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Strategic Implementation of Model-informed Drug Development for Regulatory Success

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Overview

- Share some experiences and thoughts on the effective implementation of model-informed drug development approaches
- Outline some considerations for optimizing the likelihood of regulatory success with model-informed approaches
- Happy International Day of Women and Girls in Science!

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Evolution & Industrialization of Pharmacometrics

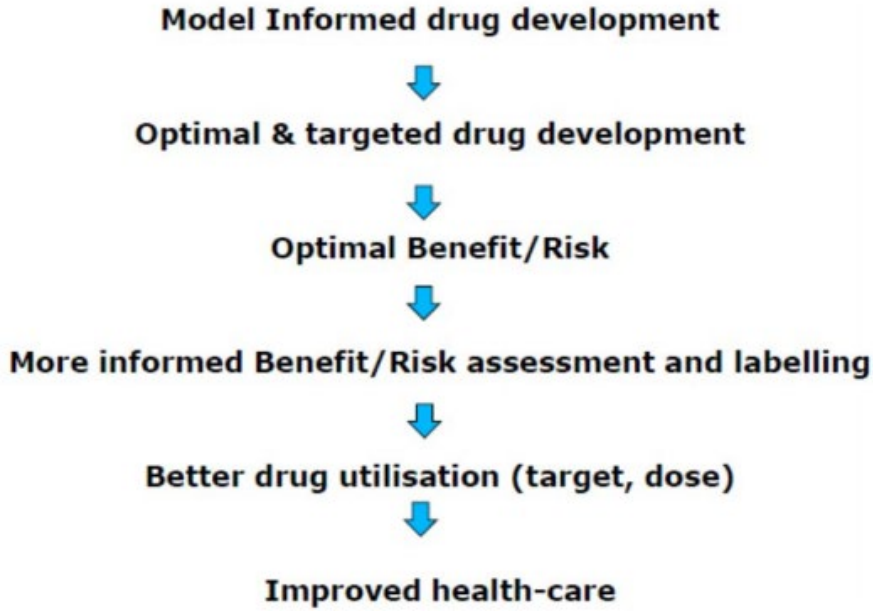
- The discipline of pharmacometrics
  - JPB 1982 – Introduction of a new journal section, Benet & Rowland
- Academic programs starting in 2001: 20+ universities now offering curriculum including pharmacometrics (MS & PhD)
- FDA Division of Pharmacometrics (estab. 2007); EMA MSWG; PMDA public workshops; Quarterly PMX/M&S Cluster TCs (EMA, FDA, PMDA, HC)
- MIDD → MID3
  - Illustrating the expansion of this thinking beyond the original starting point of dealing with sparse data in Phase 3
  - Importantly, extensions tie together a continuum of quantitative methods: pharmacometric approaches include PBPK, QSP/QST, population-based M&S

Meanwhile ….

- Numerous examples of success …. with many published
- FDA reviewers are prolific, sharing examples of regulatory wins, multiple uses, commonality of approaches, etc.
- Continued and expanding research, achieving progress in exploring new and improved methods
- Efforts at standardization continue
    - Committees of ISoP (MoEv, Data Standards, also commentary on DDI) and ASCPT Network & Community Initiatives (Impact & Influence)
    - Best practice papers (MID3, E-R, etc.)
    - Workshops à la PBPK Best Practices chaired by FDA in Nov 2019

Optimal Pharmacotherapy for the Patient

Vision of the 2014 MSWG (EMA)



From: 2014 Activity report of the Modelling and simulation working group (MSWG, European Medicines Agency (2015); https://www.ema.europa.eu/en/documents/report/2014-activity-report-modelling-simulation-working-group_en.pdf

