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

Sandra Suarez Sharp

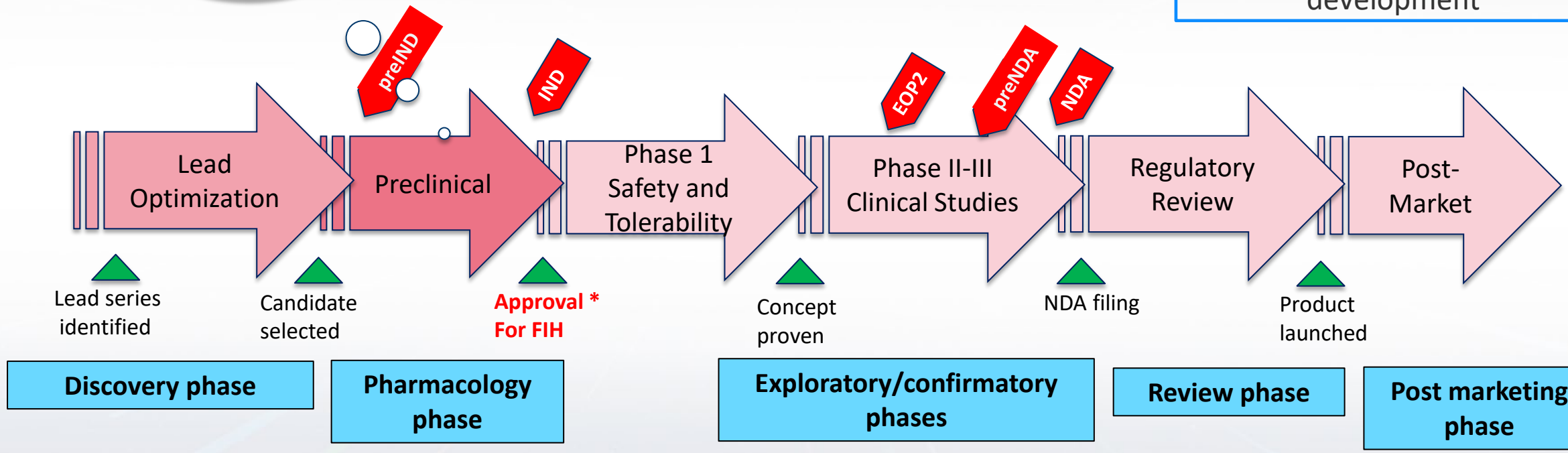
Vice President, Regulatory Affairs

Please note: this presentation, including questions from the audience, is being recorded and may be made available.

Phases of Drug Product Development – Milestones

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

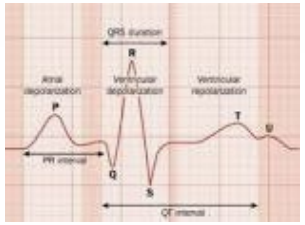
The motto "begin with the end in mind"* is particularly appropriate for preclinical development



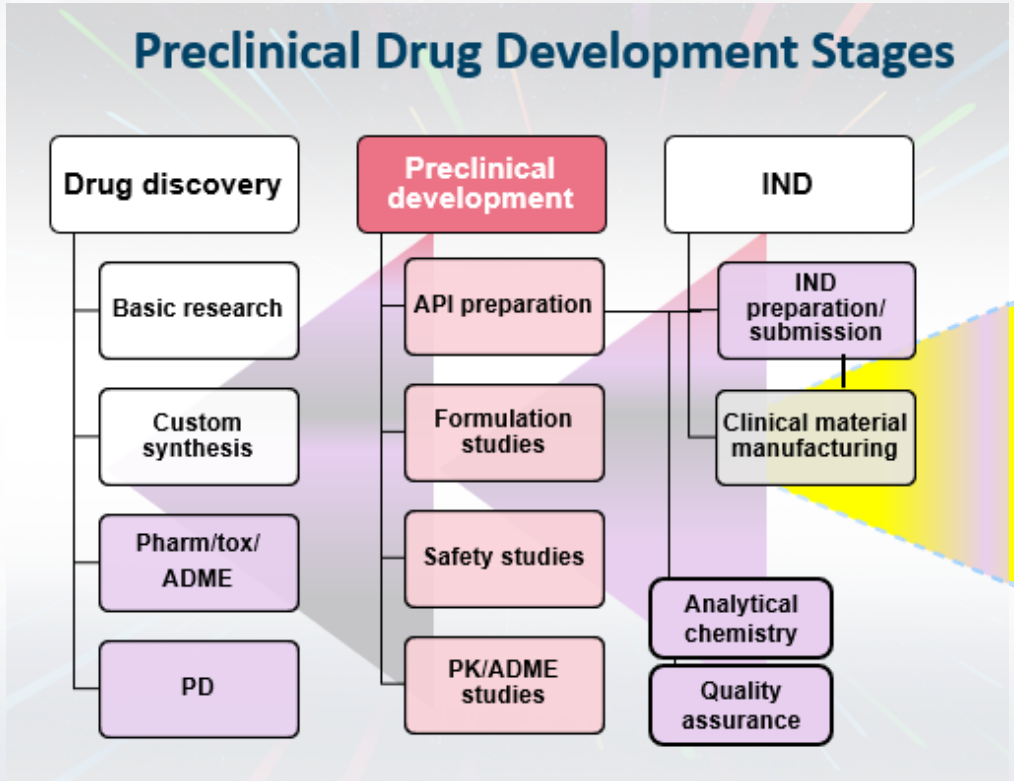
FIH: First in Human
EOP2: End of Phase 2

