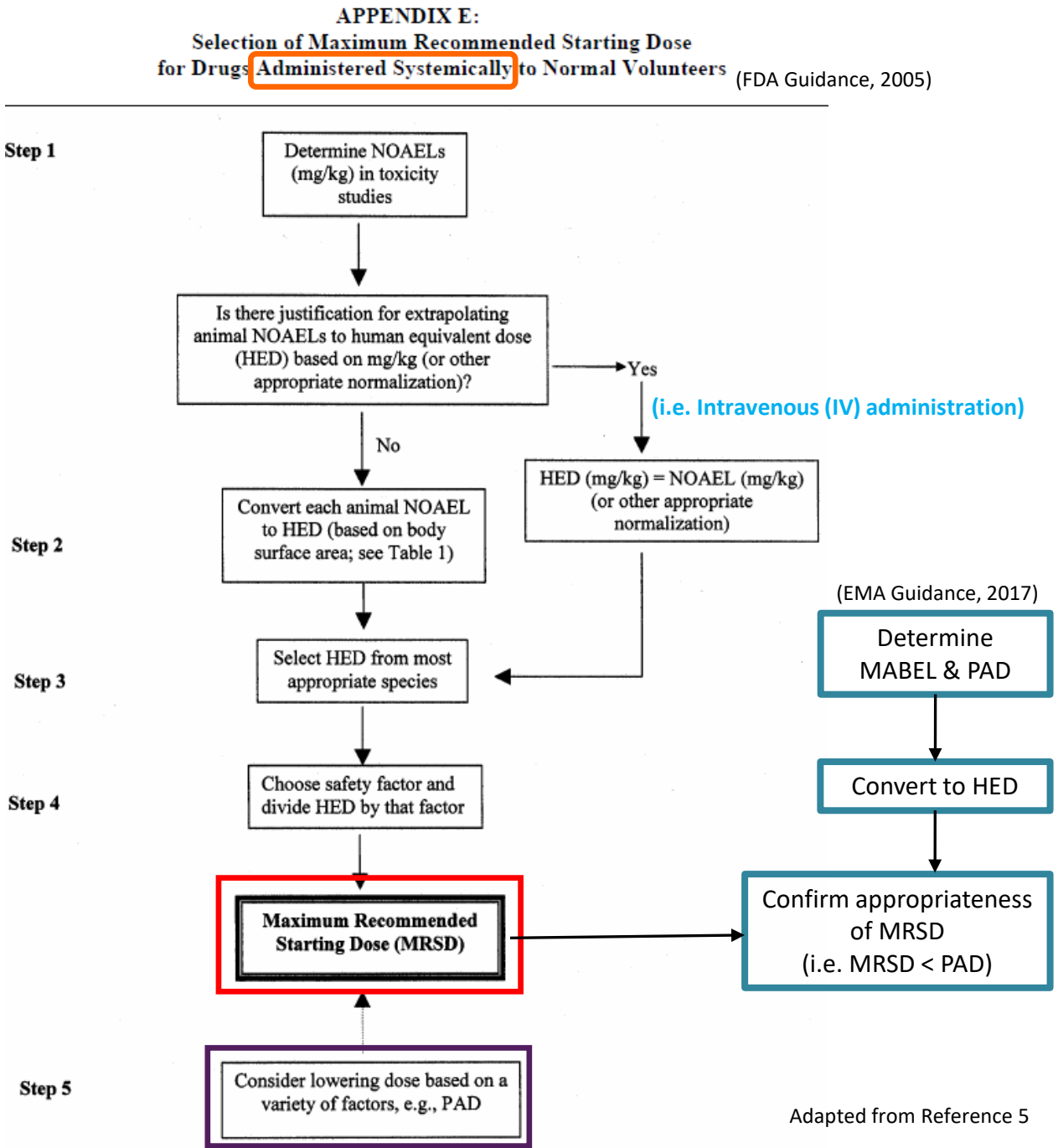
$$\textbf{MRSD (mg/kg)} = \frac{\text{HED (mg/kg)}_{\text{most relevant species}}}{10}$$

average adult human weight= 60 kg

MRSD (mg/kg) x 60 kg= MRSD (mg)

