Focus Group 2 – Use of modeling and simulation in LA product development.
Leaders: Tim Hallett and Justin Earp
Rapporteur: Craig Hendrix

Outline – pre-Session questions.
Pharmaceutics and model validity.

- How M&S improves CMC?
- Excipients and particle size, charge, other parameters most influencing PK?
- Key physiological processes (in vitro, preclinical, in vivo) explaining human disposition?
- Why PBPK models are ineffectual at the moment?
- How well does M&S predict real clinical data?

Development applications of interest.

- M&S PK translation from pre-clinical to FIH pediatric dose selection.
- Use of IVIVC development of LA ARV delivery.
- Can we model population impact of a new intervention added to a mix of variably efficacious products?

Regulatory (focus of this).

- When/how use M&S in lieu of clinical efficacy trials of LA (e.g., changes in formulation/dosing)?
- Learn more of the strategy from a modeling and simulation perspective for: 1) taking an NCE forward into LAI development vs 2) taking an agent already pressure tested with oral development first.

Model risk assessment was a recurrent theme during the session.
Framework for model risk assessment emerged from the discussion (Kuemmel et al, CPT PSP 2020).
IMAGE of square (risk 1 to 5)

- Goal: Match model confidence credibility with model risk for a given use context.
- The framework describes model risk as a function of:
  - Decision consequence defined in terms of AEs (y-axis).
    An incorrect decision results in none (low risk); mild-moderate (medium risk); or severe (high risk) AEs.
  - Model influence on decision-making defined in terms of clinical data availability (x-axis).
    Risk level (low; medium; or high) depends on the amount of clinical data (rich data – low risk; sparse data – high risk).
- Concluding that a model is high risk does not mean that it should not be done – need to either:
  - Increase the stringency of the analysis.
    Increase model credibility via more extensive verification, validation, and application (ASME).
  - Reduce the risk by constraining the model use context.
    Don't require as much of the model for downstream decision-making.

Range of M&S Applications.

- Early development target identification – low risk.
- PK and PKPD bridging applications – advance clinical development with a minimum number of trials (*In vitro* to pre-clinical; preclinical to FIH; humans to special populations– typically adults first).
    - Approval of pediatric LA anesthetic: single study, weight-based dosing algorithm, assumed no PD age differences.
    - Pediatric pulmonary arterial hypertension trial: Changed the PD biomarker from adult exercise-based endpoints to pulmonary hemodynamic markers.
    - Drug-drug interactions – assumption is that PBPK modeling alone identifies high-risk, strong inhibitors or inducers, followed by clinical confirmation studies; low and moderate inhibitors/inducers are assumed to be less risky by extrapolation and are not tested.
- Formulation differences and new molecular entity (NME) challenges.
- Clinical trial simulation to optimize RCT design.
    - Compete designs against each other and choose the one that most efficiently and clearly answers the question.
- Dose recommendations (interpolation).
    - Easiest application – after studying various doses, the final dose recommendation is somewhere in between.
- Rare diseases – M&S may be high risk (clinical data is often sparse), but high impact for a population.
- Population Product Choice Mix Modeling of multiple drugs/strategies to account for differential efficacy, uptake, and persistence.

Extended, high impact discussions.

Formulation and NME challenges.

- Using M&S to rapidly repurpose oral drugs for new indications has high impact; M&S accelerates even oral agents.
- The real challenge for M&S for LAIs is NMEs (drug and excipients).
    - When no clinical data on PK or PD, what are the PK targets, and how do those inform what drives the PD points you are choosing.
    - Even when confident of the PK model, how does PKPD drive dose selection (C_{max}, AUC, time above MEC targets).
    - Receptor binding information can help, but assumes an on/off mechanism, which is not always correct (e.g., C_{max} dependent PD).
    - Add PKPD of toxicity (drug, LA excipient) – same drivers as efficacy?
- Drug combinations add a level of complexity (i.e, TB/HIV).
- Additional LA challenges.
    - Prevention setting. How to optimize protection when the time to peak concentration is slow; need effective counseling for the initial period of risk.
    - Long tail impacts diagnostics and antimicrobial resistance.

Tissue and route of administration.

- Sites of action vary with the context of use.
  - Systemic, liver, lung macrophages, mucosal sites; intracellular sites may be relevant, depending on the mechanism of action.
- Plasma is generally a good surrogate for tissue PK, and dosing route is generally not influential, but there are exceptions.
  - Oral delivery may increase drug exposure in the liver vs other routes.
  - Mucosal dosing (HIV PrEP) for high mucosal concentration and low systemic exposure to reduce toxicity.
- Evidence of PK and PD discrepancy calls for additional exploration.

Bioequivalence – facilitating generic formulations to reduce cost and improve access.

- Small molecule BE standards are well-defined, commonly applied, and flexible.
  - Can be modified for narrow therapeutic index drugs to enhance safety (reduce generic-to-generic switch liability).
- Biosimilars follow a shortened, yet far more complex path – want to avoid that complexity.
- LA BE challenges that need to be considered.
  - Can we ignore formulation differences and simply apply existing BE criteria?
  - High inter-individual variability and occasion variability within participants.
  - Very long duration – are there PK shortcuts (e.g., partial AUCs to reduce complexity)?
  - Correlates of protection remain unclear for LA, especially with so few failures.
  - PK/PD is not always a priority when the drug works – learning opportunities can be missed.
  - When Ka is rate-limiting by design, do depot formulation lessons map onto carrier/lymphatic approaches?
- Consensus on the need for a BE workshop representing diverse perspectives (regulatory, industry, academia, clinical, community) – perhaps, LEAP could have a role as a partner or sponsor.
  - Address challenges and establish a common framework for LA BE.
  - Identify gaps in knowledge to optimize BE criteria and study design.

Population-level impact of product choice mix modeling and simulation.

When would M&S be considered to inform a regulatory decision?

- New intervention is less effective than the existing product (strict intention-to-treat terms or failed non-inferiority) but has attributes that indicate superior logistical or end-user characteristics (behavioral) such that uptake, adherence, and persistence (UAP) are greater than existing options in at least some populations.
- Clinical choice studies (accounting for efficacy, toxicity, and UAP) indicate that addition of the new product to the current option mix improves population-level health, thus meeting an unmet need.
- Unless “inferior products” are given regulatory approval, they will not be included in the analyses (pharmacoeconomic, etc) for policy makers and payers who decide which products belong in the option mix.

  Warrants a larger discussion with diverse perspectives.

Response from “in the know” participants.

- The US FDA pays particular attention to the unmet need in the market.
- Use of modeling and simulation data depends on the division, mostly considered exploratory.
- There is potential for exceptions, such as rare diseases and difficult patient sampling or recruitment issues.
- If enrollment is feasible, divisions are not motivated to change the regulatory precedent around the nature of clinical data that they require.