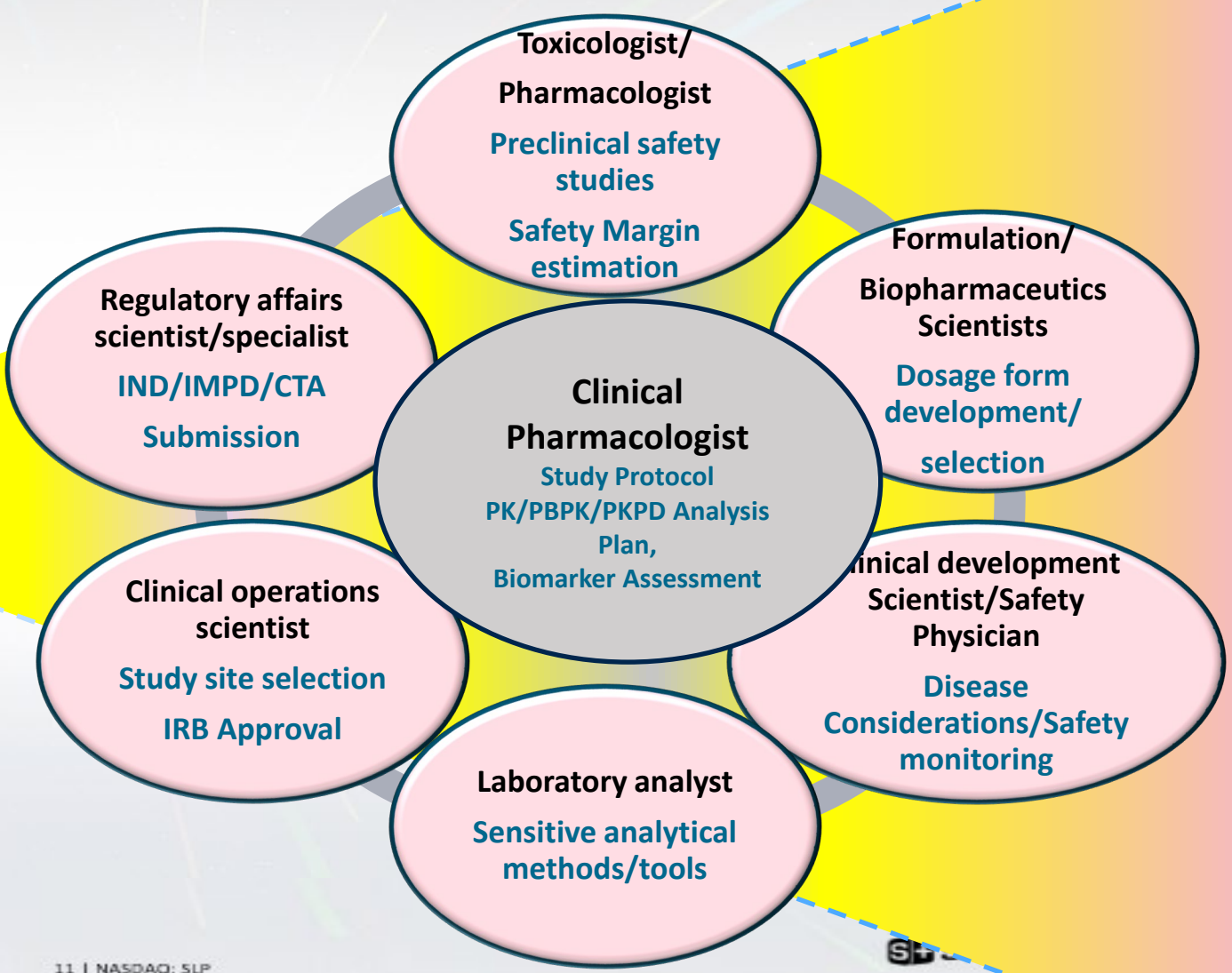
The Purpose of FIH Trials

- To evaluate an investigational drug in humans for the first time
- To study the human clinical pharmacology, tolerability and safety of the investigational drug
- To understand how effects seen in non-clinical studies translate into humans
- To inform the decision processes for the continuation of dosing



