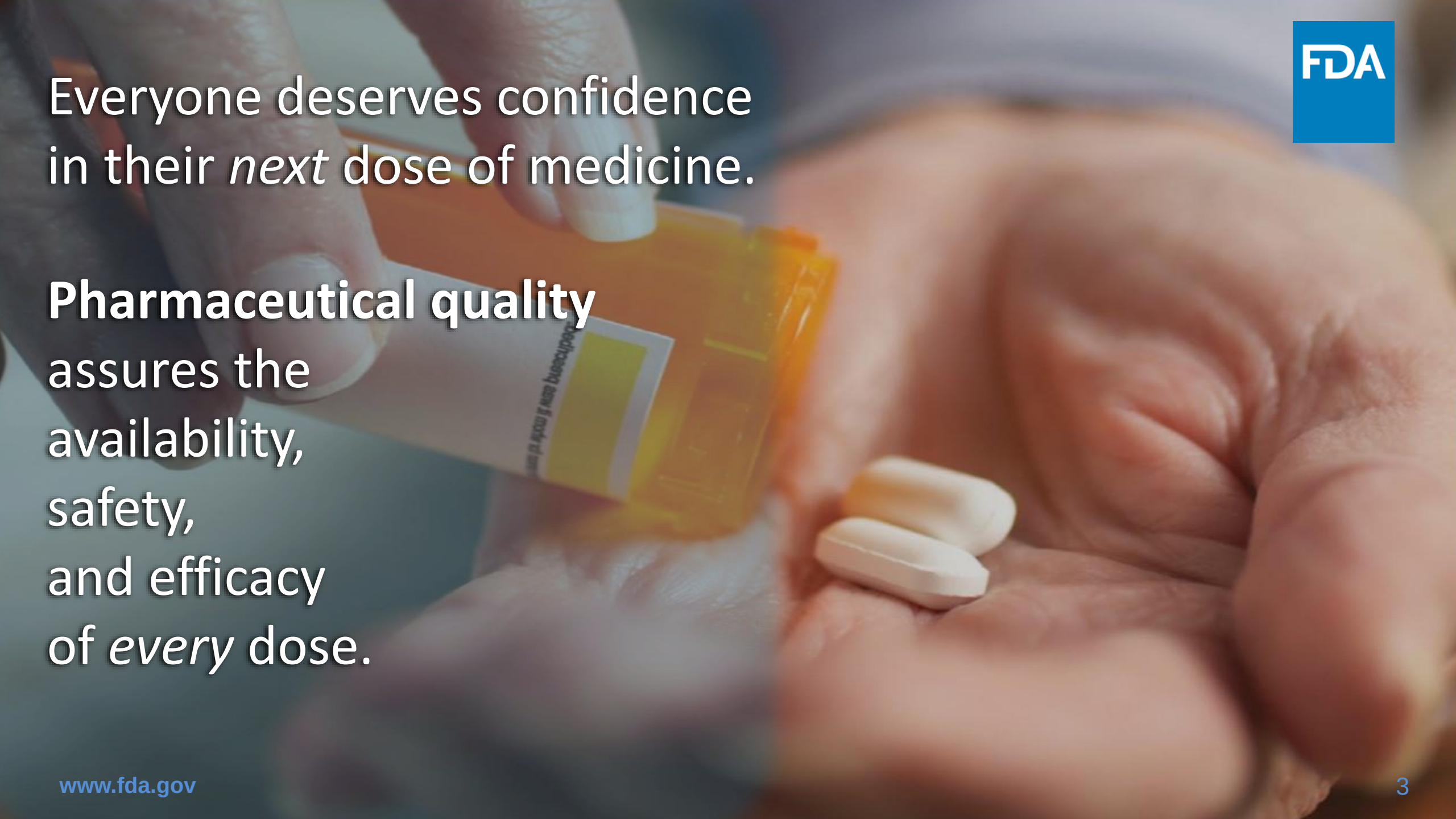
Hot Topic F: Considerations for Model Development—data inputs, disposition, and absorption parameters, dealing with sparse data

August 30, 2023

Rebecca Moody, Ph.D.
Division of Biopharmaceutics
FDA/CDER/ONDP/OPQ

DISCLAIMER

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.



Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Building PBBM with no IV data: A regulatory perspective

1. General comments – overview

Stakeholder no.	General comment (if any)
1	The guideline is mainly focused on DDI and paediatric dosing, but it would be useful to integrate other applications of PBPK modelling as Mechanistic Absorption Modelling. When discussing about qualification it would be helpful to make the difference between drug dependent parameters and physiological/biochemical/structural parameters. The guideline proposes 3 different ways for the qualification: (a) CHMP qualification, (b) qualification in the application and (c) qualification by learned societies. The 1st one concerns the vendors, the 2nd one concerns the sponsor and the 3rd one we do not know. Clarifications would be helpful as the vendors could "easily" qualify the physiological/biochemical/structural parameters whereas the sponsors could focus on drug dependent parameters and modelling. We are concerned by the number of compounds/studies recommended or requested to qualify the PBPK modelling for an intended purposes. In different areas there are only a few number of data sets or published cases available. But combined with a strong scientific rational it can be really valuable to support results of PBPK modelling and simulations. For many years, PBPK modelling is used to define safety thresholds in the environment area on the basis of (fortunately) a few number of case studies and strong scientific rationales. At some point, the draft guideline suggests that IV data is mandatory for the PBPK model building. There are examples of drug development for which IV administration is not needed (or even possible). But it does not mean that a trustable PBPK model cannot be built on the basis of oral data only. The draft guideline suggests use the very last version of the PBPK platform

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/CHMP/59169/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation' (EMA/CHMP/458101/2016)