Higher/lower safety factors may be used with justification

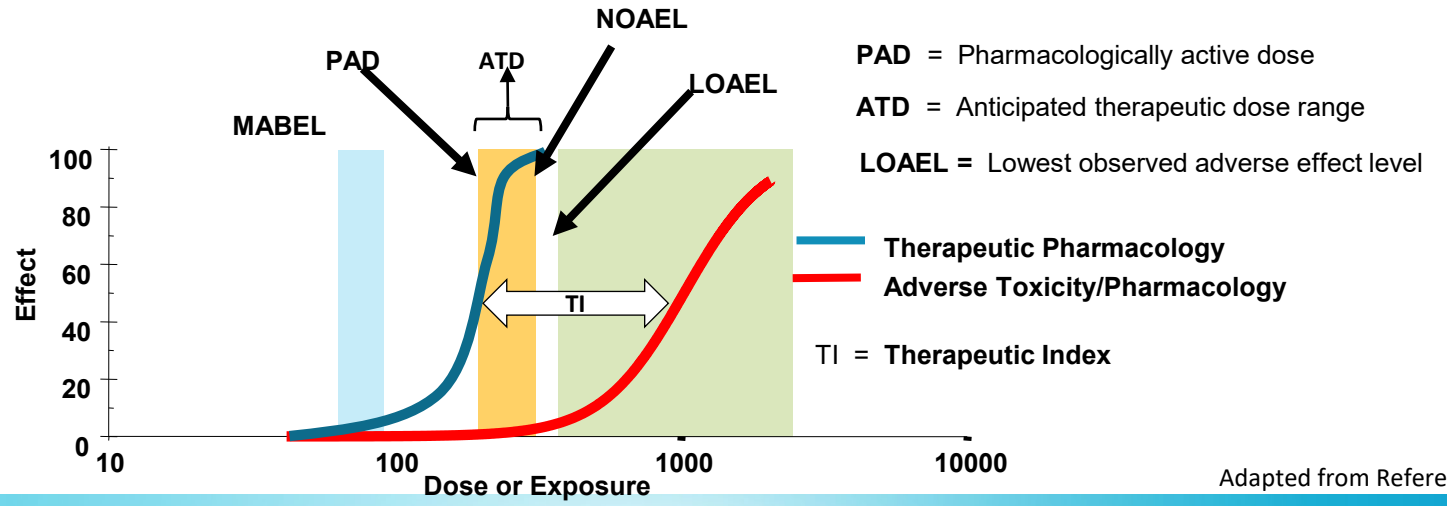
MRSD Flow Chart As Per Regulatory Guidance



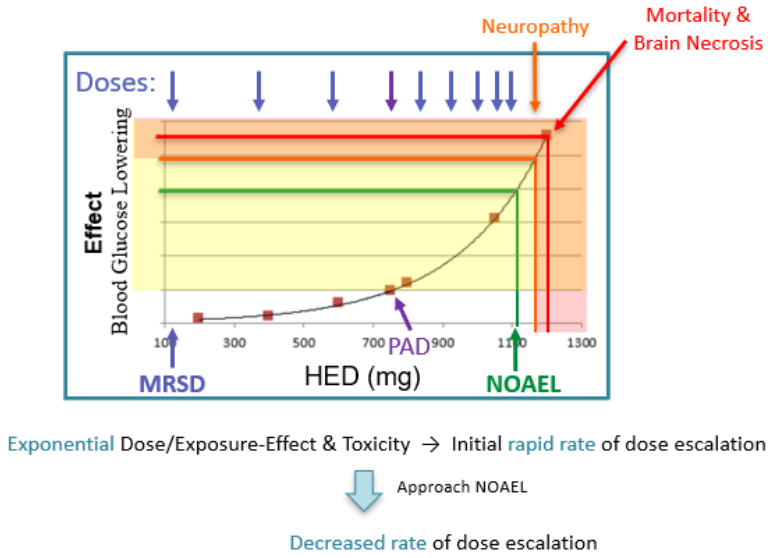
Adapted from Reference 5

General Considerations for Dose Escalation

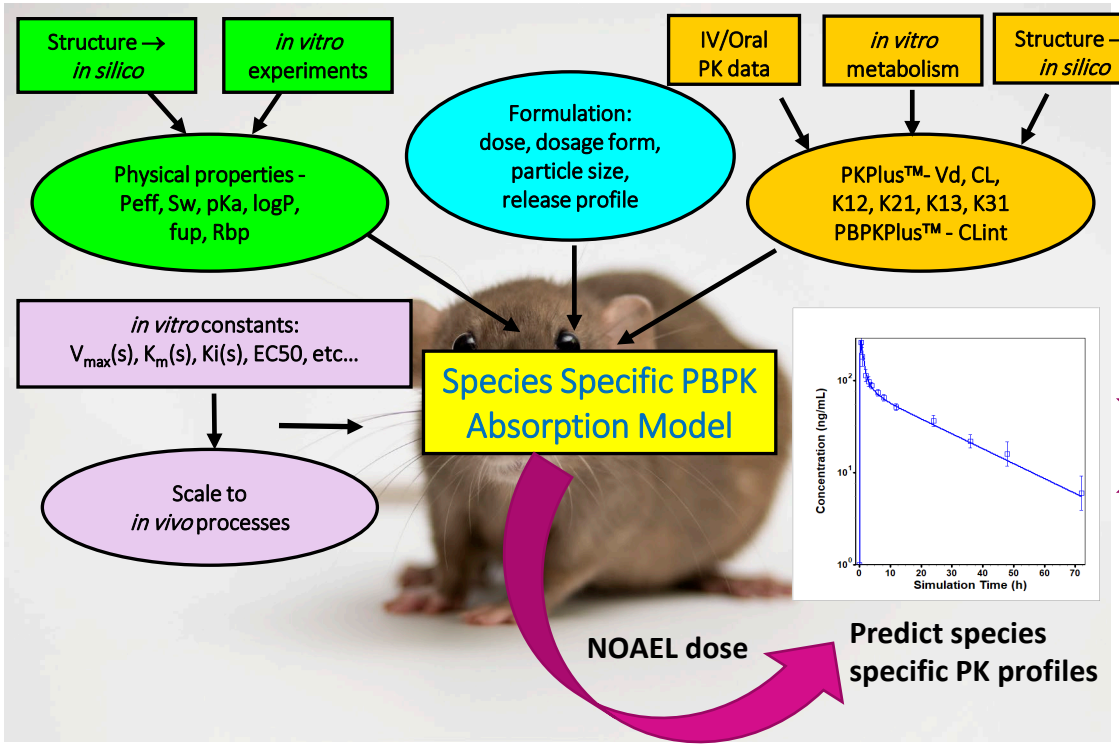
- The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined
- The size of the dose increments should consider the steepness of the dose/exposure-toxicity or dose/exposure-effect curves and uncertainties in the estimation of these relationships
- Whether PK increases more than dose-proportional
- Apply learn-and-confirm approach based on emerging clinical findings
- The maximum fold increase in dose/exposure, as well as a maximum number of cohorts to be evaluated, should be determined a priori



