FDA expectations in building a safe space to gain regulatory flexibility based on Physiologically Based Biopharmaceutics Modeling (PBBM)

REdI and M-CERSI Workshop

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Outline

• Role of Biopharmaceutics
• Safe space
  – Definition and benefits of safe space
  – 3 approaches to build safe space
    • IVIVR (bracketing approach) and conventional IVIVC
    • PBBM based IVIVR/IVIVC
    • Exposure-response analysis
  – Advantages of PBBM over conventional approach
  – Common regulatory applications of PBBM
• Case studies based on PBBM
• Summary/Take Home Message
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.

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Patients expect safe and effective medicine with every dose they take.
Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects.
Role of Biopharmaceutics

Patient-centric drug product quality

In vitro dissolution
Drug product quality (Critical material attributes/critical process parameters)

Biopharmaceutics
Clinically relevant drug product specifications

In vivo drug performance
Safety and efficacy
Systemic exposure
Safe space

• Definition: **Boundaries defined by in vitro specifications** (dissolution or other relevant drug product quality attributes), within which drug product variants are anticipated to be **bioequivalent** to one another.

• Benefits:
  – Assuring consistent performance throughout drug product life cycle via product specification setting
  – Enabling regulatory flexibility
  – Waiving/reducing the number of clinical studies needed in support of major manufacturing changes
  – Providing an opportunity for taking a major step in accelerating drug product development/lowering the cost of drug development

Approaches to build safe space

Safe space (Bioequivalence space)

- IVIVR (bracketing approach)
- Conventional IVIVC
- Exposure-response analysis

PBBM based IVIVR/IVIVC

IVIVR: in vitro in vivo relationship; IVIVC: in vitro in vivo correlation; BE: bioequivalence
Advantages of PBBM over conventional approach

• Assisting the development of a biopredictive dissolution method

• Leveraging the scientific community’s knowledge and experience through pooling physicochemical data, in vitro characterization, preclinical and clinical data
Common regulatory applications of PBBM in support of drug product quality

Dissolution
- Bio-predictive ability of dissolution method
- Clinically relevant dissolution AC/wider AC

Clinically relevant specifications of CMAs and CPPs
- CMAs (e.g., particle size, polymorphic form)
- CPPs (e.g., milling, compression force/hardness process evaluation)

Quality related Bio-waiver
- Waiver request based on physiologically based IVIVC/IVIVR

Formulation impacts
- Formulation-related food effect
- API form change or formulation change on PPI interactions
- Prediction of product performance by looking at GI local drug concentration and regional absorption

PBBM regulatory submissions in the past decade

12
Case studies based on PBBM: FDA’s experience

• Case study 1:
  – Model objective: to build safe space
  – PBBM-based IVIVR
  – Virtual BE

• Case study 2:
  – Model objective: to build safe space
  – PBBM-based IVIVR
  – Virtual BE
Case study 1

- Objective: To build safe space for a cardiovascular drug in NDA submission
- Immediate release tablet
- 3 strengths: compositionally proportional
- BCS class 4
Data provided in this case study

- Physicochemical properties of drug X
- IV PK data for disposition parameters
- Metabolic pathways and rate
- In vitro dissolution data inputs
- Physiology inputs
- Oral PK data (BE batch & non-BE batch)

**Model development**
- Met pre-established validation criteria of all oral PK data (% PE≤10%)
- Rejection of non-BE batch data

**Model validation**
- Building a safe space via virtual BE trial, to support dissolution acceptance criteria
- Regulatory decision: dissolution acceptance criteria for each strength

**Model assessment**
- Predictive ability of the model,
- Non-BE batch rejected by dissolution testing and PBBM model,
- Discriminating and biopredictive abilities demonstrated for the dissolution method
Dissolution data and Applicant’s proposed acceptance criterion

Proposed acceptance criterion: Q=75% in 30 mins
Safe space identified by virtual BE

Test: Virtual Batch of High Strength
Reference: C2 Pivotal BE Batch of High Strength

<table>
<thead>
<tr>
<th>Result</th>
<th>Cmax</th>
<th>AUC</th>
<th>AUCl</th>
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<tbody>
<tr>
<td>MeanT</td>
<td>0.190</td>
<td>1.516</td>
<td>1.499</td>
</tr>
<tr>
<td>MeanR</td>
<td>0.209</td>
<td>1.639</td>
<td>1.622</td>
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<tr>
<td>GeomMeanT</td>
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<tr>
<td>GeomMeanR</td>
<td>0.199</td>
<td>1.566</td>
<td>1.548</td>
</tr>
</tbody>
</table>

