Model-Informed Drug Development in Oncology

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**Objective**

- To discuss “best practices” in **integrating** PK, PD, efficacy, and safety data into models to best inform **oncology drug development**, evaluate disease- and mechanism-specific **early endpoints** to predict long-term efficacy, and discuss potential **regulatory implications** of model-informed decisions in drug development.

1. Discuss “best practices” in integrating human pharmacokinetic, pharmacodynamic, efficacy, and safety data into models that best inform oncology drug development.

2. Describe novel imaging techniques and diagnostic and predictive biomarkers that may be utilized in oncology drug development.

3. Describe disease- and mechanism-specific early endpoints to predict long-term efficacy.

4. Evaluate the potential to shift from traditional RECIST-based endpoints such as Overall Response Rate (ORR) and Progression Free Survival (PFS) to modified RECIST approaches (e.g. imRECIST for immunotherapies) as well as to other (model-based) tumor kinetic metrics to support early decision making in Phase 1/2 as well as in confirmatory trials.

5. Discuss potential regulatory implications of model-informed decisions in drug development, including, model-based target identification, dose/exposure justification based on preclinical evidence, dose selection for first-in-human trials, quality by design, early clinical study design, dose finding/titration, confirmatory trials, product labeling, and post-marketing studies.
Model-Informed Drug Development

Development and application of pharmaco-statistical models of efficacy and safety from pre-clinical and clinical data to improve drug development knowledge management and decision-making

Model-Informed Drug Development

MIDD

- PK/POP PK
- PBPK
- Disease Models
- Clinical Trial Models
- In Silico
- Clinical Trial Simulations
- Systems Biology
- QSP
- CiPA
- PK/PD Exposure-Response
- QSAR
- QSPR

Internal Decision Support
- Target Authorization and Mechanistic Understanding
- Candidate Comparison, Selection: Human PK and Dose Prediction
- Study Design Optimization
- Predicting and Characterizing ADME Including Intrinsic and Extrinsic Factors Impacting PK Variability
- Risk/Benefit Characterization, and Outcome Prediction from Early Clinical Responses
- Dose and Schedule Selection and Label Recommendations (Including Drug Combinations)
- Comparator/Standard-of-Care Differentiation and Commercialization Strategies
- Patient Population Selection and Bridging between Populations (Pediatrics, Elderly, Obese)
PDUFA 6: Regulatory Decision Tools

- Complex Innovative Trial Designs
- Model-informed Drug Development
- Biomarker Qualification
- Real World Evidence
- Benefit/Risk Assessment
- Patient Voice
Opportunities for MIDD
PDUFA VI – Enhancing Regulatory Decision Tools To Support Drug Development and Review

• Advancing Model-Informed Drug Development
  – FDA will develop its regulatory science and review expertise and capacity in MIDD approaches
  – FDA will convene a series of workshops to identify best practices for MIDD. Topics include PBPK, design analysis and inferences from dose-exposure-response, disease progression model development, immunogenicity
  – FDA will conduct a pilot program for MIDD approaches. For sponsors participating in the pilot program, FDA will grant a pair of meetings specifically designed for this pilot program
  – FDA will publish draft guidance, or revise relevant existing guidance, on model-informed drug development
  – FDA will develop or revise, as appropriate, relevant MAPPs or SOPPs, and/or review templates and training, to incorporate guidelines for the evaluation of MIDD approaches.

MIDD Challenges

• Best practices for determining a model is fit-for-purpose (validation, performance/sensitivity metrics, platform independence)
• Identification and transparent communication of knowledge gaps
• Data/knowledge warehouses
• Varying degrees of comfort by end-users
• Clarity on regulatory expectations
• For oncology, the rapid pace of development creates a catch 22
Opportunities for MIDD
Global Convergence

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development
Pfizer Scientists

The implications of model-informed drug discovery and development for tuberculosis
Drug Discovery Today (2016), http://dx.doi.org/10.1016/j.drudis.2016.09.004
Academic Groups in UK and Sweden and GSK Scientists

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Model Informed Drug Development for Malaria Therapeutics

Cognigen Corp.; SUNY, Buffalo; Bill & Melinda Gates Foundation; Scientists from Australia, Switzerland, Thailand and UK

Model Informed Drug Development and Regulatory Decisions

An Industry Perspective
IOM Workshop, 2015

Merck

Model informed drug development : Japanese regulatory perspectives

ICH harmonisation for better health
E11(R1) Addendum to E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

The Use of M&S in Paediatric Drug Development Approach

Model Informed Drug Development and International Harmonization
October 2017

Pharmaceuticals and Medical Devices Agency, Japan
ACOP 6, 2015

WHITE PAPER
Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

Commentary on the MID3 Good Practices Paper
EMA Modelling and Simulation Working Group

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; doi:10.1002/pdp.12049
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Commissioner’s Blog on *In Silico* Tools

- Innovation Initiative
- Use of in silico tools in clinical trials for improving drug development and making regulation more efficient
- M&S to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms
- Creation of natural history databases to support model-based drug development

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• Shiew Mei Huang
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• Jessica Benjamin
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