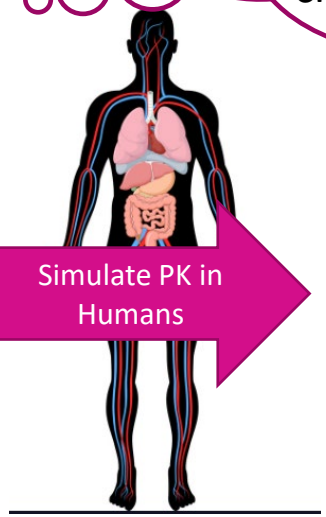
Adapted from References 1,4, 5



The Role of PBPK in FIH Dose Prediction



PBPK application is most relevant in situations where e.g., there is saturation of absorption. The results of this analysis could influence the choice of NOAEL/HED



Simulate PK in Humans

Projected human dose for the selected drug candidate

Strategies of PBPK Model Building for FIH Application

Review Article | Open Access | Published: 07 February 2019

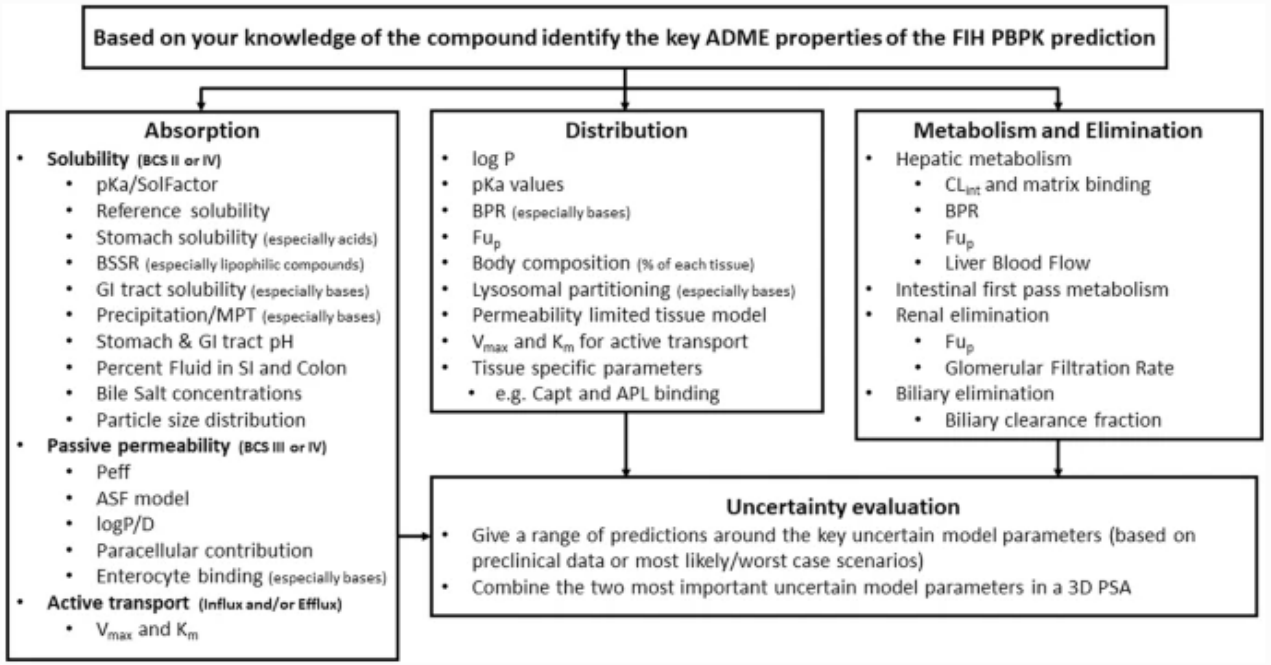
Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

