Outcomes from BOS1

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M&S in internal decision making

- Quantitative systems pharmacology
  - Critical questions need quantitative answers
  - integrated multidisciplinary models: carry quantitative knowledge forward along value chain
  - multidisciplinary contribution of modeling skills
  - Integrating knowledge enhancing decisions focusing on impact
- M&S assisting Phase 2A design
  - Outcome results can provide learning about translation between preclinical and clinical and/or species differences in relationship between different biomarkers.

Role of M&S in Internal decision

Used for basic Research

Early Development

- Use for translational exercises for FIH / MABEL
- Use for progress in Clinical Trials (ex. Phase 1ª-2)
- Strategic decisons: compare with competitors, select best in class.
- Build models based on data share and databases (TI-Pharma)

Opportunities and Gaps

- Need for agree on prioritization of platforms (toxicity signals, DILI, QT, etc…)
- Need to agree on scientific aims and agreement on models to be developed
- Build stepwise from simple to complex
  - Inter and extrapolation
- Build and share databases
- TI Pharma: mechanism-based PKPD modeling platform
- Outcome: PKPD model library for partners
- Business type approach to data infrastructure & collaboration

Opportunities and Gaps

- 20-30Y experience by Sponsors
- Regulators are less experienced
- Experience share needed
- Systems PD highly promising, still maturing
- Apply to Toxicity also
- Expected to abbreviate and ameliorate drug development and attrition.

Regulatory acceptance of M&S for FIH dose selection

- NOAEL vs MABEL depends on knowledge on target
  - MABEL when target is unknown
- Safety margin always necessary for unexpected events

- Use M&S for dose escalation and maximal allowed dose
  - Include observations at lower doses in humans to refine models (real time modeling)
- M&S in submitting FIH trials (SimCyp, Gastroplus, PBPK etc)
  - Validated for general use?
  - Qualification (not validation) for particular use
  - Regulatory validation: building level confidence for multiple cmpds & mechanisms

Current Regulatory Acceptance

- For Regulators the main M&S approaches seen are related to FIH estimation and MABEL
- PK/PD modelling is considered in “FIH guideline”
- Acceptance in general high but to be case-based
- Regulatory Involvement in further early decisions is seen as desirable

Further integration into DD and regulatory decision making

- Build and share knowledge (database, models) to improve prediction of **safety and efficacy**
  - Set objectives and Set platform
  - Harmonization and development of standards (DDMore)
  - Data sharing
  - Qualification
  - Guidelines and regulatory review
- Use M&S for dose escalation and maximal allowed dose
  - Include observations at lower doses in humans to refine models (real time modeling)
  - Transparency on assumptions and quantify risks
- Validate and/or build confidence in models and modeling methods for general use
- Increase understanding of multidisciplinary modeling approaches (quantitative systems pharmacology)
- Framework to trigger (informal, scientific) interaction moments to get discuss critical questions

How to Integrate into DD and Regulatory decision-making

Confidence in Models need to be built

- In new technologies
- New methodologies
- Qualification process

Experience share, (Scientific Advice, informal meetings)

Some general Guidance may be needed

Concepts may be integrated in existing guidances

Models evaluation will be case by case