FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling, PBBM Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives

Day 2 RT: Roundtable discussions case studies 4-6 (10:45-11:45)

Focus areas: Model Validation, PK and data inputs, IV and oral data, preclinical data scaling. Independent clinical data use, non-BE, Interpolation/Extrapolation

Regulator Panel: Rebecca Moody, FDA
Luiza Borges, ANVISA
Mary Malamatari, MHRA
Flora Musuamba Tshinanu, Belgium FAMHP
Shereeni Veerasingham, HC
Shinichi Kijima, PMDA
Paul Seo, FDA

Moderator: Tycho Heimbach, Merck & Co.
Moderator: Claire Mackie, Janssen

CERSI
University of Maryland

August 30th, 2023

FDA U.S. FOOD & DRUG ADMINISTRATION

Roundtable Format

- Time slot: 1 h
- Moderators open the Session and introduce Panel members (5 min)
- Moderators will ask preprepared questions
- Panel members will answer questions (40 min)
- Note: Please treat each question as a new one.
- Note: Panel members are encouraged to asks questions among each other
- Audience members can ask questions (10 min)

Discussion Topics

- Q1. What can sponsors do to overcome non-availability of the IV data to validate a PBBM model (e.g. adding additional independent clinical study arm data, use of oral solution data, etc. ?) RRM, FMT

- Q2. How do the agencies consider model influence and decision consequence for setting model validation criteria? (What is the model being used for -> should we consider all models the same?) PS, LNB, SK, MM

- Q3. Is there a minimum number of datasets recommended for model validation? Considerations for the context of use/model application? Needing to qualify what we consider as model validation… SV

- Q4. What are the agencies thoughts on how essential is a non-BE batch for model validation (or is it case by case basis)? How far do we have to go for a non-BE batch if we have to e.g. go outside our “GMP space” to produce and how relevant would that batch be? SV, MM

- Q5. What can regulators do more to promote/encourage PBBM or MIDD in a global drug development environment? PS, RRM, LNB, SK, FMT

Introduction case study 4 (“EMD compound A“)

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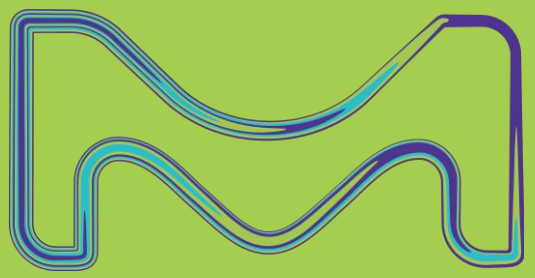
Christian Wagner
Merck Healthcare KGaA, Darmstadt, Germany

August 29 – 31, 2023



EMD SERONO MilliporeSigma EMD ELECTRONICS

Case example 4, “EMD Compound A”
Physchem, formulation, and PK properties

Physchem properties

- Small molecule used for treatment of certain cancer types
- BCS class: 4 (low solubility, low permeability)
- Hydrochloride salt, shows common ion effect in presence of chloride ions

Formulation properties

- Coated immediate release tablet, manufactured via dry granulation
- Tablets contain micronized API to increase exposure and reduce PK variability

PK properties

- Absorption decreases with increasing dose
- To be dosed under fed conditions (500 mg)
- Comparably low clearance
- PK not expected to be impacted by transporters
- “Peculiarity”: Late tmax, independent of formulation and particle size. In lack of any other explanation, lysosomal trapping assumed.

Case example 4, "EMD Compound A"
Summary

Background

- DS particle size specs were defined based on "classical" batch analysis approach (Ph3 batches; DS release data; DP manufacturability)
- Can alternative approaches, such as PBBM, be used to justify DS particle size specs?