Value of Pharmacometric Approaches

Population-based modeling and Exposure-response analyses

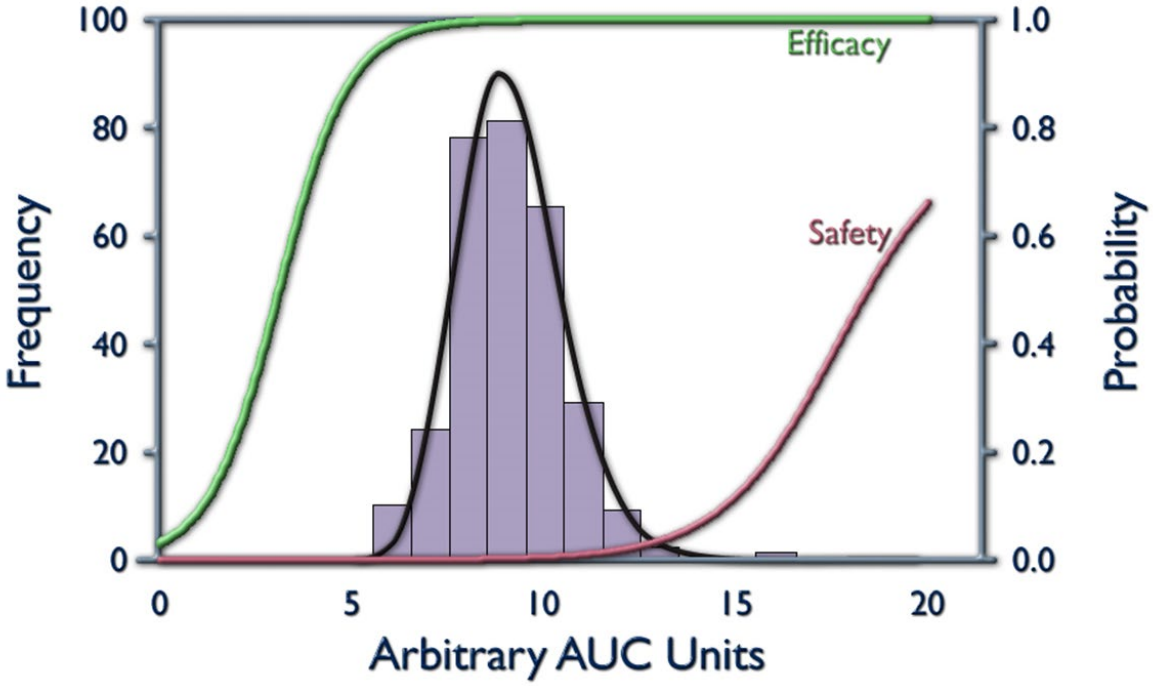
What questions do we answer:

- *PK-related:* dose proportionality, time invariance, effects of intrinsic/extrinsic factors on PK, drug-drug interactions

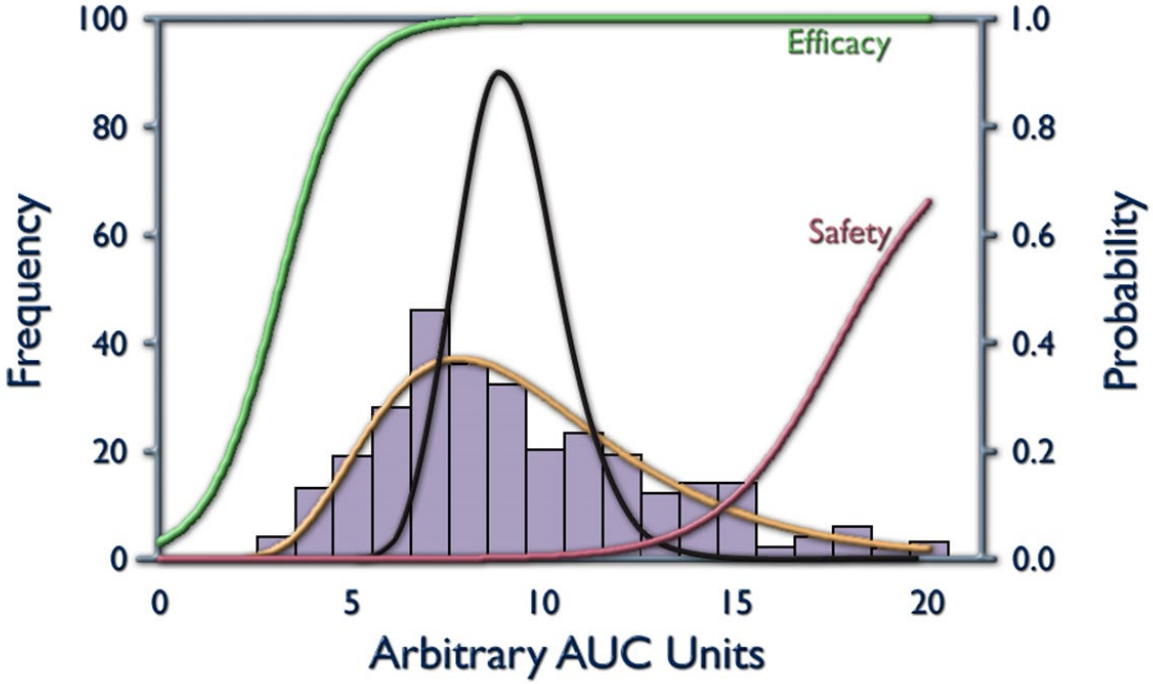
- *PK/PD-related:* E-R relationship, quantification of placebo effect and the time-course of response, determinants of safety and efficacy, risk-benefit characterization