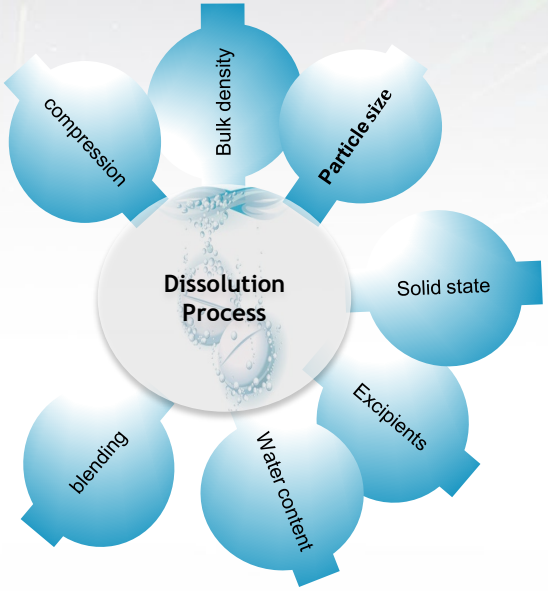
Multidisciplinary Integration – Key for Successful Transition to FIH

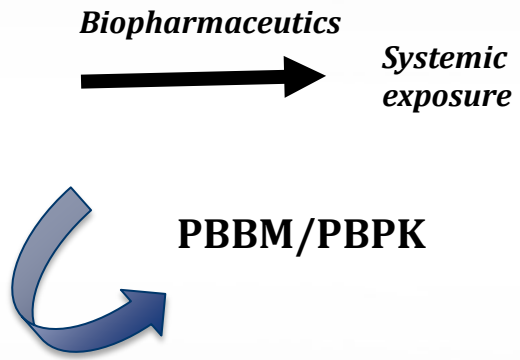


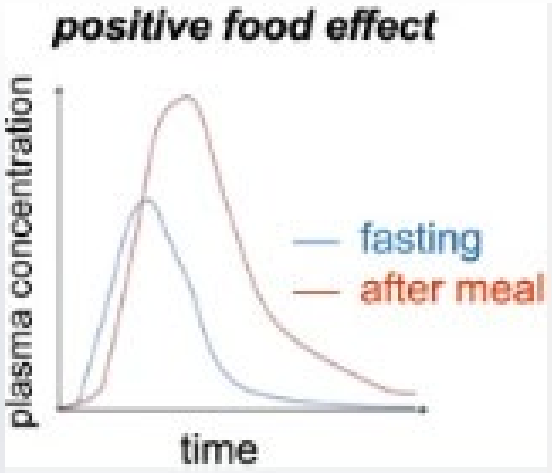


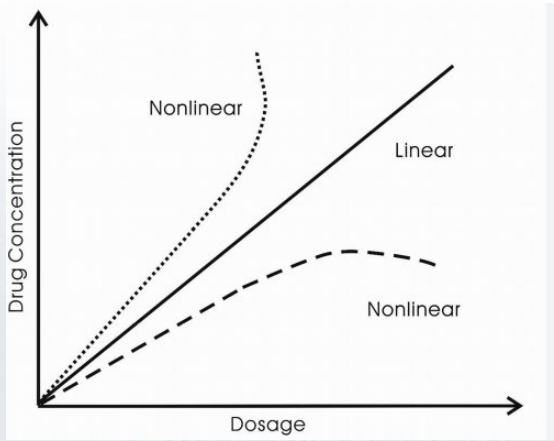
The Role of Drug Product Quality/Biopharmaceutics – Data Collection Considerations

- Determination of strength and potency
- Qualification of materials to be used
  - Solubility-pH profile
    - Solubility in biorelevant media
    - Potential degradation profile
  - Product and process related impurities
  - Potential for disproportionation