Neil A. Miller, Micaela B. Reddy, Aki T. Heikkinen, Viera Lukacova & Neil Parrott

Clinical Pharmacokinetics **58**, 727–746 (2019) | Cite this article

14k Accesses | **71** Citations | **5** Altmetric | Metrics

- Start with a QSPR + PBPK compound assessment
- Flow diagrams for each essential component of a FIH prediction using PBPK
- Uncertainty analysis is critical because of the unknown factors at this stage



QSPR = Quantitative Structure–Property Relationship

PBPK in FIH Predictions for Regulatory Decision Making

CPT Pharmacometrics Syst Pharmacol. 2015 Apr; 4(4): 226–230.
Published online 2015 Apr 17. doi: 10.1002/psp4.33
PMCID: PMC4429576
PMID: 26225246

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner,[1] P Zhao,[1] Y Pan,[2] V Hsu,[1] J Grillo,[1] SM Huang,[1] and V Sinha[1,*]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

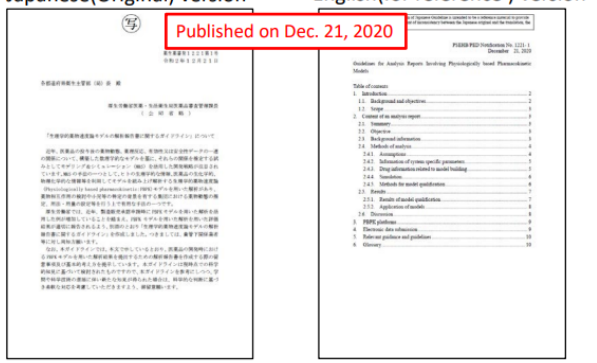
FIH prediction using PBPK is important for decision-making and allows additional learning of the molecule and coping with situations when other methods may not be adequate.