- *Simulation-related:* Sparse sampling strategy options, optimal trial design for Phase 2 or 3 (sample size, sample timing, dosing, etc.), probability of success, special population (pediatric) dose selection support and labelling

Population Exposure-Response Relationships
Wide Therapeutic Index



Population Exposure-Response Relationships
Impact of PK Variability on Therapeutic Index



Value of Exposure-Response Analysis

- Variability in PK can make dose a poor measure of systemic exposure
- Information on individual systemic exposure (C_{av}, AUC, C_{max}, C_{trough}) is important in the evaluation of:
  - Adverse advents
  - Exaggerated drug effect
  - Lack of response
- Sparse PK sampling and population PK/PD analysis allow for evaluations of safety and efficacy at both the patient and population level
- "Exposure response information is at the heart of any determination of the safety and effectiveness of drugs"

(FDA Guidance for Industry - Exposure-Response Relationships, 2003.)

Applications of Exposure-Response Analyses

- Establish clinical proof of principle
- Provide a rationale for the recommended dose
- Interpret unexpected findings
- Provide supportive evidence of effectiveness
- Explore whether adverse events are related to exposure

Overgaard et al., Establishing Good Practices for Exposure-Response Analysis of Clinical Endpoints in Drug Development; *CPT Pharmacometrics Syst Pharmacol. (*2015); 4(10): 565–575.

Importance of Pharmacometric Analyses in *Regulatory* Decision Making

Regulatory Decisions	Role of Pharmacometric Analyses
Approval Basis	1. Provide evidence of effectiveness
Designing Trials	1. Select dose or exposure range for registration trials 2. Derive optimal sampling schemes (exposure and response)

…….. or …….

"… the goal of MIDD is to derisk drug development and public health decision making and robustly inform optimal pharmacotherapy."

Madabushi R, Wang Y, Zineh I. A Holistic and Integrative Approach for Advancing Model-Informed Drug Development; *CPT Pharmacometrics Syst Pharmacol.* (2019) 8, 9-11.

Table adapted from: Bhattaram et al. (2005) AAPS J. 7(3): Article 51, E503–12.

Alternative Pharmacometric Approaches: Overlap & Differences in Applications

QSP/QST Modeling:

- Describing PD effects in organs/tissues over time
- Exploration/confirmation of mechanism (targets & biomarkers)
- Support drug design, identify responders/non-responders, inform interventions based on interplay between pharmacology and the underlying biological system

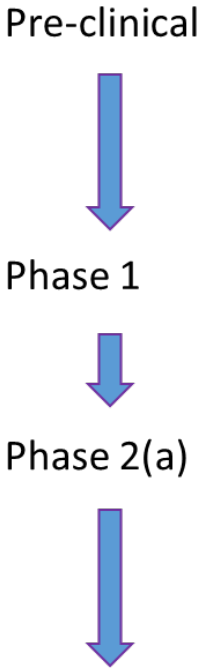
PBPK Modeling:

- Describing PK in organs/tissues over time
- Predicting DDI
- Extrapolation in pediatrics, other subpopulations

Population PK/PD Modeling:

- Identify sources of variability in dose → concentration → response
- Dose and regimen optimization
- Extrapolation of therapeutic effects to unstudied populations

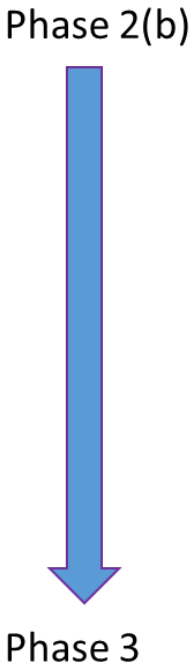
Applications of Population M&S in Drug Development: Pre-clinical Through Phase 2a



- Obtain population distributions of PK profiles in various animal species, also useful in bridging to FIH
- Develop structural PK model based on rich data
- Identify sub-populations with altered PK and PK/PD and, when prospectively planned, can be used to eliminate Phase I studies

Chien et al., AAPS J 2005;7(3)55 (http://www.aapsj.org).
Schmith et al., Pharm Res, Vol 14, No 1, 1997.