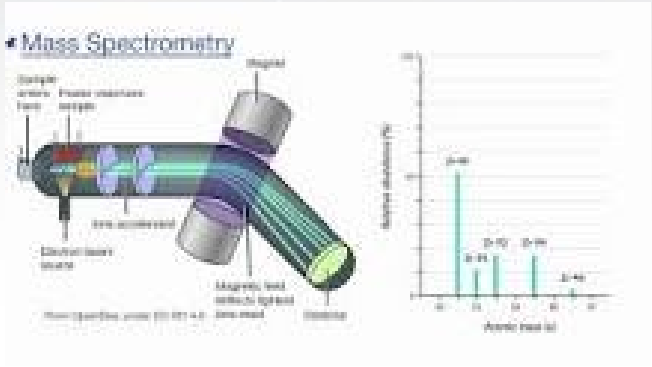


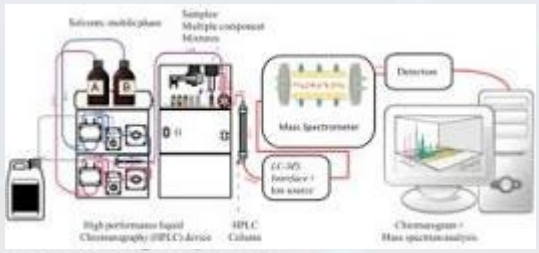


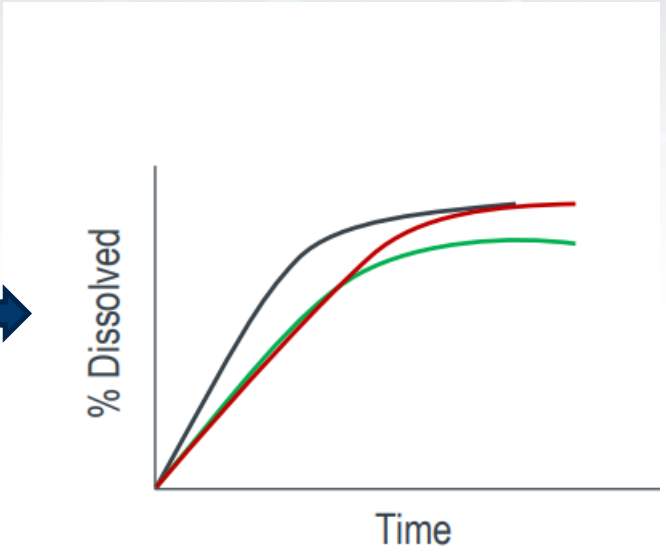


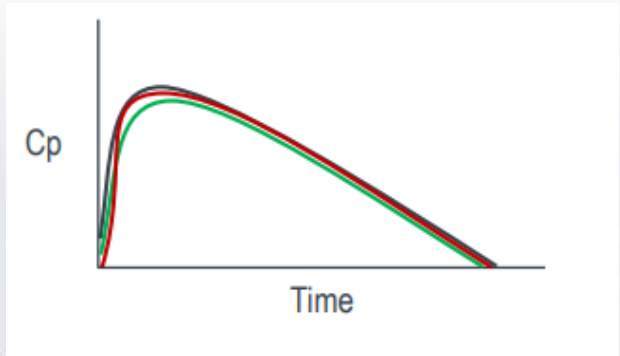


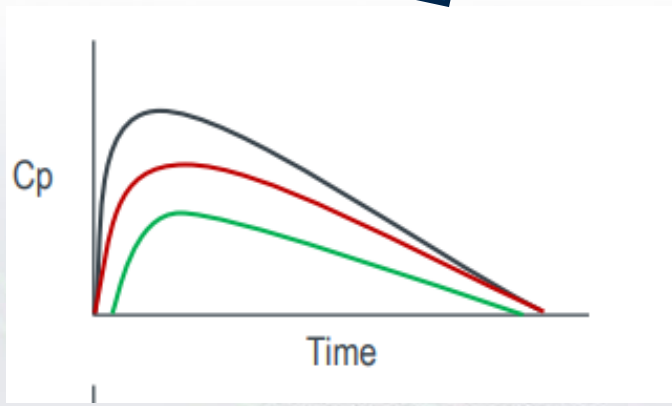
Analytical Methodology/Biopharmaceutics – Data Collection Considerations



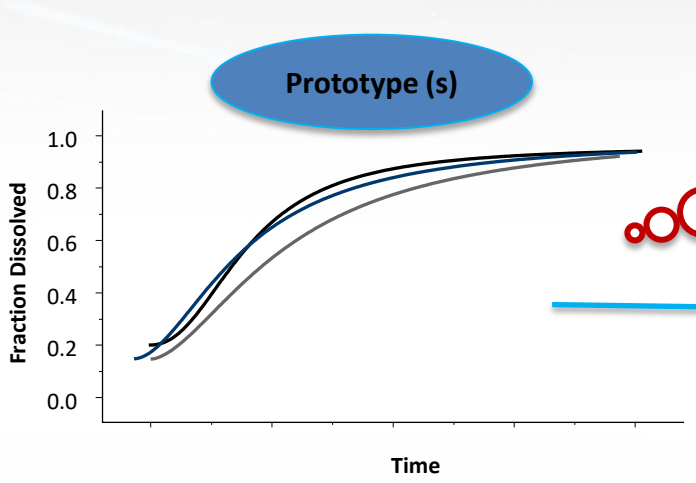








Path for Formulation Selection/Development of Biopredictive (Fit for Purpose) Dissolution Method using PBBM/PBPK

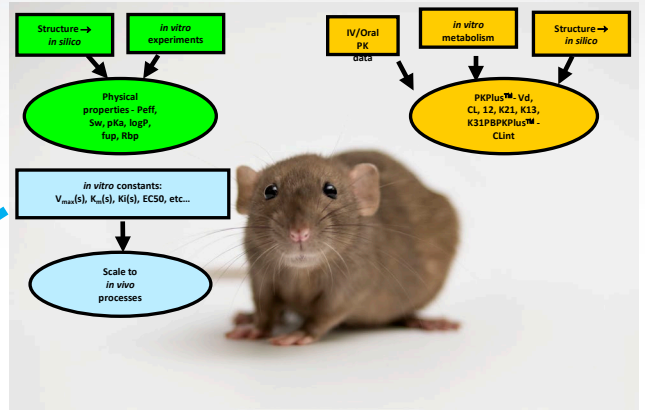


Biorelevant and discriminating dissolution method(s)

Gastroplus (GP)