Question addressed to regulators

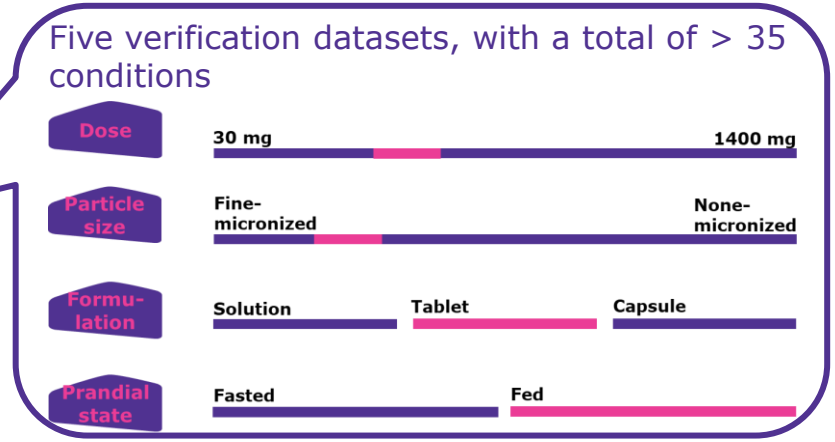
"Does the Agency agree that the acceptance criteria for the drug substance particle size distribution (D10, D50, D90) of "EMD Compound A" can be justified on the basis of the PBBM approach, or does the PBBM only qualify for supportive data?"

Aim of PBBM

1) Establish relationship between DS particle size and absorption/PK of EMD Compound A
2) Use this relationship to set DS particle size specs (D10, D50, D90)

PBBM approach

1) Model building: *In vitro* solubility (common ion effect); Caco2 permeability; PSD from DS batches; Clinical PK: IV and OS
2) Model validation: Various conditions (see Figure on the left)
3) Model application: Establish relationship between PSD and absorption/PK



Results

Establish relationship between particle size and PK

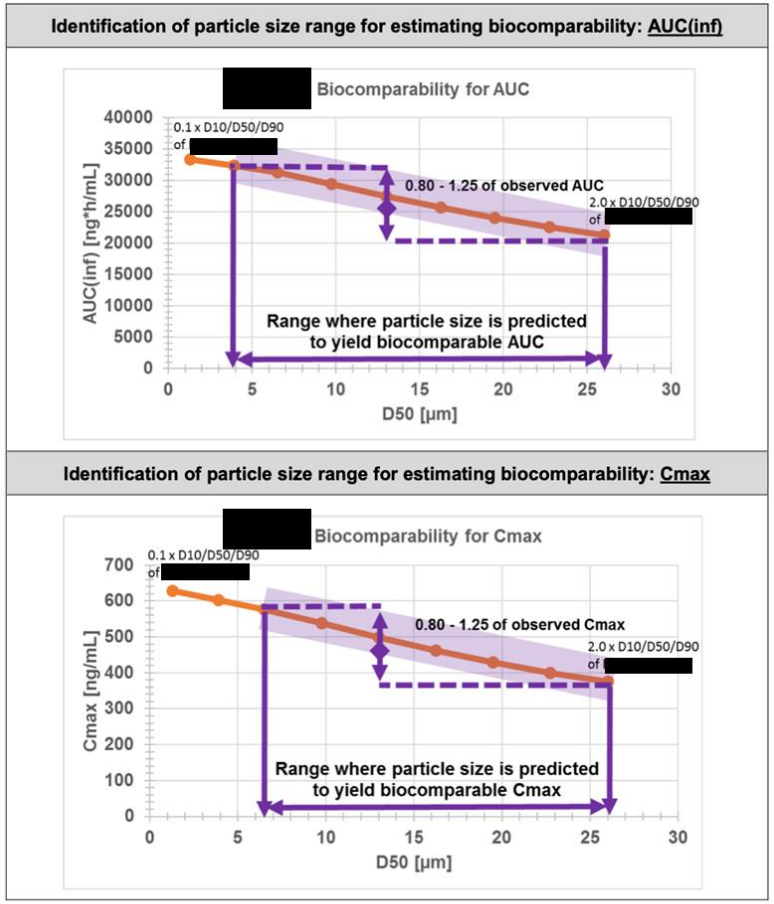


Figure 10 Identification of particle size range for estimating "biocomparability"

Identify PSD

PBBM-based PSD is very similar compared to final spec based on classical batch analysis approach

	Proposed specifications based on PBBM*
D10	1.5-6.0µm
D50	6.5-26µm
D90	16-64µm

*Based on 500mg TF2 formulation data

Case Study 5
Summary Slides

Summary of Case Study 5

Model Objective/Regulatory Question -

Does the agency agree that the out of specification batch based on QC dissolution is bioequivalent to the original product?

