Regulatory Education for Industry (REdI) and CERSI Workshop

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

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College Park, MD

BREAKOUT SESSION C DAY 2:

Best practices for model development and Validation/ verification and criteria for defining prediction success

Moderators and scribes: Min Li (FDA); Arian Emami Riedmaier (AbbVie); James Mullin (Simulations Plus); Xavier Pepin (AstraZeneca)

Session Background

Proposed Questions	Moderator	Scribes
1. What are the main steps in PBBM development in support of drug product quality? Should a general flow chart be created?	Min	Xavier, Jim, Arian
2. What minimal data (drug data/system data/clinical data) should be used to support model development depending on the phase/objective of the model ? Definition of model development and model verification datasets ?	Jim	Min, Xavier, Arian
3. When should model optimization be conducted ? a. Variation reported for input parameter : natural (e.g., polymorphism in enzyme expression) or due to the measurement of input parameters or due to output clinical data b. Absent measurement but likelihood from equivalent type of compound (eg. Precipitation for a free base)? c. Variation reported for output parameter	Jim	Min, Xavier, Arian
4. How should a model parameter be optimized? a. whether fitting multi model parameters or one-by one? b. How can we go around identifiability issues?	Arian	Min, Xavier, Jim
5. How should we set validation criterion(a)? a. Should it be established a priori and linked to: i) The impact of the modeling? ii) the variability of clinical data? b. Should they be consistent with IVIVC guideline?	Xavier	Min, Jim, Arian

Key Points from BO Session C, Day 2, Question 1

What are the main steps in PBBM development in support of drug product quality? Should a general flow chart be created?

1. Identification of model objective(s)
2. Model development
   - Structure; parameters; assumptions
   - Input data (data collection/integration): drug data, system data and clinical data
   - Model refinement if needed
3. Model validation
   - Data selection (how to define, which sets for which phase?)
   - Fit for purpose

Key Points from BO Session C, Day 2, Question 2

What minimal data (drug data/system data/clinical data) should be used to support model development depending on the phase/objective of the model?

Drug data: e.g., solubility, permeability, particle size, precipitation, dissolution, drug release mechanism, ADME…

System data: Anatomical structure, physiological parameters (GI tract)…

Clinical data: BA/BE studies, pharmacokinetic studies (e.g., different dosage forms, formulations, doses, etc.)…

The minimal data needed should be determined by:

Model objective (e.g., discovery/screening, preclinical, FIH, support dissolution method development, product development, specifications, post-approval changes)

Impact of the model application

Key Points from BO Session C, Day 2, Question 2

Dataset(s) for model development and model verification/validation

- The same or different data?
- How large should the validation dataset be?

* ***Tentative definitions for facilitating discussion in this session***

Validation: to assess the degree to which the computational model is an appropriate representation of the reality of interest which can be demonstrated by comparing the computational model predictions with the results from the comparators, e.g., clinical PK observations.

Verification: to ensure that the mathematical model is implemented correctly and then accurately solved.

Key Points from BO Session C, Day 2, Question 3

When should model optimization be conducted?

1. An important unknown input parameter exists that has material affect on the absorption, distribution, or metabolism and thus Cp-time profile of a drug.
   - Generally related to the chemistry/biopharmacuetics or metabolism rate (Km/Vmax).
   - Generally a bad idea to optimize physiologic parameters, expression levels, etc. These have been reported in literature and a lot have work has gone into generating accurate physiologies for the platforms.
   - Models exist for poor or extensive metabolizers in some cases, but you may need to have different Km, Vmax or expression levels for different subpopulations. In the built-in models, we adjust expression, but sometimes the mutation affects Km more.
   - Can be a system or physiologic parameter if evidence exists it is affected by the administration of the drug (ie gastric emptying or gastric pH).
   - When new evidence exists (ie lower colonic fluid volume)
   - Disease states may require optimization of physiologic parameters. Some built in models are available but not every disease state is covered and sometimes adjustments may need to be made for a given population.

Key Points from BO Session C, Day 2, Question 3 Cont…

2. A scientific/chemistry explanation, lack of a measurement validity/variability should generally be present for justification.
   - Assuming precipitation for a base early on before there is *in vitro* info. This is usually accompanied by visual evidence in the Cp-time profile so is not without justification.

