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CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Submitting Scientific Data from Different Sources: A Focus on Pharmacometrics Model Files and Datasets

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Disclaimer

- **The opinions expressed in this presentation are the presenter's and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA).**

Problem Statement

- When most people think about study materials submitted with a regulatory submission, the focus is on:

- These materials cover a large majority of materials submitted to and, in turn, reviewed by disciplines

- Concurrent with these materials, modeling and simulation results are submitted for review

What is Modeling and Simulation

- Modeling and simulation facilitates integration of data from many sources
- Leverages accumulated information for informed decision making

PK

Efficacy

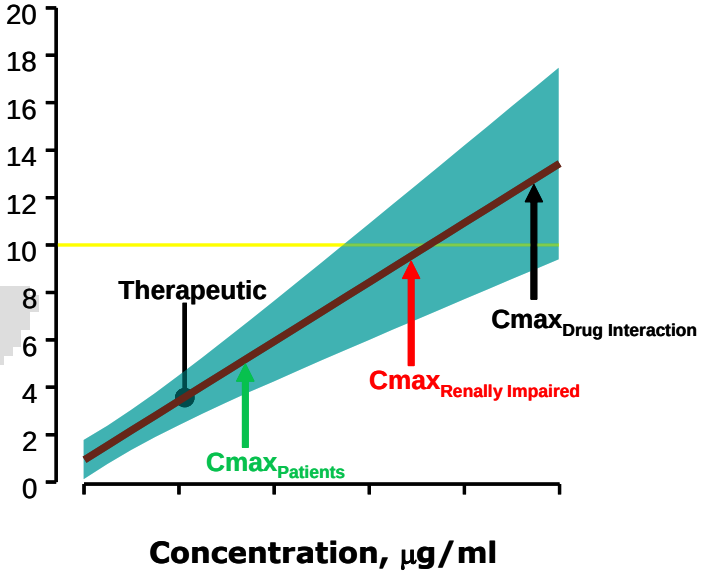
Safety

Covariate

Data Assembly

Analyses

Output



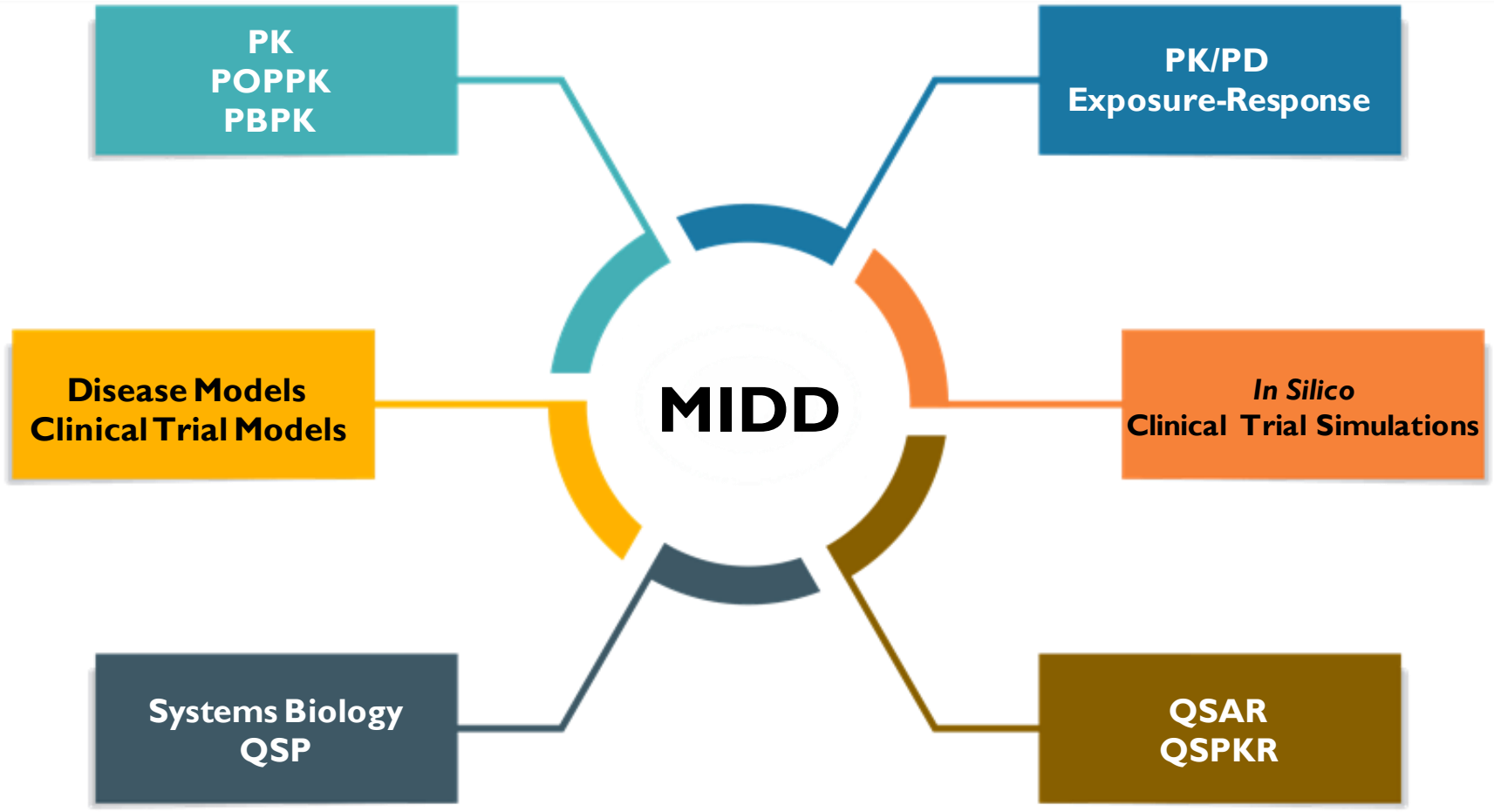
Decision and Action

Translate M&S output into action

Why is Modeling and Simulation Used in Drug Development – It Varies

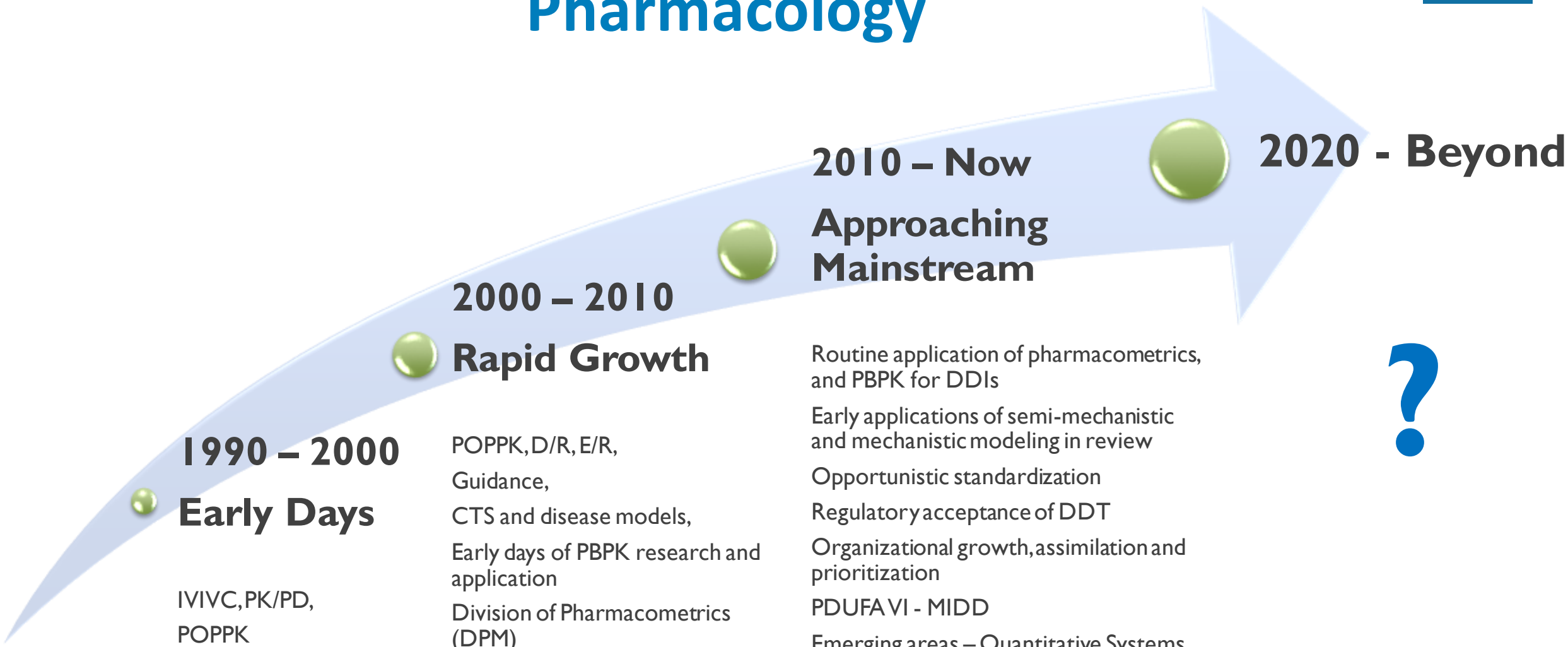
Data Generated	In vitro PD Animal PK & PD	First-in human PK & PD Preliminary safety and efficacy	PK & PD data relating biomarkers and endpoints to safety and efficacy	More robust safety and efficacy with sparse PK in broader target population
Analysis Tools	Quantitative systems pharmacology, drug-disease-trials models, pharmacokinetic-pharmacodynamic modeling, dose-response/exposure-response analysis, population pharmacokinetic modeling, physiologically-based pharmacokinetic modeling, in-vivo/in-vitro correlation			
Decisions	Target Selection Feasibility	Go-No Go Regimen selection	Go / No-Go Decisions Phase 3 Dose Selection Intrinsic/Extrinsic factors	Data driven dose modifications for safety and efficacy

More Recently: Model-Informed Drug Development (MIDD)



Bruno 2019 [PMID 30951201]