Background

Weak base BCS II compound

Immediate Release Oral dosage Form

Issue description

2 batches on ICH stability showed out-of-specification (OOS) results for QC dissolution

All other stability tests conformed to shelf-life specifications

No root cause could be identified for the OOS result

What is the impact on drug exposure of not meeting the QC dissolution specification?

PBBM Model Development, Verification and Application

Develop a PBBM using compound and formulation specific input parameters

Validate the PBBM by comparing predicted versus observed PK data for different formulations

Assess the clinical impact of not meeting the QC dissolution specification for the 2 batches on stability

Compound Specific parameters

MW, logP, Peff, Solubility in aqueous and biorelevant media, 3 compartment model derived from human solution PK

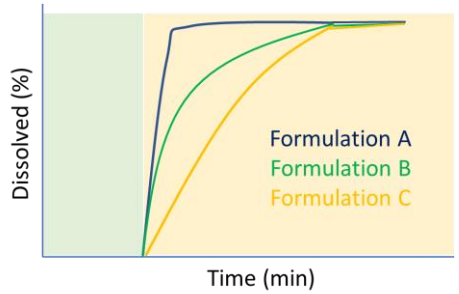
Formulation Specific parameters

Dissolution profile was integrated as z factor derived from physiologically relevant dissolution testing (PBDT)

Availability of clinical data (bioequivalent and non-bioequivalent batches) to validate the model

Formulation	C_{max}	AUC
B versus A	↓ ~10%	↓ ~5%
C versus A	↓ ~25%	↓ ~22%

90% CI within BE criteria; 90% CI outside BE criteria



PBBM Model can differentiate between BE and non-BE batches

Verified PBBM Model was applied to assess bioequivalence of OOS batches compared to reference using PBDT of these batches as input.

PBBM predicted both batches on stability would be bioequivalent to a reference batch for both Cmax and AUC

Widening of QC dissolution specification accepted by multiple health authorities (unclear on the contribution of the model)

Case Study 6
Summary Slides

Summary of Case Study 5

Model Objective/Regulatory Question -

Does the agency agree that the X% of polymorphic impurity is allowed in the drug product in light of clinically relevant specifications?

Background

BCS II compound

Neutral species in physiological pH range

Immediate Release Oral dosage Form

Issue description

Model was developed to justify that presence of X% of polymorphic impurity in the drug product will not have any impact on the systemic exposure/clinical performance of the drug.

PBBM Model Development, Verification and Application

Develop a PBBM using compound and formulation specific input parameters

Compound Specific parameters
MW, logP, Peff, Solubility in aqueous and biorelevant media, Distribution and Clearance parameters were derived by population PK model

Formulation Specific parameters
Dissolution profile was integrated as z factor derived from physiologically relevant dissolution testing (PBDT)
Novel workflow developed to assess impact of polymorphic impurity on the PK

Validate the PBBM by comparing predicted versus observed PK data for different formulations

Model was validated against the clinical data available for other critical quality attributes