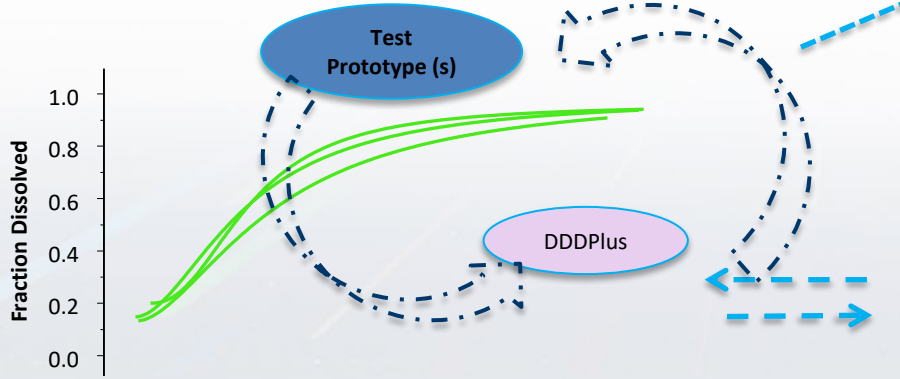
PBPK Absorption model/PBBM

GP



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

Example of Quality/Biopharmaceutics Risk Evaluation

PRODUCT PROPERTY/ IMPACT OF CHANGE/ CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	Risk	Risk Mitigation/Comments
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 83.3% Dry blend Capsule fill weight: 300 mg
Microbial limits	3	3	3	**Moderate**	API is hygroscopic Drug product release and stability controls do NOT include tests for microbial content or water content (methods list microbial testing??)
Dissolution	4	4	5	**High**	Immediate release drug product. Low solubility API. Dissolution medium contains surfactant. Clinical relevance was not provided. Tighten acceptance criterion to reject for aberrant batches

The Role of Preclinical Safety – Data Collection Considerations

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

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, effects)				
Pharmacokinetics *In vitro* metabolism (across species microsomal met) *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

General Considerations for Estimating a Starting Dose in FIH Clinical Trials

- As per regulatory FDA guidance[4], the NOAEL should serve as the starting point for determining a reasonably safe starting dose
  - Estimation of an equivalent exposure for humans (HED)

- 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, nonclinical 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 state-of-the-art modelling (e.g., PBPK) and/or using allometric factors

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

- Identity 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]

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

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

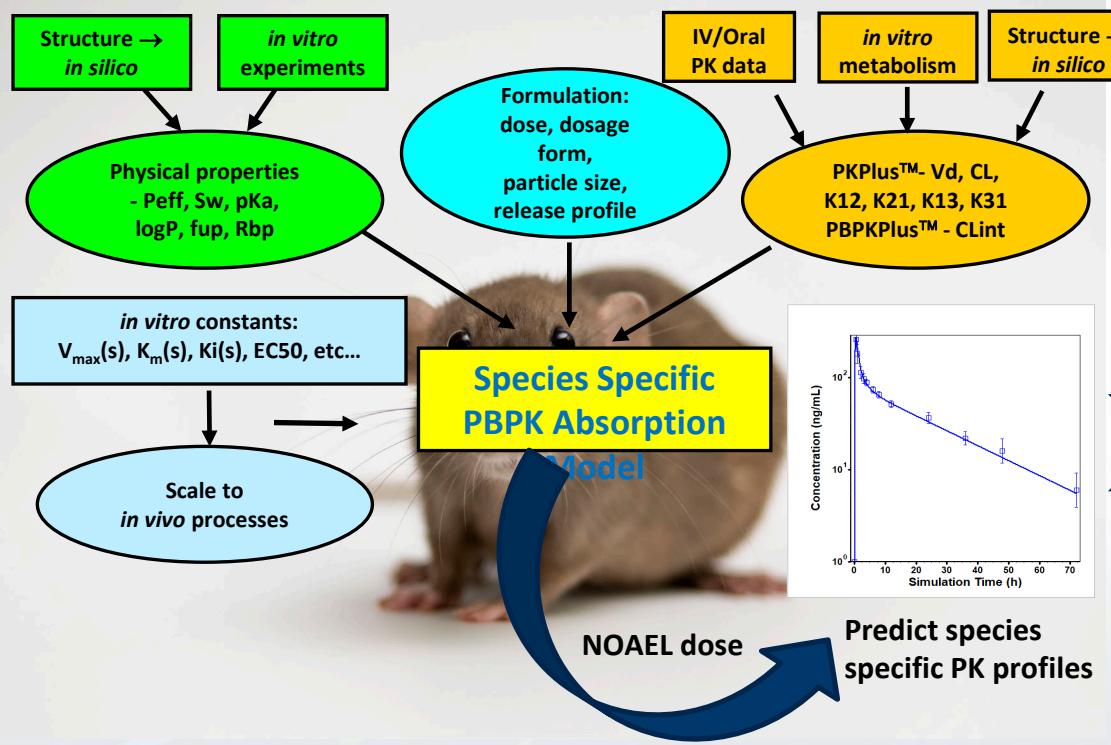
$$\textbf{MRSD (mg/kg)} = \frac{\text{HED (mg/kg)}_{\text{most relevant specie}}}{10}$$

average adult human weight= 60 kg

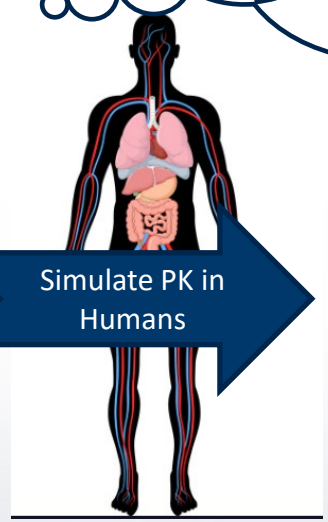
MRSD (mg/kg) x 60 kg= MRSD (mg)