Evolution of MIDD at Office of Clinical Pharmacology

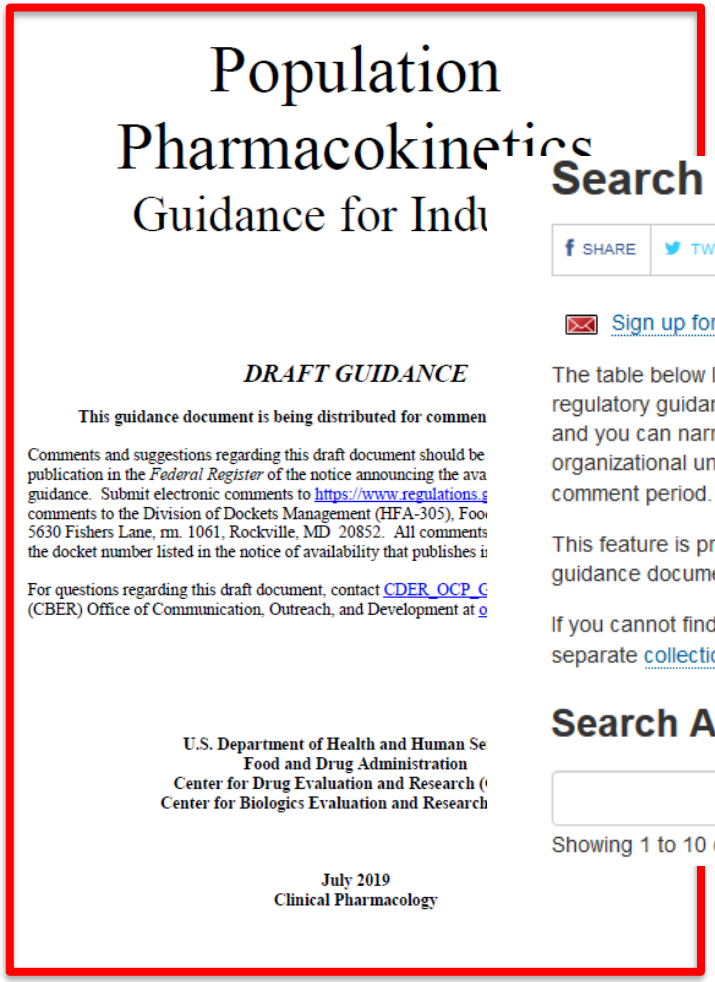


IVIVC – In vitro-In vivo Correlation;
CTS – Clinical Trial Simulation; DDT – Drug Development Tool;

Adapted from Zineh & Woodcock, CPT 2013; PMID: 23571772

A Subset of Relevant Guidances

Population PK



Population
Pharmacokinetics
Guidance for Indu

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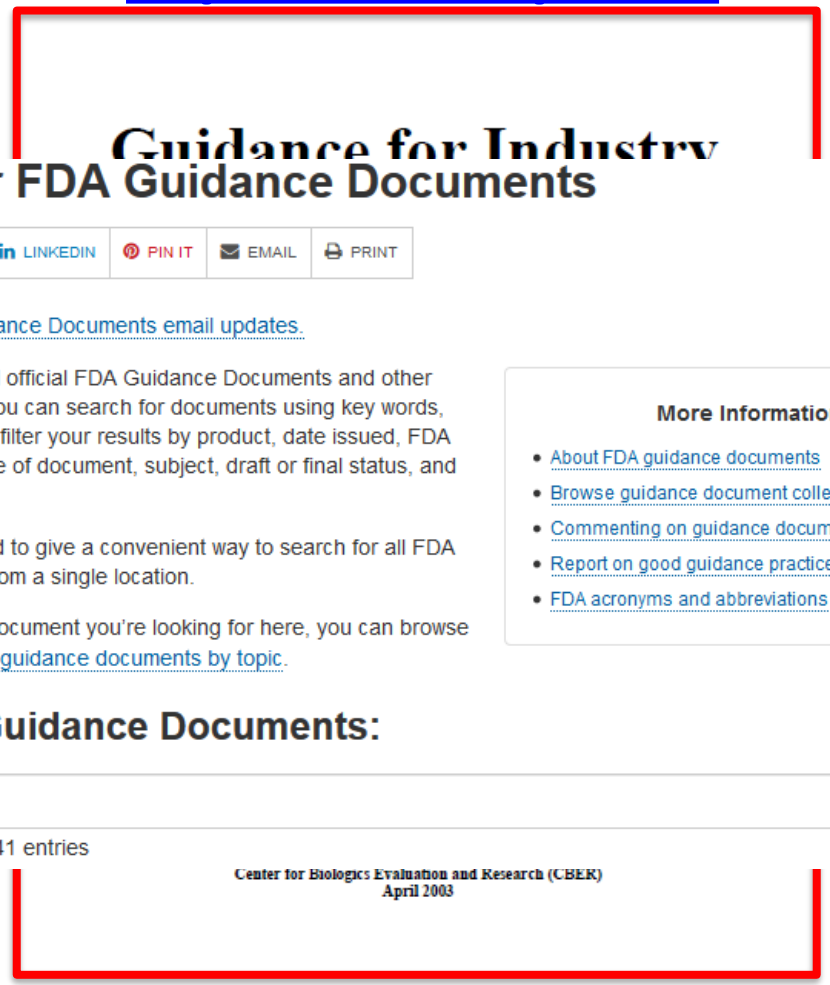
Center for Biologics Evaluation and Research