PMDA MIDD Workshop
March 24, 2021

Guidelines for Analysis Reports Involving PBPK Models

Japanese(Original) version

English(for reference) version



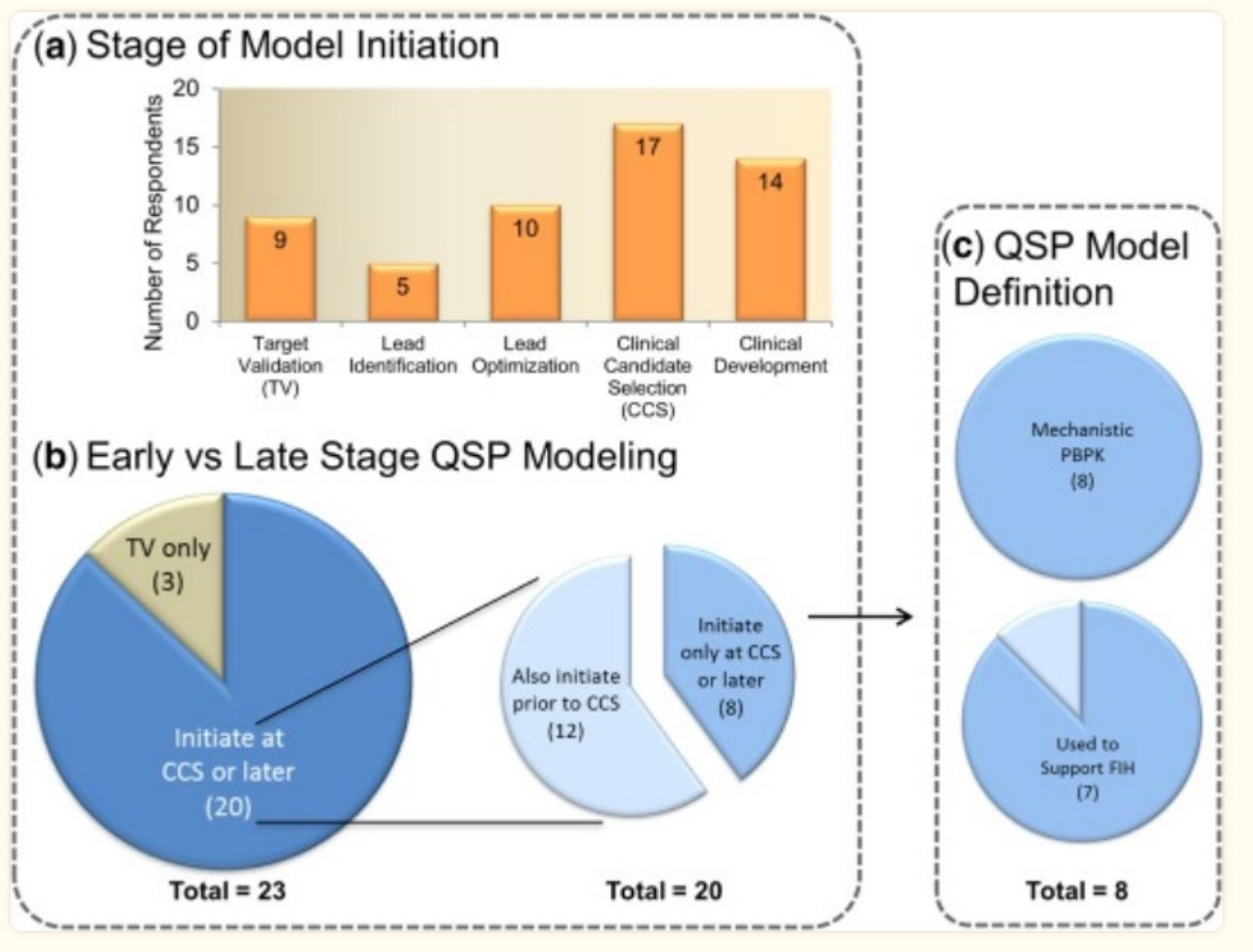
Published on Dec. 21, 2020

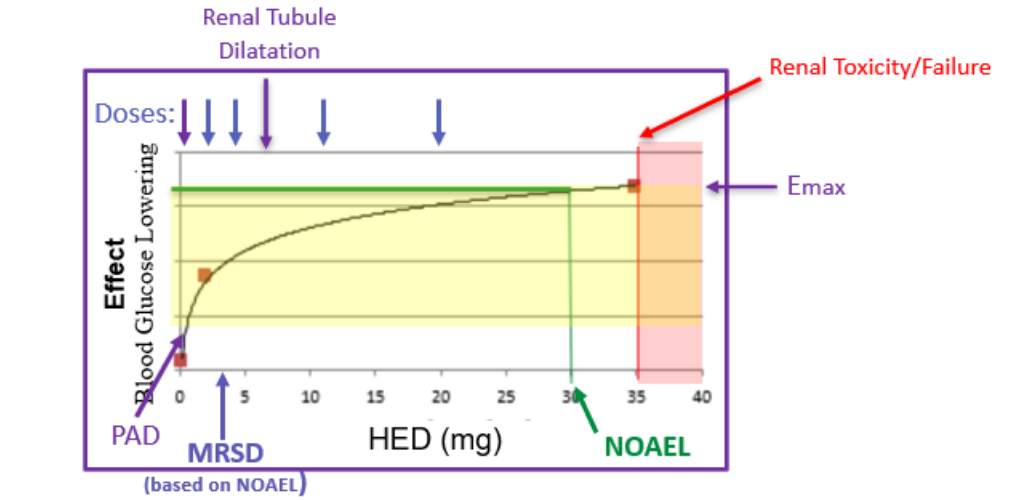
https://www.pmda.go.jp/files/000238191.pdf

https://www.pmda.go.jp/files/000238192.pdf

PBPK model analyses are considered useful, particularly in qualitative/quantitative prediction of drug interactions and the setting rationale for dosage and administration in clinical trials in pediatric subjects. PBPK model analyses may also be used to investigate the initial dose in first-in-human studies.

Industry Experience on the Use of PBBK in Support of FIH





Logarithmic Dose/Exposure-Effect & Toxicity → Initial slow rate of dose escalation

Approach Maximum Effect (Emax)