Applications of Population M&S in Drug Development: Phase 2b Through Phase 3



- Develop PPK and PK/PD (drug-disease) models to understand the time course of disease progression and dose-response
- Perform simulations of trial outcomes to estimate probability of success under various design considerations
- Assess need for dose adjustments, justify the recommended dose, and provide rationale for drug labeling

Chien et al., AAPS J 2005;7(3)55 (http://www.aapsj.org).

Regulatory Landscape Surrounding MIDD

Select Related FDA Guidances

- Population Pharmacokinetics, DRAFT, July 2019
- Exposure-Response Relationships, May 2003
- End-of-Phase 2 (EOP2) Meetings (procedural), Sept 2009
- Physiologically Based Pharmacokinetic Analyses – Format and Content, Sept 2018
- Interacting with FDA on Complex Innovative Trial Designs, Dec 2020
- MIDD Pilot Program (5-year: 2018-2022)
    - Enables early discussions between regulators and sponsors on M&S strategy issues

www.fda.gov
https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

FDA's MIDD Pilot Program

- Announced in April 2018, this program was initiated to "facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, referred to as MIDD approaches …" (which) " … can improve clinical trial efficiency, increase the probability of success, and optimize drug dosing/therapeutic individualization in the absence of dedicated trials."
  - Provide an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development, and
  - Provide advice about how particular MIDD approaches can be used in a specific drug development program
- Focus on: dose selection or estimation, clinical trial simulations, predictive or mechanistic safety evaluation

https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

FDA Question-based Review (QbR)

Part of the MAPP (Manual of Policies & Procedures)
Clinical Pharmacology & Biopharmaceutics Review Template for NDAs

- **Good Review Practices:** reflects the increasing importance of mechanistic understanding and clinical pharmacology principles in drug evaluation as a key component of evidence of effectiveness assessment
  - prioritized, issue-driven & consistent
  - promotes interdisciplinary communication
  - emphasizes the integration of scientific information and use of M&S to address understanding of E-R and posology
  - integrates information across studies

High-Level Clinical Pharmacology Review Questions

- To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?
- Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?
- Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?
- Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

https://www.pdffiller.com/jsfiller-desk13/?requestHash=196bf25be9fa7055372ceabbdea8d16322257fec258c24c64077918fc1355e4b&projectId=632300204#2fa060ac47b348aca5e65b689716cf2e

FDA Question-based Review Contents

General drug attributes

General clinical pharmacology

- Basis for selecting response endpoints/biomarkers?
- Are active moieties identified and measured?
- Characteristics of E-R for efficacy?
- Characteristics of E-R for safety?
- Does the drug prolong QT or QTc interval?
- PK characteristics of drug and major metabolite(s)
  - Single- and multiple-dose PK
  - PK in HVs versus patients?
  - Characteristics of absorption?
  - Characteristics of distribution?
  - Characteristics of metabolism?
  - Characteristics of excretion?
  - Renal or hepatic as a major route of elimination?
  - PK linear or non-linear?

https://www.pdffiller.com/jsfiller-desk13/?requestHash=196bf25be9fa7055372ceabbdea8d16322257fec258c24c64077918fc1955e4b&projectId=632300204#2fa060ac47b348aca5e65b689716cf2e

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FDA Question-based Review Contents (continued)

- How does PK change with time?
- Inter- and intra-subject variability of PK in HVs and patients and what are major causes of variability?

Intrinsic Factors

- What intrinsic factors influence exposure and/or response?
- What is the impact of differences in exposure on efficacy or safety?

Dosing recommendations for:

- Elderly, pediatrics, gender, race, renal impairment, hepatic impairment, etc.

Extrinsic Factors

- What extrinsic factors influence exposure and/or response?
- What is the impact of differences in exposure on efficacy or safety?

https://www.pdffiller.com/jsfiller-desk13/?requestHash=196bf25be9fa7055372ceabbdea8d16322257fec258c24c64077918fc2655e4b&projectId=632300204#2fa060ac47b348aca5e65b689716cf2e

FDA Question-based Review Contents (continued)

Dosing recommendations based on extrinsic factors?

