

Model-Informed Drug Development in Oncology

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Office of Translational Sciences | CDER | US FDA
FDA-ISOP Public Workshop
February 1, 2018

Objective

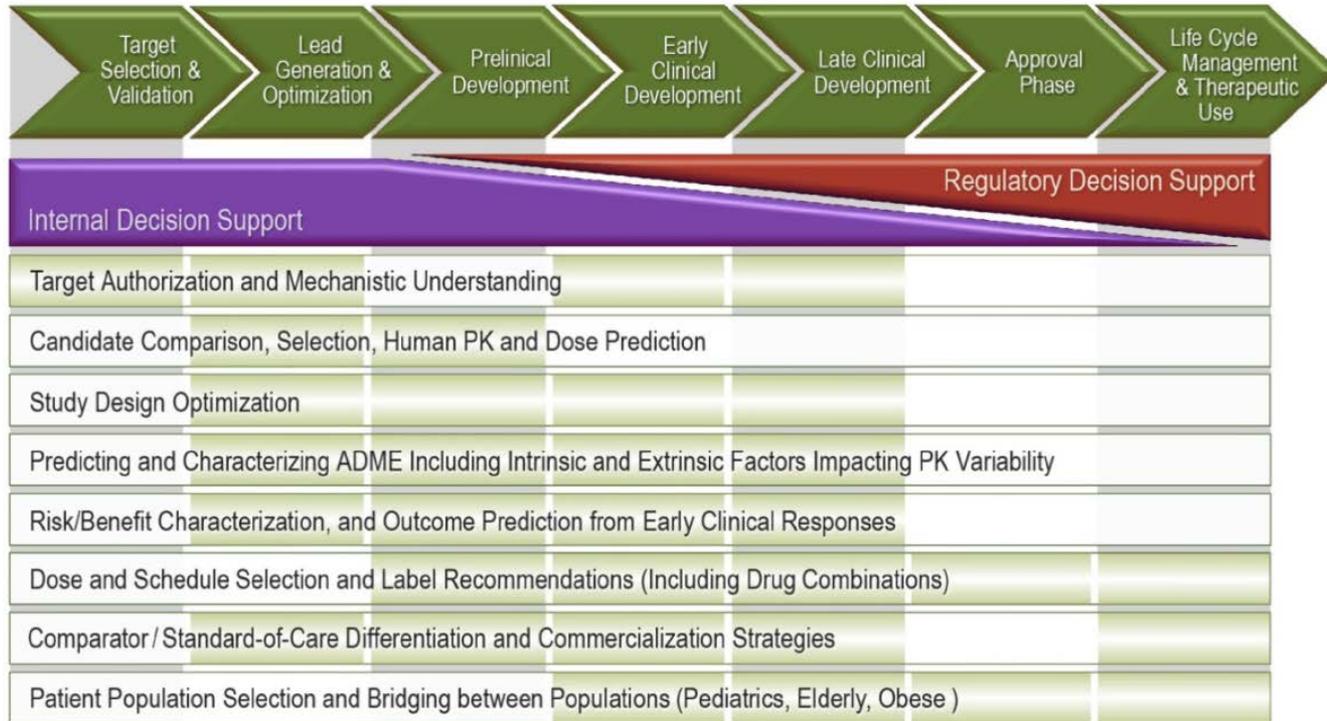


- To discuss “best practices” in **integrating** PK, PD, efficacy, and safety data into models to best inform **oncology drug development**, evaluate disease- and mechanism-specific **early endpoints** to predict long-term efficacy, and discuss potential **regulatory implications** of model-informed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