Increased rate of dose escalation

QSP= Quantitative Systems Pharmacology

Taken from Reference numbers 6, 5

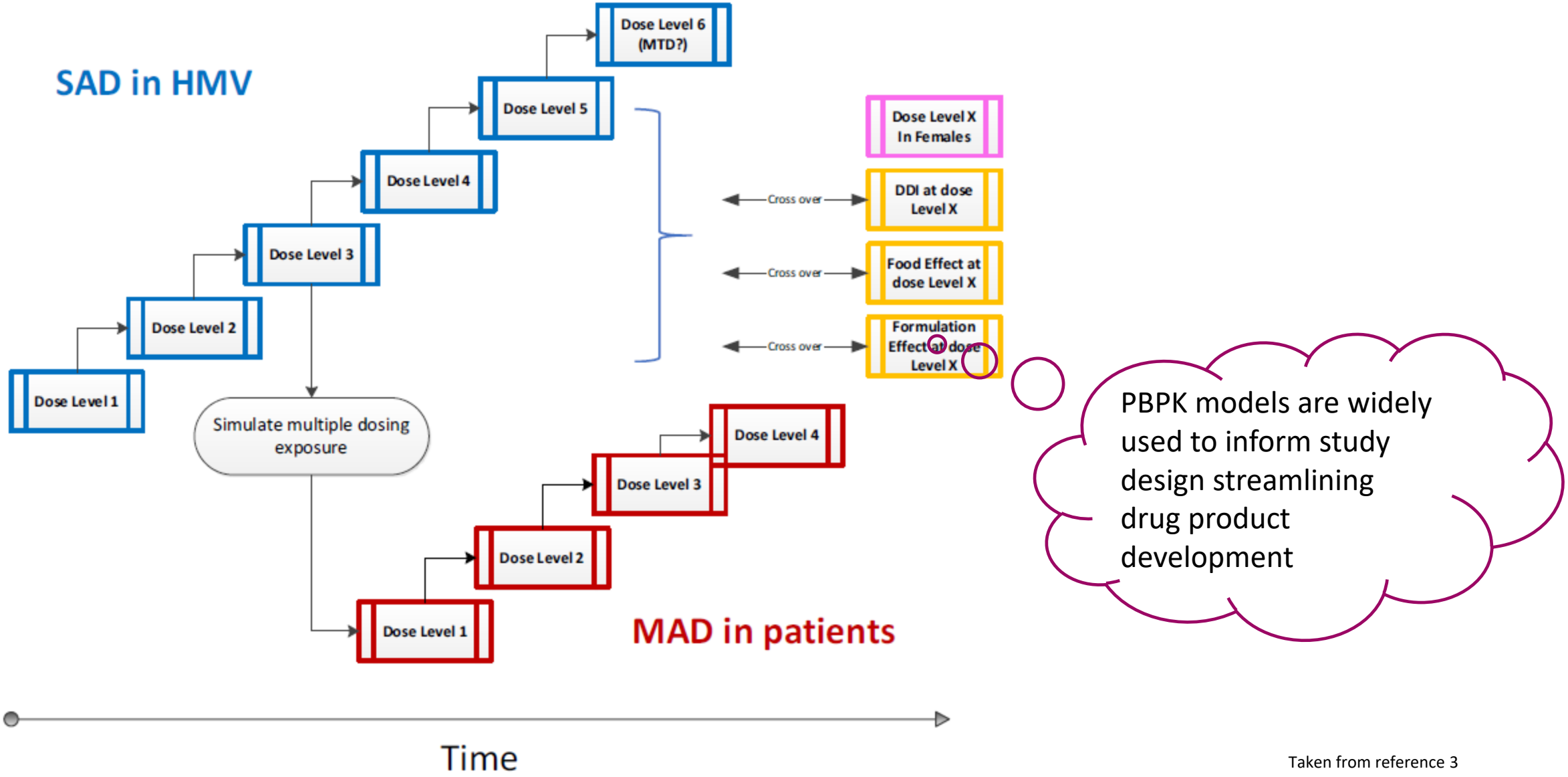
Relevance of Using PBPK in FIH Dose Prediction

Regimen	Duration	Dose levels	Comments
Single starting dose (MRSD)	single	Usually estimated based on empirical approaches	PBPK plays an important role especially for drugs with complex metabolic/transport pathways
Maximum Exposure and dose	single	Should be within the estimated human PD dose range. Exposure levels exceeding the PD dose range can be acceptable with justification (see risk assessment)	PBPK in combination with PD model can be used to justify the intended dose-range
Single dose escalation (SAD) studies	single	The dose increment should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the preclinical studies	PBPK models can be used to confirm the appropriateness of the next dose level based on emerging clinical data
Multiple ascending doses (MAD)	Usually the same (or reasonably similar) dosing schedule evaluated in preclinical studies i.e., daily, weekly, monthly, etc.	Dose levels, dosing increments, and schedule based on SAD study data. For combined SAD/MAD FIH studies, initially proposed dose levels, increments and schedule for the MAD portion may be based on preclinical data based on BSA (as done for SAD protocol)	A maximum duration of dosing should be stated in the protocol for every cohort. Should take into account the specific PK and PD characteristics of the drug, the available preclinical safety data, and all data from subjects in previous single dose cohorts. PBPK models streamline the transition from SAD to MAD studies.
Route of Administration/formulation	Should be based on intended therapeutic use, characteristics of drug/formulation		PBPK models are instrumental for simplifying formulation selection for preclinical and FIH studies

FIH Study Design Considerations

- Study Size
  - ~6-10 subjects per cohort
- Study Population
  - Healthy volunteers, but patients may be considered depending on risk-benefit ratio
  - Males/females
- Dose escalation scheme
  - Sentinel dosing scheme (sequential with appropriate period of observation within each dosing cohort for both SAD and MAD studies)
  - Sponsors may incorporate assessment of multiple dosing, food effect, relative bioavailability, QT prolongation, and/or DDI potential as part of the FIH clinical trial
  - Rule-based (e.g., 3+3) vs model-based (e.g., Bayesian) designs for oncology drugs[7]
- Specification for dose-limiting toxicities
  - Dose-stopping criteria based on exposure