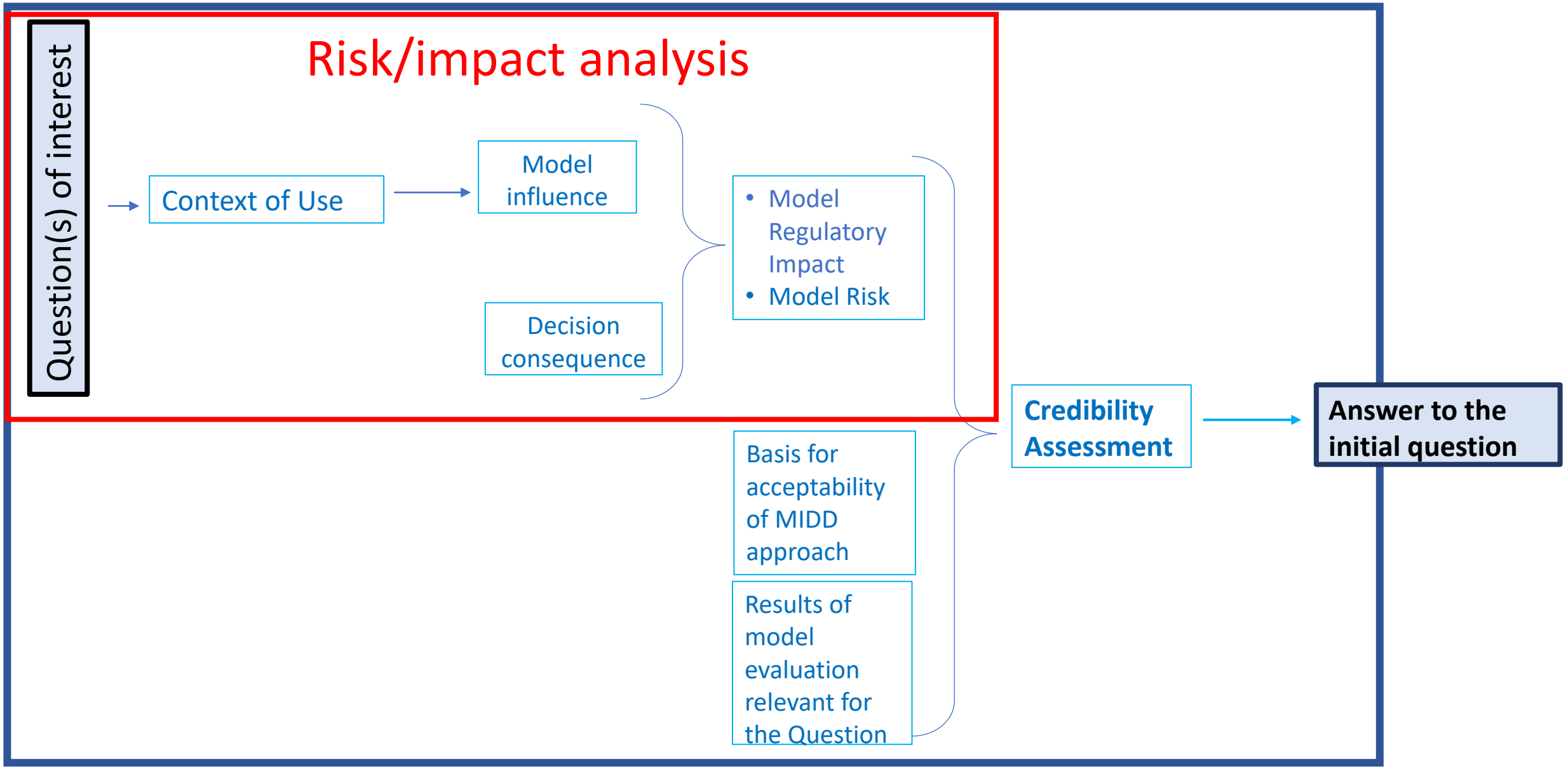
PBBM Model can predict the *in vivo* relevance of changes in formulation and process parameters