Drug-drug interactions

- Is there an in vitro basis to suspect in vivo drug-drug interactions?
- CYP substrate? Inhibitor or inducer of CYPs?
- Metabolism influenced by genetics?
- Substrate and/or inhibitor of P-gp?

https://www.pdffiller.com/jsfiller-desk13/?requestHash=196bf25be9fa7055372ceabbdea8d16322257fec258c24c64077918fc1355e4b&projectId=632300204#2fa060ac47b348aca5e65b689716cf2e

- If label specifies co-administration, has interaction potential been evaluated?
- What other co-medications are likely to be administered in the target patient population?
- Is exposure or E-R different with co-administration?
- Mechanistic basis for a PD drug-drug interaction?
- Any unresolved questions related to metabolism?

Regulatory Landscape Surrounding MIDD

Select Related EMA Guidelines and Other Docs

- Reporting the Results of Population Pharmacokinetic Analyses
- Reporting of Physiologically Based PK M&S
- M&S Q&A
- Clinical pharmacology & PK Q&A
- Role of PK in the Development of Medicinal Products in the Paediatric Population
    - Extrapolation of Efficacy and Safety in Paediatric Medicine Development
- Reflection paper on investigation of PK and PD in the Obese Population

https://www.ema.europa.eu/en

Global Harmonisation Efforts … EMA/FDA

- ‘Are Regulators Talking to Each Other Across Borders?‘
  - Based on 2019 CPT Review and editorial …. Yes, a lot!
    Cross-border dialogue is well established with “Clusters” related to specific disease areas and topics
- Does that mean they always agree? …. No.
- Two reviews of submissions to FDA and EMA, 2014-2016 by Kashoki and Kühler find considerable agreement in decisions
  - In alternative scenarios, most common were differences related to conclusions about efficacy based on the same data
- Even though the ultimate decision may be in sync, the questions which need to be addressed and issues of concern can be quite different

Teixeira T et al. *Clin Pharmacol Ther.* 107(3), March 2020, 507-13.
van der Graaf PH. *Clin Pharmacol Ther.* 107(3), March 2020, 481-3.
Kashoki M et al. *Clin Pharmacol Ther.* 107(1), Jan 2020, 195-202.
Kühler TC et al. *BMJ Open* 2019;9.

Learn & Confirm ……
Predict → Learn → Confirm

- Modeling is an evolutionary process
- Process involves collecting data, using modeling to test assumptions and generate knowledge, using model/knowledge to simulate and make predictions (inform decision-making) and design new trials, collect new data to test new assumptions, etc.
- Models improve and are refined as they are continually informed by new data
- When initiated early in development, there should be an expectation that the model(s) evolve throughout development

Sheiner LB. *Clin Pharmacol Ther. 6*1(3), March 1997.
Suri A et al. *Clin Pharmacol Ther.* 98(3), May 2015.

Example PPK/PD Model-Informed Development Program

Model Iteration	Applications	
PPK model based on available data from Phases 1-3: 2-3 stages common	Characterize PK; understand effects of covariates; generate individual exposure estimates	
	Evaluate the feasibility of fixed dosing via model-based simulations	
	Develop plan to evaluate viability of alternative dosing strategies	
PK/PD model for biomarker	Confirm MOA; understand impact of exposure (dose) on magnitude of response	
E-R models for 1ry, 2ry efficacy endpoints	Characterize E-R efficacy relationship; understand effects of covariates on likelihood of efficacy	Simulate probability of success with proposed P3 design based on PPK and E-R models; Simulate doses for peds or other special populations
E-R models for important AEs	Characterize E-R safety relationship; understand effects of covariates on risk of AEs	
Update PPK, PK/PD and E-R models incl available pediatric data	Refine pediatric dose predictions; evaluate and compare alternative sample sizes and sampling strategies for later phase pediatric trials	

Exposure-Response Good Practices

- Start with a clear understanding of the questions and link analyses to questions
- Consider pooling the data from different studies to get a broader dose/exposure range
  - be careful to address the complexities that come with pooling data from studies with different designs and populations and endpoints
- Know the assumptions and limitations of the analysis methods
  - In particular, be careful about confounders
- Choose the appropriate method for your data and your question
  - Account for placebo response, dropout if needed
  - Start with a single endpoint and assess whether time-course is needed
- Assess the impact of covariates and consider on which parameters you will assess
- Visualization of the data is important

Overgaard et al., Establishing Good Practices for Exposure-Response Analysis of Clinical Endpoints in Drug Development; *CPT Pharmacometrics Syst Pharmacol. (*2015); 4(10): 565–575.