Example of Study Schema for FIH Trial with Multiple Objectives



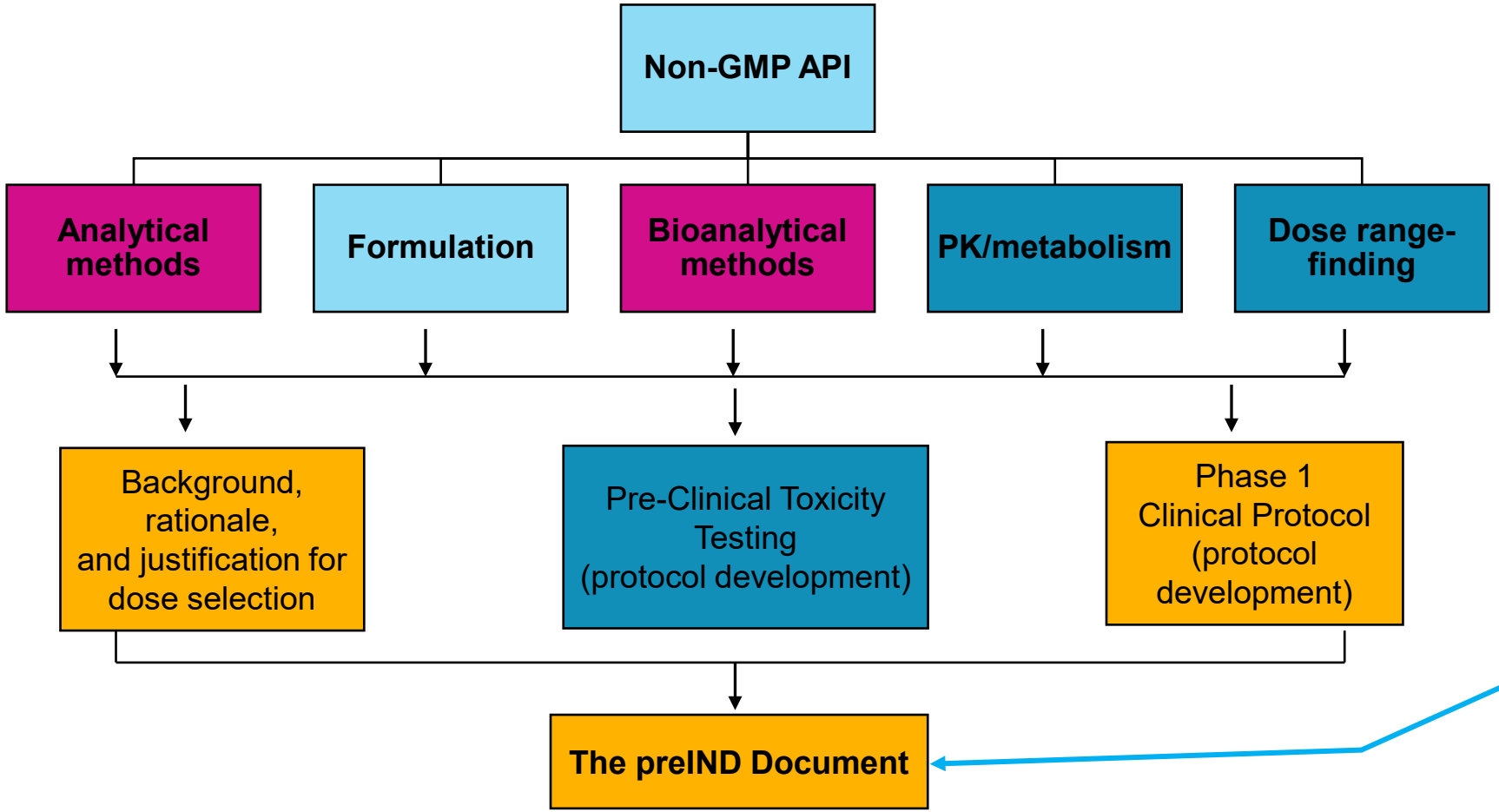
PBPK models are widely used to inform study design streamlining drug product development

Taken from reference 3

Example of Risk Identification/Mitigation Strategies for Successful Transition to FIH Trials

Item	Description	Level of Risk/ uncertainty	Mitigation Strategy (ies)
Mode on action	Similar to an already approved drug	low	NA
Nature of Target	Target expression and pharmacodynamics well understood	Low	NA
Drug solubility	Drug solubility may limit exposure at the target dose based on preclinical data and PBPK	High	Based on the drug substance characteristics, a lipid formulation was chosen which improves the drug solubility and fraction absorbed as shown in preclinical studies.
Extent/quality of preclinical data			
Extent/quality of in vitro data	Good understanding on in vitro drug substance properties and formulation behavior. In vivo digestion of lipidic formulation understood	Low	NA
Dose proportionality	The AUC is less than proportional to dose indicating complex metabolism/presence of transporter	High	• Use of PBPK model to inform revision of protocol based on emerging clinical data
Presence of polymorphism	Yes	high	• Use of PBPK model to inform revision of protocol based on emerging clinical data
Population to be studied			
Presence/absence of biomarkers			
Overlap SAD/MAD	Yes	Medium	• Strict implementation of stopping rules • Use of PBPK model to inform revision of protocol based on emerging clinical data • Implementation of protocol that include adaptive designs