Higher/lower safety factors may be used with justification

The Role of PBPK in FIH Dose Prediction



PBPK application is most relevant on situations where e.g., there is saturation of absorption



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

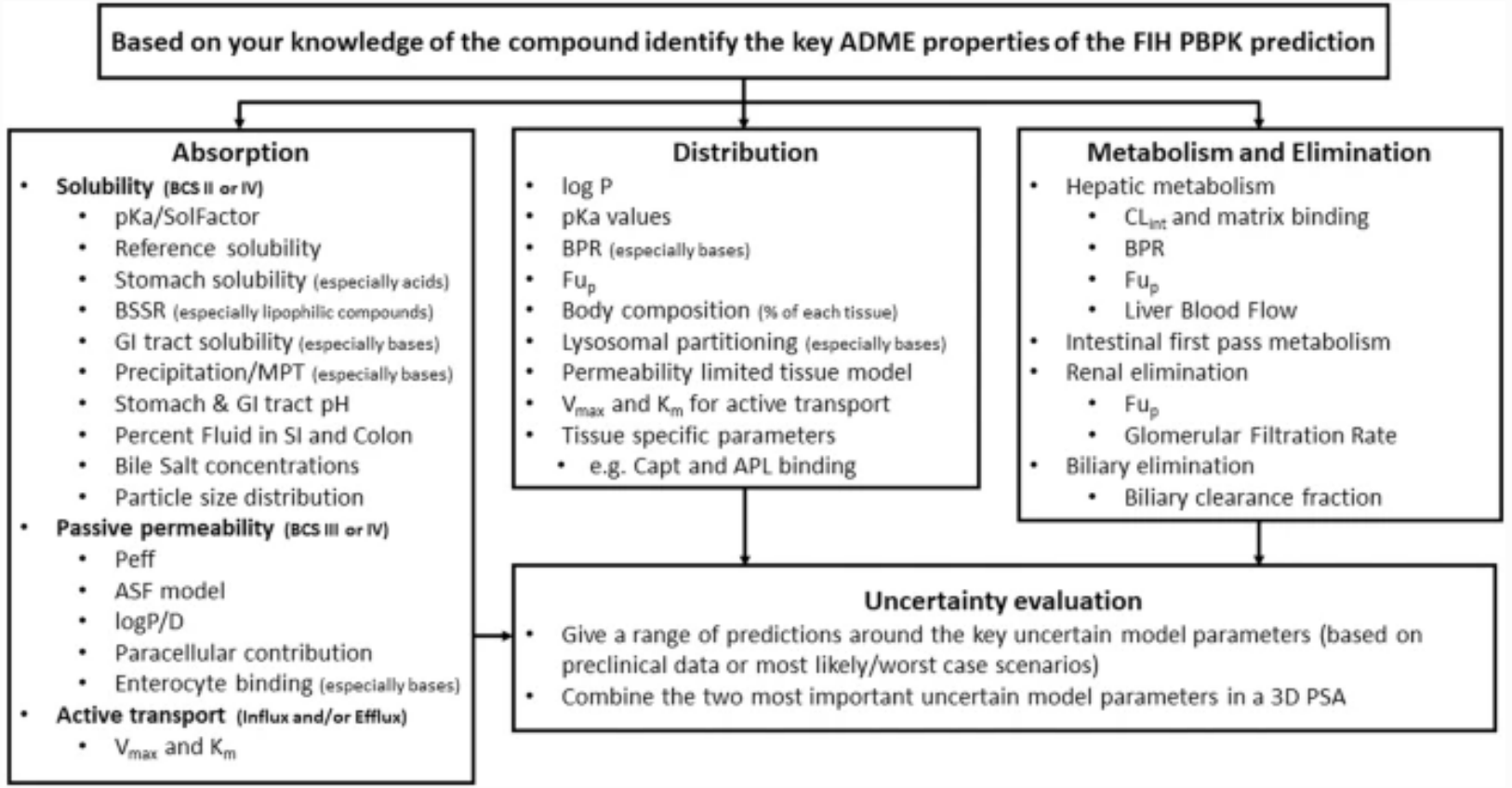
Neil A. Miller, Micaela B. Reddy, Aki T. Heikkinen, Viera Lukacova & Neil

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

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

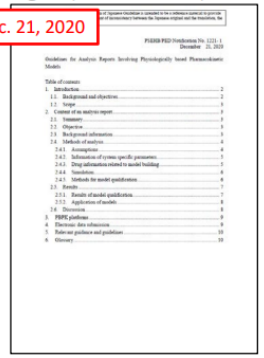
Guidelines for Analysis Reports Involving PBPK Models

Japanese(Original) version

Published on Dec. 21, 2020

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

English(for reference) version



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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

7.2. Starting dose for healthy volunteers

In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed. The NOAEL is a generally accepted benchmark for safety when derived from appropriate animal studies and can serve as the starting point for determining a reasonably safe starting dose. The exposures achieved at the NOAEL in the most relevant animal species used (which might not necessarily be the most sensitive species) should be used for estimation of an equivalent exposure for humans. Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using allometric factors.