July 2019
Clinical Pharmacology

Exposure-response



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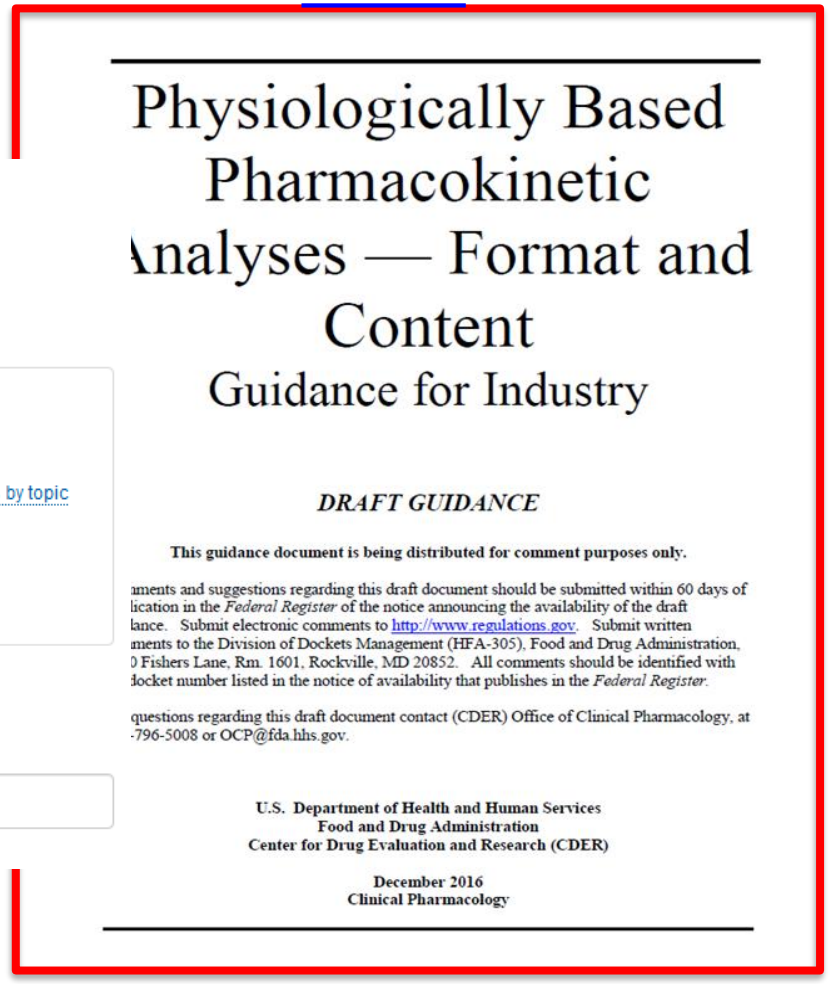
Center for Biologics Evaluation and Research (CBER)
April 2003

PBPK*



Physiologically Based
Pharmacokinetic
Analyses — Format and
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2016
Clinical Pharmacology

FDA Guidance Webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

*Also PBPK guidance published by OPQ: The Use of PBPK Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Some Specific Applications of Each

Population PK

Drug Development

- Alternative dosing schemes in clinical studies
- Study sample size and sampling scheme
- Deriving exposure-metrics for exposure-response analysis
- Dosing in pediatric patients

Inform Drug Use

- Characterization of drug pharmacokinetics
- Specific populations
- Drug-Drug Interactions

Exposure-response

Drug Development

- Link animal and human findings
- Provide evidence for mechanism of action (PoC)
- Provide guidance for designing trials

Evaluate Safety and Efficacy

- Contribute to evidence of effectiveness
- Provide support for primary efficacy studies
- Support new target population, use in subpopulations, or alterations to the dosing regimen, form, or route of administration

PBPK*

Drug Development

- Predict the potential for drug-drug interactions
- Dosing across different patient populations