MID3 Good Practices

Planning, conduct and documentation recommendations

Most important are:

- Clear objectives
- Transparency on assumptions and their impacts
- Adequate communication of key findings and recommendations to stakeholders
- Sufficient materials to enable reproduction

For internal decision making: analysis plan and memo/brief report

For regulatory interaction: analysis plan, simulation plan, and report

Marshall SF et al. *CPT Pharmacometrics Syst Pharmacol.* (2016) 5, 93-122.

Survey Says ….

- 2017 survey on MID3 addressing then-current industry good practices, regulatory expectations and future perspectives
  - 18 industry, 13 EMA, 11 FDA respondents
  - "Good match with some gaps" among MID3 good practice, company practice and regulatory expectations
    - Consensus that MID3 good practices may serve as a starting point or be referenced in regulatory guidelines
  - Modest to substantial increase in the degree of impact of MID3 on decision making over the past 5 years
- Take-aways: educating decision makers, early strategic planning and input from regulators are key, professional organizations play a crucial role

Marshall S et al. *CPT Pharmacometrics Syst Pharmacol.* (2019) 8, 87-96.

Essential Components to Successfully Navigating Regulatory Hurdles with MIDD

OVER-communicate

Learning & Awareness:
- landscape
- relevant reg issues/guidances/tools
- other similar/recent programs
- training on methods/techniques

Execution:
- develop & follow a strategic plan
- design of studies:
  (what to collect, when to collect, how to collect)
- know how to follow the plan
- pay attention to the details

Ecosystem:
- tools (software, canonical documents)
- education of decision makers
- project mgmt support and planning
- quality system (processes)

Marshall SF et al. *CPT Pharmacometrics Syst Pharmacol.* (2016) 5, 93-122.
Overgaard et al. *CPT Pharmacometrics Syst Pharmacol. (*2015); 4(10): 565–575.

Recommended Analysis (Simulation) Plan Content

- Intro w Objectives and Background
- Data (selection of studies/data, description of designs and data collected, assembly: software, rules for inclusion/usability, handling of missing data, formatting)
- EDA (outlier identification, correlations)
- Methods
  - Software
  - Assumptions that may impact the conclusions
- Methods (continued)
  - Model building, selection, refinement, evaluation, qualification, application, clinical significance, etc.
  - Simulations (statement of questions to be answered, specification of input-output model, virtual population generation, trial design and execution model (if appropriate), replication, statistical analysis and criteria for addressing the questions, etc.)

Marshall SF et al. *CPT Pharmacometrics Syst Pharmacol.* (2016) 5, 93-122.
Owen JS and Fiedler-Kelly J. Intro to Pop PK/PD Analysis with NONMEM, Wiley (2014).

Reporting: Tell the Story

The truth, the whole truth, and … your rationale

- Reporting is about both communication and supporting reproducibility*
- Writing in real-time may alleviate issues of recall and the need to re-trace steps
- Alignment on messages with stakeholders will help to support focused writing and ensure that the modeling reports are not out of sync with the rest of the submission
    - Starts with agreement on the analysis plan and a clear statement of purpose/questions
- Follow the recommendations in the FDA Guidances and EMA Guidelines, in addition to best practices, but try to put yourself in the reviewer's shoes (audience perspective)
    - Why? …. A clear and complete statement of your rationale is important
    - Show your work …. include/discuss the things you tried that didn't work or that increase your confidence in what you did, with enough detail/support to believe you
    - Help me help you (address the relevant and required questions/issues)
    - Higher quality of report and peripherals leads to an easier review
- Provide organized and well-documented datasets, analysis scripts, and define files for all major modeling steps and analyses

*Dykstra K et al. *J Pharmacokinet Pharmacodyn.* (2015) 42:301-314.

Reporting: Tell the Story

Suggestions from FDA*

Do's:

- Include a concise top level summary of findings and justify dose adjustments based on totality of information and data;
- Clearly indicate which analyses supported decision making;
- Include comparisons between observed and predicted results;
- Stratify VPC plots by relevant covariates;
- Provide a flow chart indicating how data and scripts connect;
- Ensure that ID numbers in modeling datasets can be linked to IDs in clinical reports/data

Don'ts:

- Forget to discuss the application of the modeling results;
- Describe covariate effects based on significance only;
- Describe covariate effects in relation to PK (CL, V) or PD parms only, neglecting their effects on exposure or response;
- Include only diagnostic plots of the entire dataset;
- Provide electronic data files with no ability to follow how datasets and scripts fit together