Key Points from BO Session C, Day 2, Question 4

Optimizing a PBPK Model

- Criteria for validation
  - IVIVC or BE criteria?
  - Consider variability in population and sample size?
  - Consider all parameters or just C_{max} and T_{max}?

- How many parameters should be optimized based on one dataset?
  - Same number of equations/datasets as unknowns
  - Is this always feasible? Fit-for-purpose models

Key Points from BO Session C, Day 2, Question 4

How can we avoid identifiability issues

- Measure some of the unknown parameters
- Reduce the number of unknowns (group related parameters into one single parameter)
- Re-define the unknown parameters
- Generate data that can be used in calibration of a different in vivo dataset

Key Points from BO Session C, Day 2, Question 5

5. How should we set validation criterion(a)?

a. What type of criterion to use and what observations/predictions ?

b. Should it be established a priori and linked to:

i) The impact of the modelling?

ii) The variability of clinical data?

c. Should it be aligned to the IVIVC guideline ?

Key Points from BO Session C, Day 2, Question 5

Which criterion(a) for model validation/verification and which observations/predictions ?

Average absolute percent prediction error (% PE) (AAPE)

$$AAPE = Geomean\left(\left|\frac{predicted_i - observed_i}{observed_i}\right| \times 100\right)$$

0 to ∞. 0 indicates perfect fit. IVIVc criterion: Eg Level A if AAPE<10% for Cmax and AUC

Average Fold Errors (AFE)

$$AFE = 10^{\frac{1}{n}\times\sum Log\left(\frac{predicted_i}{observed_i}\right)}$$

0 to ∞. 1 indicates perfect fit. AFE indicates biais <1 : underprediction, >1 : overprediction

Absolute Average Fold Error (AAFE)

$$AAFE = 10^{\frac{1}{n}\times\sum\left|Log\left(\frac{predicted_i}{observed_i}\right)\right|}$$

1 to ∞. 1 indicates perfect fit. AAFE quantifies average absolute error

C_{max} and AUC or Full profile Cp(t)

Key Points from BO Session C, Day 2, Question 5

b. Should it be established a priori and linked to:

i) The impact of the modeling?

Stage	Potential use of PBBM	Impact (low/Moderate/high)	Validation criteria for the model	Acceptance of model
Development	Determining the clinical relevance of the dissolution method/data	Moderate	AFE for prediction of relevant clinical scenarios	0.8-1.25
	Virtual BE to test different batches of drug product and waive clinical relative BA*	High	AFE for prediction of relevant clinical scenarios	0.8-1.25
	Define the size of the safe space (based on CMA or CPP)	Moderate	AFE for prediction of relevant clinical scenarios	0.8-1.25
	Justify the proposed specifications for CMA and CPP	Moderate	AFE for prediction of relevant clinical scenarios	0.8-1.25
	Predict the impact of pH related DDI	Moderate	AFE for prediction of relevant clinical scenarios	0.5-2
	Predict the impact of food	Moderate	AFE for prediction of relevant clinical scenarios	0.5-2
	Predict the impact of beverages	Moderate	AFE for prediction of relevant clinical scenarios	0.5-2
	Virtual BE and sensitivity analysis to predict within and between subject variability + Geomean exposure ratio and aid powering of future clinical trials	Low	AFE for prediction of relevant clinical scenarios	0.8-1.25
	Predict different population than the model (paediatrics, elderly, disease) to inform dosing scenarios	Moderate	AFE for prediction of relevant clinical scenarios	0.5-2
	LCM development : determine the target dose and release profile to improve product medical value (with PK-PD/PK-Tox models)	Low	Not needed	
Post approval changes	Get regulatory flexibility to change specifications within safe space	Low	Not needed	
	If product batch dissolution is comparable (comply with f2) using clinically relevant dissolution method = waive clinical BE evaluation *	Low	Not needed	
	If batches show different dissolution with the clinically dissolution method (fail f2) but are shown to be BE in a virtual trial = Waive clinical BE evaluation *	High	AFE for prediction of relevant clinical scenarios	0.8-1.25
Notes	*: restrictions may apply for poorly permeable drugs based on some excipient changes			

Key Points from BO Session C, Day 2, Question 5

b. Should it be established a priori and linked to:

ii) The variability of clinical data?

Average PK profile prediction within observed clinical boundaries

AFE for Cmax and AUC within SD of observed clinical data

Overall Conclusions