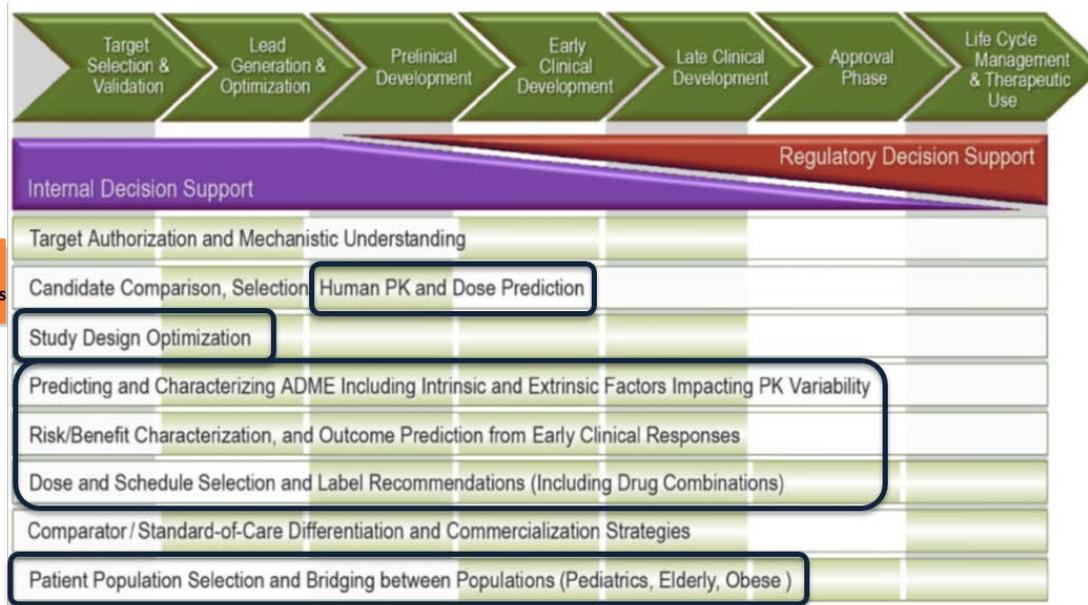
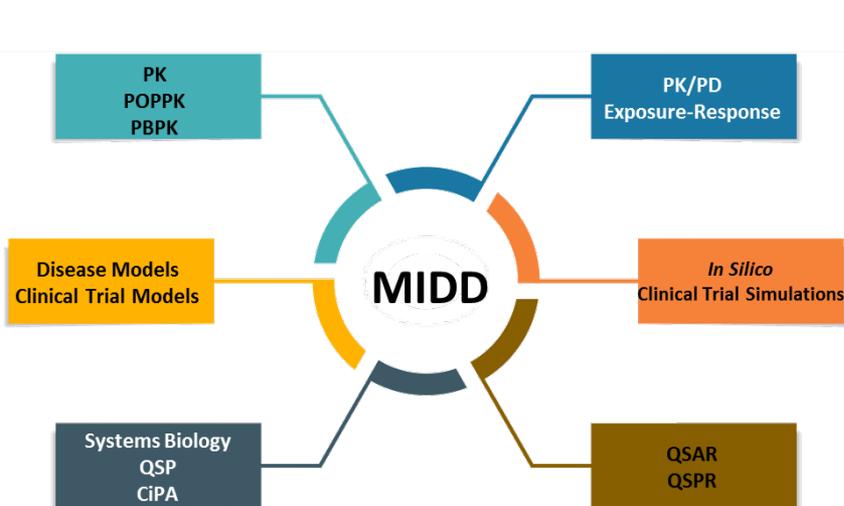
Model-Informed Drug Development



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

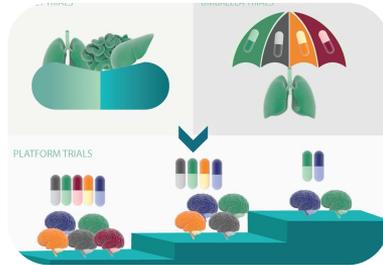


Model-Informed Drug Development

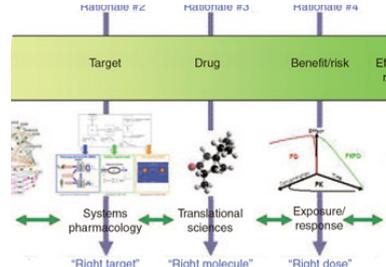


PDUFA 6: Regulatory Decision Tools

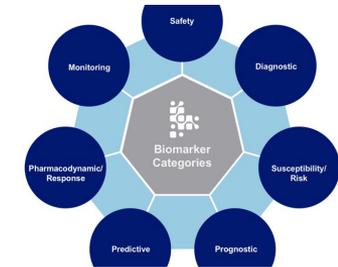
PDUFA VI
The Prescription Drug User Fee Act



Complex Innovative Trial Designs



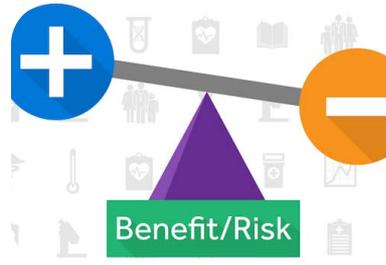
Model-informed Drug Development



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



European Federation of Pharmaceutical
Industries and Associations

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

Clin Pharmacol Ther. 2013 Jun;93(6):502-14

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

Commentary on the MID3 Good Practices Paper

EMA Modelling and Simulation Working Group

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 416–417



Pharmaceuticals and Medical Devices Agency, Japan

ACOP 6, 2015

Model informed drug development : Japanese regulatory perspectives

Model-Informed Drug Development for Malaria Therapeutics

Annu. Rev. Pharmacol. Toxicol. 2018. 58:567–82

Cognigen Corp.; SUNY, Buffalo;
Bill & Melinda Gates Foundation;
Scientists from Australia,
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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



Model Informed Drug Development and Regulatory Decisions

An Industry Perspective

IOM Workshop, 2015

Today and Tomorrow

Merck

Commissioner's Blog on In Silico Tools

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

We're at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.



To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.

- 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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