*Florian J. Electronic Submission of Pharmacometrics Data Sets and Reports for Regulatory Submissions, presented August 3, 2017; Joint Statistical Meetings. https://higherlogicdownload.s3.amazonaws.com/AMSTAT/55557379-e8d6-4476-bccf-8ef2ef3dc4ef/UploadedImages/JSM_Jeff_FDA_2017_v3.pdf

Modeling Report Contents

FDA Population PK Guidance (2019), EMA Reporting Guideline (2008)

- **Executive Summary**
  (purpose, key findings, recommendations)
- **Synopsis**
  (*plain language summary* of objectives, data, methods, conclusions; should address sufficiency of data to evaluate different drug exposures in relevant subpopulations; present results in terms of effect on exposures; include graphics to support differences in exposure in subpopulations)
- **Introduction**
  (Background, Objectives, PK)
- **Data**
  (studies included/excluded and why and designs, disposition, LOQ, demographics, covariates [incl methods if derived] and their correlations)
- **Methods**
  (criteria for model building and selection, structural, covariate and variability model descriptions, outlier handling, missing data, equations, estimation method, assumptions [and the impact of these], model evaluation methods, simulations planned, software, deviations from planned analyses)

Population PK Guidance for Industry. US FDA, July 2019.
Guideline on Reporting the Results of Population Pharmacokinetic Analyses. EMA CHMP, June 2007.

Modeling Report Contents (continued)

FDA Population PK Guidance (2019), EMA Reporting Guideline (2008)

- **Results**
  (base and final models & parameter estimates, model building steps, qualification assessments, model applications, relevance of covariate effects, tables, figures (incl raw data), and listings: run log, comparison of base to final models, diagnostic/goodness-of-fit plots, incl those stratified by covariates)
- **Discussion**
  (interpretation of results [adequacy or limitations of data, rationale for approach, verification of assumptions, assessment of uncertainty, consistency with stand-alone
- **Discussion (cont'd)**
  clinical pharmacology study results], clinical relevance of findings, alternative dosing regimens; drug development and regulatory decisions based on these results
- **Conclusions**
  (*plain language* summary of major findings)
- **Appendices**
  (run record, methods/codes for key figures)
- **Electronic files**
  (provide the ability to reproduce but also tie together with individual study reports and datasets [may need ID number coding])

Population PK Guidance for Industry. US FDA, July 2019.
Guideline on Reporting the Results of Population Pharmacokinetic Analyses. EMA CHMP, June 2007.

Modeling Report Contents

FDA PBPK Analyses – Format and Content Guidance

- **Executive Summary**
  (objectives/rationale, model development and simulations overview, key conclusions)
- **Intro**
  (synopsis of physicochemical, PK and PD properties; E-R relationships; PBPK regulatory history; cross-reference other PBPK reports)
- **Materials and Methods**
  (overview of modeling strategy, modeling parameters, simulation design, electronic files, software and version)
- **Results**
  (model verification & modification, model application)
- **Discussion**
  (interpretation of results: how modeling addresses questions; limitations of approach and impact on results and interpretation)
- **Appendices**
  (tables, figures)

Physiologically Based Pharmacokinetic Analyses – Format and Content Guidance for Industry. US FDA, Aug 2018.

Modeling Report Contents

EMA Reporting of PBPK M&S

- **Objective and regulatory purpose**
- **Background information**
  (background to put PBPK in context in clinical development; physicochemical properties, PK and PD properties, mass balance diagram; summary of clinical studies; E-R relationships; justification of target plasma exposure)
- **Qualification**
  (qualification of the platform; name and version of commercial software)
- **Model parameters**
  (assumptions: data to support and impact on model and outcome, testing of assumptions; system-dependent parameters and modifications of defaults; drug parameters and drug model
- **Model parameters (cont'd)**
  structure incl sources of values, justification)
- **Model development**
- **Simulation of intended scenario**
  (study design, target population)
- **System and drug model evaluation**
  (sensitivity analysis, predictive performance)
- **Results**
  (model evaluation and simulation results, plus sensitivity analyses, tables of descriptive stats plus figures, model files)
- **Discussion**
  (contribution to the regulatory decision making, how uncertainty may influence decisions)

Guideline on the reporting of physiologically based (PBPK) pharmacokinetic modelling and simulation. EMA CHMP, Dec 2018.