Inform Drug Use

- Support dosing recommendations for certain drugs when they are co-administered with metabolic enzyme modulators
- Often used to fill information gaps that would otherwise require a dedicated study

Where are These Materials Placed

Where are These Materials Placed

- **Most commonly, materials are placed in:**
  - 5.3.3.5 Population PK Study reports and related information

- **Less commonly:**
  - 5.3.1.2 Comparative BA and bioequivalence (BE) Study reports and related information
  - 5.3.1.3 In Vitro - in Vivo correlation Study reports and related information
  - 5.3.2.2 Reports of hepatic metabolism and drug interaction studies
  - 5.3.4.2 Patient PD and PK/PD Study reports and related information
  - 5.3.5.3 Reports of analyses of data from more than one study
  - 5.3.5.4 Other Study reports and related information

- **Then occasionally in:**
  - All other 5.3.3, 5.3.4, and 5.3.5 Modules
  - All other 5.3.5 Modules
  - M4 and M5, though this is usually for PBPK analysis

The Comprehensive Table of Contents Headings and Hierarchies: https://www.fda.gov/media/76444/download

Modeling and Simulation Materials Versus Typical Study Reports and Datasets

CLINICAL STUDY REPORT	MODELING AND SIMULATION
• Focuses on results from a single study	• Often combines data across multiple studies
• Data sets provided following existing data standards available in Data Standards Catalogue	• Data set may vary depending on the problem or software used in the analysis
• Analyses are typically reviewed without relying on codes provided by a sponsor.	• Presented analyses and approaches cannot be reviewed without full modeling files, description of software used, and options
• Scripts may be provided. Pathways and naming conventions for the files makes it difficult to rerun materials as is	• Scripts may be provided. Pathways and naming conventions for the files makes it difficult to rerun materials as is

How Modeling and Simulation Results Are Prepared, Submitted, and Reassembled

Analysts at Pharmaceutical

- Perform analyses to be submitted with an application
- Construct a project workflow with model datasets and scripts appropriate for software and approaches used
- Write a study report of results
- Copy and rename files to align with ‘expectations’ for a submission
- Provide instructions for assembly
- Provide materials to regulatory for submission

Analysts at FDA

- Receive materials as part of a submission
- May have to look in multiple locations to find the materials
- Follow the instructions provided by a sponsor
  - Identify what datasets are need to recreate and review analyses
  - Rename files, and at times, create a directory structure
- Triage problems that arise or send information requests to sponsors

Multiple steps requiring renaming, disassembly, renaming, and reassembly

Solutions Provided to Eliminate Pinch Points

- Recognition that modeling datasets and scripts may have needs that differ from more traditional clinical study reports and datasets
- Updates to Specifications for File Format Types Using eCTD Specifications
  - New updates related to model datasets and scripts added in 2017 and 2021

2017-03-02	2.0	Updated version, new file formats added: • Document file types: .xls, .xlsx • Audio/Visual file types: .fla, .f4v, .mpg • Data file types: .csv • Modelling & Simulation file types: .cmp, .wks, .lbr • Modelling & Simulation Reporting file types: .lua, .sas, .r, .ctl
2021-03-15	5.0	Updated file formats added: Modeling & Simulation file types: .cmpx, cmpz, .wksx, .wksz, .lbrx, .lbrz, .mdb, .pbk, .opd, .psd, .spd .c, .cpp, .m, .mat, .rmd, .phxproj, .py, .jl, .cas, .dat

Additional Activities Underway

- Ongoing effort to update externally facing webpages with language describing submission of model scripts and datasets
  - Emphasize updates to Specifications for File Format Types Using eCTD Specifications
  - Emphasize modules where different analyses are submitted

Get the word out!

- Engage with professions societies and at conferences about changes so groups are aware – what has changed, why has it changed, etc.

- Reiterate and encourage discussion of plans for submission with the Agency if there are any questions

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THANK YOU


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