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

September 23-25, 2019

College Park, MD

BREAKOUT SESSION B DAY 2:

Strategies to handle parameter uncertainty and variability within and between subjects

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Session Background

- Physiologically-based biopharmaceutics modeling invariably has to deal with parameter uncertainty and subject variability.
- Uncertainty is not a property of the system itself. Lack of data, experience or fundamental understanding make it difficult to precisely quantify parameters of interest.
- Subject variability relates to intrinsic variations of the physiological system. It can be observed and registered, but (unlike uncertainty) it cannot be reduced.

Session Background

.The goals of Session B on Day 2 are to discuss:

- The main sources of parameter uncertainty at different stages of PBBM
- How to reduce parameter uncertainty for model development
- Methods to analyze the impact of model uncertainty on predictions
- Ability of PPBK platforms to capture variability in absorption in populations.
- Modeling of drug product variability arising from manufacturing.
- Pathways to develop and harmonize strategies for handling uncertainty and variability.

Neil

1. What are the main sources of parameter uncertainty in physiologically based modeling (MAM/PBPK/PBAM/PBBM) at different stages of drug development?

- Prior to First Clinical Study
  - Pre and post absorption uncertainty
  - Uncertainties in …input parameters / mechanisms / translation ?
  - Which BCS classes?
- Early Clinical Development
  - Reduced uncertainty post absorption (IV data/ mass balance)?
  - NHV vs patient populations
  - Preliminary IVIVR?
- Late Clinical Development
  - Dissolution IVIVC?
  - Formulation related uncertainty

2. What is the best practice for reducing uncertainty in model parameters?

- Improved understanding and measurement of the system (e.g. gauge R&R studies).
- Are current experimental approaches adequate to support validation of mechanistic models?
- How can uncertainty in *in vivo* release, *in vivo* solubility, GI motility/transit times, Peff, precipitation mechanism, luminal transporter expression levels be treated to support bottom-up model development?
- Choosing a model structure commensurate with the modeling objectives ("fit for purpose").

3. How should the impact of model uncertainty on predictions be studied?

- PSA
  - how to decide on parameters?
  - how to set the ranges explored?
  - what are the limitations?
- Is a Monte-Carlo approach (Virtual Trial or Population Simulations) a useful way to convey the combined uncertainty due to multiple parameters?
  - how to select the distributions?
  - inclusion of co-variation/correlation?
  - interpretation of the results?
- Criteria used to compare simulations to clinical data – 2-fold, 1.5 fold, Abduljalil proposal?

4. How much confidence do we have in the use of existing PBPK platforms to capture variability in absorption in populations?

- Are model descriptions of non-healthy populations adequate to allow for confident extrapolation?
- To what extent is intra-subject variability leveraged when developing physiologically-based absorption models?
- Given the multitude of physiologically-related parameters (assigned “default” values) in PBPK platforms, what is the recommended approach to study the impact of subject variability on model predictions?
- How should the balance between averaged versus individual modeling be determined when using physiologically-based approaches?

5. How can we better model drug product variability? What is needed to advance this area?

- How can manufacturing variability be ‘modeled in’ to predict drug release from its formulation given that mechanistic drug *substance* release models (e.g. Noyes-Whitney) do not necessarily extrapolate to drug *products*?

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6.How can industry, academia and regulators best work together to develop strategies on handling uncertainty and variability?

- How to achieve more standardization of assay across companies to increase comparability and translation?
- Agreement on reporting best practice?
- Need for more workshops & publications dedicated to this topic?
- Consortia – challenges to share individual level data needed to assess variability.