1. General comments – overview

Stakeholder no.	General comment (if any)
1	The guideline is mainly focused on DDI and paediatric dosing, but it would be useful to integrate other applications of PBPK modelling as Mechanistic Absorption Modelling. When discussing about qualification it would be helpful to make the difference between drug dependent parameters and physiological/biochemical/structural parameters. The guideline proposes 3 different ways for the qualification: (a) CHMP qualification, (b) qualification in the application and (c) qualification by learned societies. The 1st one concerns the vendors, the 2nd one concerns the sponsor and the 3rd one we do not know. Clarifications would be helpful as the vendors could "easily" qualify the physiological/biochemical/structural parameters whereas the sponsors could focus on drug dependent parameters and modelling. We are concerned by the number of compounds/studies recommended or requested to qualify the PBPK modelling for an intended purposes. In different areas there are only a few number of data sets or published cases available. But combined with a strong scientific rational it can be really valuable to support results of PBPK modelling and simulations. For many years, PBPK modelling is used to define safety thresholds in the environment area on the basis of (fortunately) a few number of case studies and strong scientific rationales. At some point, the draft guideline suggests that IV data is mandatory for the PBPK model building. There are examples of drug development for which IV administration is not needed (or even possible). But it does not mean that a trustable PBPK model cannot be built on the basis of oral data only. The draft guideline suggests use the very last version of the PBPK platform

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/CHMP/59169/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation' (EMA/CHMP/458101/2016)

Outcome (if applicable)
added. **IV data is not mandatory but its usefulness is recognised.** Any version of the software, if appropriately qualified, is accepted.

Case Study

Background & Model Objective

- Post-approval, Applicant noted increase in need for dissolution testing at Stage 2 and Stage 3.
- Drug Product is IR Tablet, BCS Class 2 DS (with pH dependent solubility).
- Applicant submitted PBBM to assess the clinical impact of not meeting the dissolution specification and to support widening of the AC.

Model Strategy

DEVELOPMENT
Develop Mechanistic Absorption Model

VALIDATION
Compare predicted vs observed PK for several formulations

APPLICATION
Define Dissolution Safe Space

Compound Specific Parameters
logP, pka, solubility, MW

Formulation Specific Parameters
in vitro dissolution (z factor)

Disposition Model
Derived from human solution PK

3 tablet formulations

non-BE batch included

mean PK profile and virtual population simulation

Predict impact of batches not meeting current dissolution specification and explore edge of failure

PBBM Model:
Development, Validation, Application

- All compound specific parameters were experimentally obtained
- Compartmental model derived from low dose oral solution PK data in healthy subjects
- Z-factor dissolution model

PBBM Model:

Development, Validation, Application

- Ability of model to predict PK parameters of 3 different formulations (one which was non-BE in a relative BA study)
- Ability of model to predict PK parameters at different doses
- Ability of model to predict PK parameters in fed state vs fasting state

PBBM Model:

Development, Validation, Application

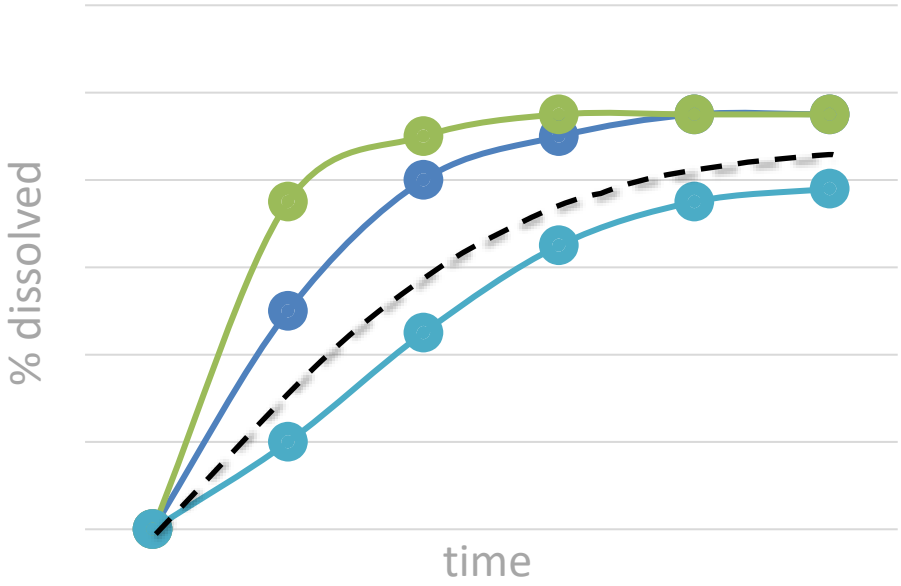
Treatment	Cmax Prediction Error	AUC Prediction Error
A	-12.1%	-12.8%
B	-4.5%	-11.1%
C	1.8%	0.9%

Prediction Error acceptable under Fed Conditions, but greater than 20% PE for Fasting Conditions

PBBM Model:

Development, Validation, Application

- 10 virtual crossover trials



Formulation	Cmax	AUC
Ref vs Ref		
Ref vs Slow		
Ref vs Slowest		

PBBM Summary

- Model was considered acceptable and supported widening of the dissolution acceptance criterion
- Additional considerations in decision making:
  - Discriminating ability of the dissolution method, other drug product controls, Clinical PK data (e.g., Tmax).

Final Thoughts

- IV data is preferred
- If IV data is not available, building disposition model for PBBM with p.o. may be possible if mechanisms impacting gut bioavailability are well understood (e.g., through mass-balance study). Use of other data (e.g., oral solution PK, popPK, SAD, MAD, DDI studies) to build and support disposition model may be acceptable.
- Evaluation will be made on a case-by-case basis.

Thank you!