Quality Considerations

Quality Assurance Activities: processes that ensure data integrity, reproducibility

- includes training of personnel, software validation

Quality Control/Verification activities:

- *risk-based approach* can be applied to data, models, analysis plans, reports
- Scientific Review: inside or outside the organization (independent expert review)
    - Forensic Pharmacometrics

Model Credibility Assessment - Harmonized approach to model assessment based on V&V40 (a verification and validation standard developed by the Am Soc of Mech Eng) – first applied to PBPK models; also applied in EMA

Bonate PL et al. *AAPSJ* Dec 2012; 14(4): 749-58.
Grasela TH et al. Forensic Pharmacometrics: Part 1 – Data Assembly; ACoP Poster, Oct 2009.
Grasela TH et al. Forensic Pharmacometrics: Part 2 – Deliverables for Regulatory Submission; PAGE Poster, June 2010.
Viveconti M et al. *Methods* 185 (2021) 120-7.

Role of Canonical Documents

- Canonical analysis plans and modeling reports can be created for to capture not only the structure and sections of a document, but also the intended content in each section
  - Assist authors and facilitate compliance with regulatory recommendations
  - Enforce organizational standards to improve efficiency
  - Alleviate errors of omission and commission
  - Facilitate review practices
  - Improve quality of documents
  - Can be incorporated into reproducible reporting systems

Pharmacometrics and Systems Pharmacology 2030

- The continued evolution of systems approaches will lead to the routine use of quantitative models to prospectively predict clinical outcomes before initiating trials
- Expect further integration of systems models, results of clinical assessments, and postmarketing data to turn data into knowledge but also as a platform for R&D, with less reliance on clinical trial data
- More collaborations with adjacent fields: incorporation of pharmacometrics in health economic decisions, cost-effectiveness, and leveraging of RWD
- Labels will include more precision dosing recommendations and software may enable use of models for individualized dosing in clinical practice
- Library of accessible QSP models from which pharmacometricians could extract a reduced model
- Further integration of QSP, PBPK and pharmacometrics will lead to influence on reimbursement, dose decisions at the bedside and improved global health

Mentré F et al. *CPT Pharmacometrics Syst Pharmacol.* Jan 2020, 107(1): 76-8.

Major Take-aways

- Full potential of MIDD can be realized by: increasing multidisciplinary stakeholder acceptance, further developing standards and best practices which will increase the efficiency of regulatory review, and increasing capacity and expertise

Madabushi R, Wang Y, Zineh I. A Holistic and Integrative Approach for Advancing Model-Informed Drug Development; *CPT Pharmacometrics Syst Pharmacol.* (2019) 8, 9-11.

- MIDD approaches can be implemented effectively, optimizing the likelihood of regulatory success by considering ….
  - Clear statement of questions to be addressed
  - Careful selection of optimal approach given the data, timelines, other considerations
  - Setting up an ecosystem to support use of model-informed methods
  - Paying attention to the details in execution
  - Keeping in mind the audience in reporting
  - Keeping communication lines open, internally and with HA's

Simulations Plus' Cognigen Division History & Demographics

- Founded in 1992:
  Ted Grasela, Cindy Walawander and Jill Fiedler-Kelly
- Early staff demographics (n=10): 70% female
- Today, Simulations Plus' Cognigen division is 60% female:
  - 57% of scientific consultants
  - 45% of programming staff
  - 100% of project managers
- All of us have multiple roles professionally and personally and have been impacted by COVID-19

Happy International Day for Women and Girls in Science!

Female role models?

- Marie Curie, Gertrude Elion, Jennifer Doudna and Emmanuelle Charpentier
- Growing list of female execs in pharma and biotech
- Female healthcare/essential workers, teachers, counselors
- Numerous women who have been instrumental in the growth & evolution of pharmacometrics and quantitative pharmacology

Happy International Day for Women and Girls in Science!

Female role models?

- Women of SLP: scientists, programmers, developers of
  Simulations Plus, Cognigen, DILIsym Services, & Lixoft

Farah AlQaraghuli
Heather Barcomb
Anetta Claussen
Inger Darling
Mitali Gaurav
Darcy Hitchcock
Amanda Hong
Hannah Huang
Rebecca Humphrey
Aksana Jones
Sindhuri Kondragunta
Elizabeth Ludwig
Kelly Maxwell
Denise Morris
Julie Passarell
Luann Phillips
Jessica Roberts
Susanne Sardella
Christina Battista
Pallavi Bhargava
Lara Clemens
Diane Longo
Lisl Shoda
Kyunghee Yang
Revathi Chapa
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Thank you