The PreIND Stage: Regulatory Interactions/Briefing Document

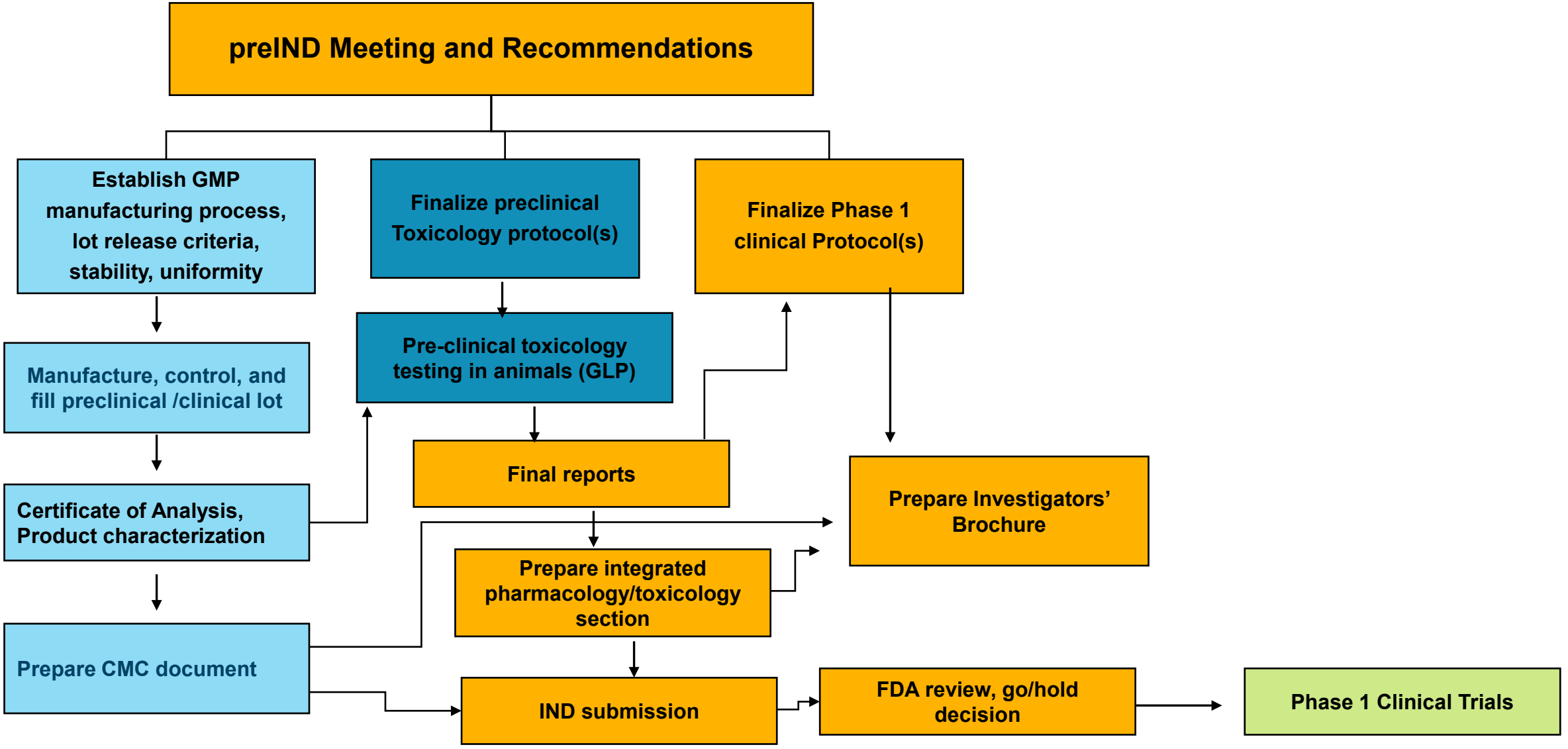


Request pre-IND meeting:

- **Product name, indication**
- **Type of meeting (e.g., Type C)**
- **Purpose of the meeting**
- **Proposed agenda**
- **Suggested time/format (e.g., face to face)**
- **List of questions**

Adapted from references 8, 9

Incorporation of Agency's Feedback



Take Home Message

Smooth transition from preclinical to clinical (FIH) studies requires the collaboration of multiple disciplines working towards the same goal

- It is essential to implement risk assessment to evaluate the degree of uncertainty on the data generated and implement the appropriate strategies to mitigate any risk
  - This should be guided by the creation of check lists that are shared among all team members/all relevant disciplines
- PBPK models should be implemented as early as possible in drug product development to e.g., streamline formulation selection, development of biopredictive dissolution methods and inform the choice of dose, dose-range and dose escalation for FIH studies

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Questions

Sandra Suarez Sharp

Vice President, Regulatory Affairs, Simulations Plus, Inc.

Sandra.Suarez@simulations-plus.com

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