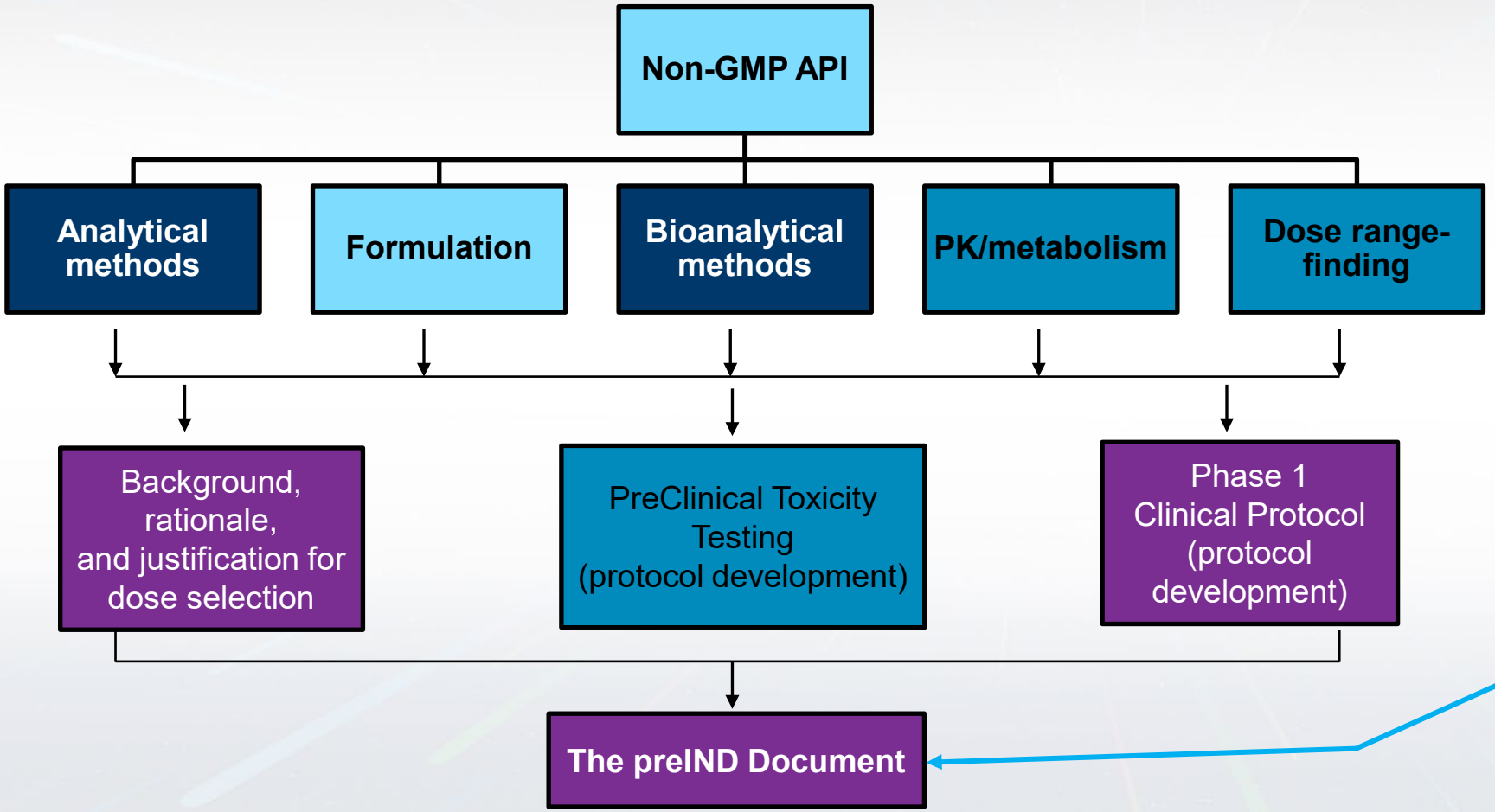
Relevance of Using PBPK in FIH Dose Prediction

Regimen	Duration	Dose levels	Comments
Single starting dose (MRSD)	single	Usually estimated based on empirical approaches	PBPK plays an important role specially for drug with complex metabolic/transport path
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	PBPK in combination with PD model can be used to justify the identified dose-range
Single dose scalation (SAD) studies	single	The dose increment should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the non-clinical studies	PBPK model can be used to confirm the appropriateness of next level based on emerging clinical data
Multiple ascending doses (MAD)	Usually the same (or reasonably similar) dosing schedule evaluated in nonclinical 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 non-clinical 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