Assess the clinical impact of polymorphic inpurity

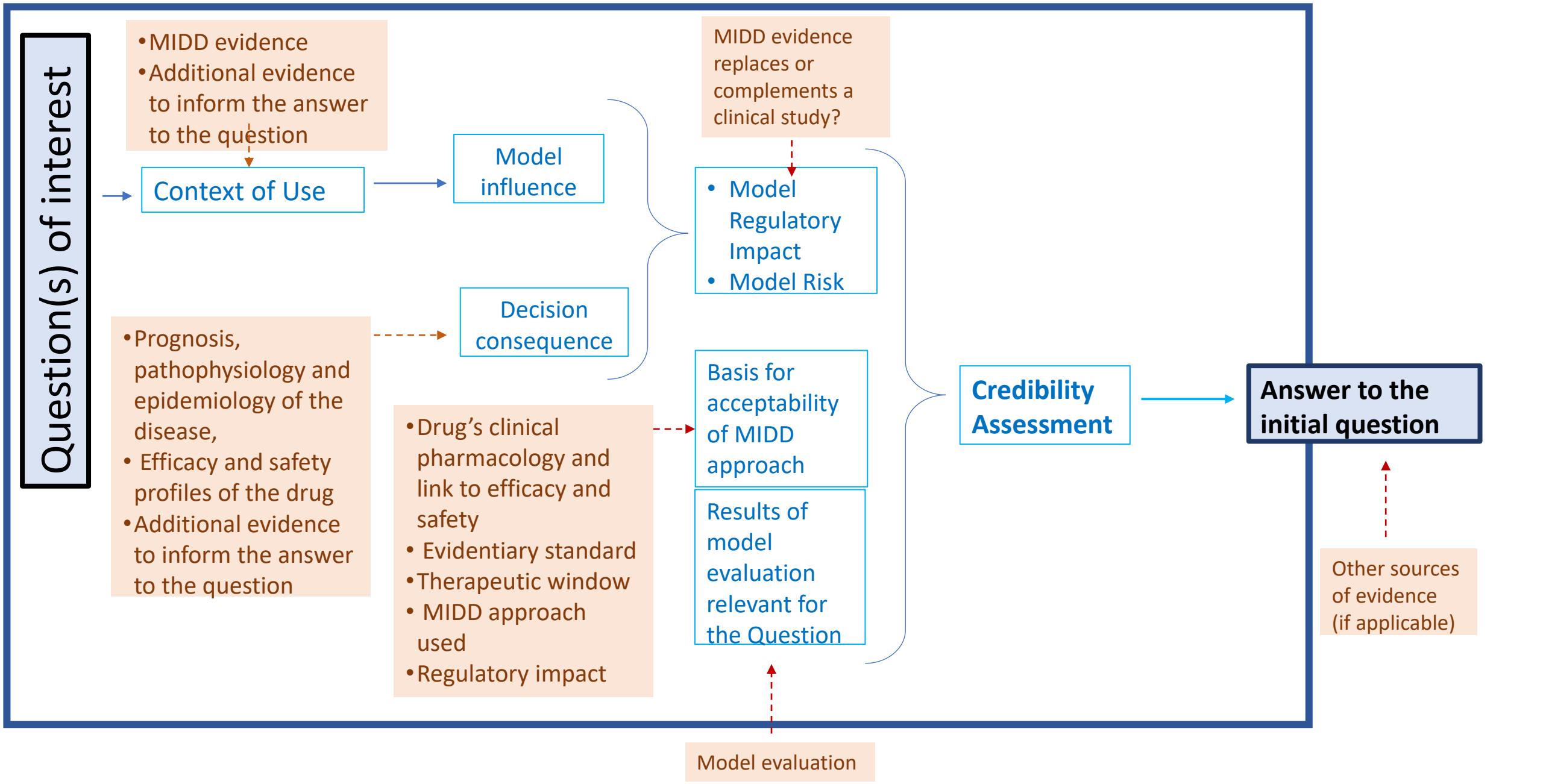
Verified PBBM Model was applied to assess the impact of polymorphic impurity in the drug product on *in vivo* exposure.

Majority of health authorities accepted clinically relevant specification (X% polymorphic impurity) compared to acceptance criteria based on the Limit of Detection/Limit of Quantification of analytical techniques

Credibility Assessment framework



Credibility assessment framework



Credibility assessment framework