90% CI (MeanT-MeanR)
85.416 --> 97.187 86.793 --> 98.124 86.71 --> 98.146

90% CI (GeomMeanT/GeomMeanR)*100
91.63 92.97 92.95

Regulatory flexibility:
Q=75% at 30 minutes
Safe space identified by virtual BE

Not bioequivalent

Q=80% at 30 minutes, while Q=75% at 30 minutes not BE
Case study 2

- Objective: to build safe space for an oncology drug in NDA submission
- Immediate release capsule
- BCS class 4
- Wide particle size range used in pivotal clinical trials
Data provided in this case study

- Physicochemical properties of drug Y
- IV PK data for disposition parameters
- Metabolic pathways and rate
- Physiology inputs
- Oral PK data highest strength
- PSD inputs

**MODEL DEVELOPMENT**

Met pre-established validation criteria for all oral PK data at different doses, or of different PSD

**MODEL VALIDATION**

Model assessment:
- Predictive ability of the model,
- Discriminating ability demonstrated for the dissolution method

**MODEL APPLICATION**

Build a safe space via virtual BE trial, to support the proposed API PSD

Regulatory decision: API PSD D10, D50, D90
Safe space identified by virtual BE

virtual BE based on a cross-over study design between (T): upper bounds of particle size within the specification vs. (R): lower bounds

Regulatory flexibility: Setting wide DP specification (drug substance particle size)
Presence of safe space overrides the value of dissolution similarity
Safe space and design space

Safe Space
All batches within safe space are BE

Design space
(Multidimensional combination and interaction of CMAs & CPPs to assure quality)

Knowledge space
(Manufacturing knowledge obtained during DP development)
Summary of case studies

• **Virtual BE trials** are to generate predictions of in vivo product performance, to perform BE assessments between any batches within the safe space and to inform regulatory decisions.

• **Non-BE batch data** is preferred to demonstrate model robustness and to propose a safe space boundary beyond that is supported via BA/BE data and within model validated range.

• The presence of **safe space supersedes the value of dissolution similarity.**

• The use of PBBM-based IVIVR/IVIVC contributes to:
  – Building of a safe space based on expected in vivo performance (**BE criteria used**) with the possibility of expanding regulatory flexibility for pre- and post-approval changes,
  – Establishment of *in vitro and in vivo* link,
  – Potential reduction in the number of required in vivo BA/BE studies (e.g., due to formulation or manufacturing process changes) to support changes during drug development or post-approval changes.
Common deficiencies observed in PBBM based IVIVR/IVIVC submissions

- **Not mechanistically sound model:**
  - Lack of parameter plausibility,
  - Assumption of 100% bioavailability, while incomplete absorption was indicated by in vivo study,
  - No justification for input parameter values,
  - Insufficient or irrelevant verification

- **Inappropriate formulations:**
  - Selection of the formulations not based on model purpose,
  - Release mechanism/rate controlling excipient type changed in the formulations to achieve different release rate

- **Inadequate in vitro dissolution:**
  - Lack of discriminating ability,
  - Lack of bio-predictive ability

- **Insufficient model structure information:**
  - Mean in vivo data with large variability used to build the IVIVC model,
  - Different scaling factors used in IVIVC for different formulations,
  - No mechanistic framework accounting for impact of quality attributes on absorption

- **Questionable simulation results:**
  - Parameter variability not representative of real scenario
Take home message (1): Recommended PBBM workflow to build safe space

- **Deconvolution of PK data** (≥three release rates) to obtain in vivo dissolution
- **Development of correlation between in vivo and in vitro dissolution**
- **Predictability/validation of the IVIVC**
- **Setting safe space (based on model predictions)**

**Base model development using IV and oral solution data**

- **Model modification/refinement using p.o. clinical data**
- **Model verification/validation using independent clinical data**

**Rank order (≥two release rates) supported by in vivo data**

- **Proposed safe space within model validated range**
- **Proposed boundary beyond that is supported via BA/BE or model validated range**

**Virtual bioequivalence (BE)**

- **Setting safe space (based on virtual BE trial data)**
Take home message (2): Expectations on modeling submissions to build safe space

- A modeling summary report elaborating modeling strategy
- Modeling flow covering model development, optimization and verification/validation
- Rationale and supportive information on model parameters
- Hypothesis and algorism
- Formulations and in vitro dissolution:
  - Number of formulations demonstrating different release rate and rank order
  - Release mechanism
  - Discriminating ability of the in vitro dissolution method towards CMAs and CPPs
- Clinical study:
  - Study design and subject numbers
  - In vivo concentration profile data
  - Non-BE data preferred
- Virtual BE trials:
  - Description of intra- and intersubject variability
  - Justification of the number of subjects used in virtual BE trials
- IVIVC:
  - Description of conventional or mechanistic-based
  - Description of two stages or one stage
  - Reliability of UIR estimation
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