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 confirm the dose calculated based on NOAEL • 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

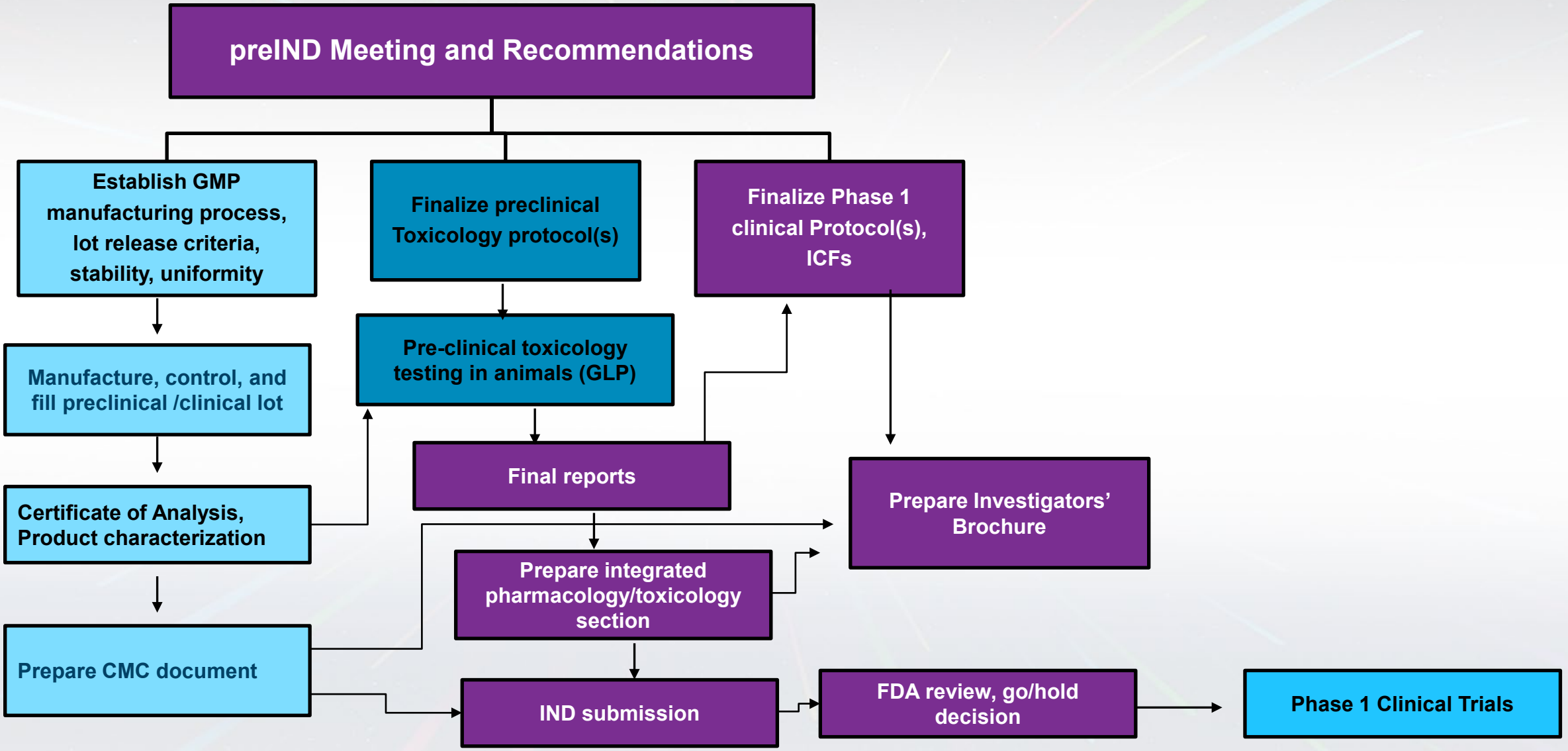


Request pre-IND meeting:

- **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 reference 5

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 and implement the appropriate strategies to mitigate any risk
- PBPK models should be implemented as early as possible to e.g., streamline formulation selection, development of biopredictive dissolution methods and inform the choice of dose, dose-range and dose scalation in FIH

References

1. European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf (2018). Accessed Oct 2, 2022.
2. ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m3r2-non-clinical-safety-studies-conduct-human-clinical-trials-marketing-authorisation_en.pdf (2009) Accessed Oct 3, 2022.
3. Shen, J et al. Design and Conduct Considerations for First-in Human Trials. Clin Transl Sci (2019) 12, 6–19; doi:10.1111/cts.12582
4. Food and Drug Administration, Center for Drug Evaluation and Research. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. https://www.fda.gov/media/72309/download. Cited (2005). Accessed Oct 2, 2022
5. Steinmetz, K.L., Spack, E.G. The basics of preclinical drug development for neurodegenerative disease indications. *BMC Neurol* **9** (Suppl 1), S2 (2009). https://doi.org/10.1186/1471-2377-9-S1-S2

SimulationsPlus

MIDD+

Model Informed Drug Development + 2023

Q&A

Questions & Answers