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Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls
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Donna Williams, an autistic artist, author and renowned autism advocate, was diagnosed with breast cancer in 2011.
Outline

- Setting the scene

- Physiology Based Dissolution Testing
  - What is?
  - PBDT vs QC?
  - Bridging?

- Case study I
  - Clinically Relevant Specifications in late development

- Case study II
  - Clinically Relevant Specifications during continuous improvement

- Closing remarks
Biopharmaceutics in drug product development

**Discovery**
- New molecular entities
- Drug substance characterization

**Early development**
- Drug product characterization
- Formulation & process selection and optimization

**Late development**
- Formulation and process upscaling
- Clinically relevant specifications & controls

**Continuous improvement**

Formulation Lock and DP Criticality Analysis Define CQAs, CMAs, CPPs

**in vivo data**
- QC dissolution method
- Physiology Based Dissolution Test
Physiology Based Dissolution Test

**Gastric Phase**
- 250 mL FaSGF (pH 1.6)
- 30 min

**Intestinal Phase**
- 75 rpm
- 37°C
- + 250 mL cFaSSIFv1
- 500 mL FaSSIF (pH 6.5)
- 120 min

https://doi.org/10.1021/acs.molpharmaceut.7b00198
### PBDT method
- **Fixed conditions** (simulating the human physiology) – No MD needed
- No RA guidelines (acceptance?)
- Reproducibility & validation?
- Complex media
- No sink conditions
- Natural source surfactants as in bile
- Used for formulation screening and selection

### QC method
- Conditions are tailor-made for each DP
- According to the **RA guidelines**
- Discriminating in order to reject batches that are “different”
- **Reproducible, Robust, Validated**
- Sink conditions
- **Simple set-up & media**
- Used for stability and release testing
Bridging?

QC results

2-phase FaSSIF

2-phase FeSSIF
Focus on BCS II / IV compounds

Common strategies to address low drug solubility

https://doi.org/10.1124/pr.112.005660
QC dissolution test for ASDs

• For BCS class 2/4 drugs, HAs expect a discriminative dissolution method (not having fast dissolution profiles)

• However
  • Amorphous DS dissolves very fast (by design)
  • Surfactant is added to reach sink conditions to reach 100% dissolution and avoid precipitation
  • The surfactant (SLS, Tween20, Brij, CTAB, ...) is stronger than biosalts

• Selected to obtain the most discriminating method for formulation variations in CQAs
  • Mostly over-discriminating towards in vivo
  • Try to correlate with in vivo data
PBDT for ASDs

• **Reflective for its performance in vivo**
  - Spring-parachute can be characterized
  - Mimics human GI fluids
  - QC dissolution method is more limited

• **PBDT can be used as input for PBPK modelling**
  - PBDT: dissolution rate (formulation)
  - PBDT: ADME (API)
  - PBPK can be used to model the PBDT profiles that lead to a similar in vivo exposure (clinically relevant specifications)
Case study 1

BCS class II compound
Neutral species in physiological pH range
Oral solid development
Crystalline drug substance has low µg/ml solubility in biorelevant media

Biopharmaceutics assessment
- Facilitate choice of enabling platform
- Guide formulation concept selection and development
- Establish clinically relevant specifications
CRC strategy workflow

**Step 1a:** CA analysis
- API properties
- Formulation
- Process

**Step 1b:** Build PBPK Model

**Step 2:** Develop CQA Dissolution Test(s) using tablets with highest risk CQA identified in step 1

**Step 3:** Understand significance *in silico* and *in vivo*, further validate PBPK model with clinical data

**Step 4:** Identify CQA or safe space limit

**Step 5:** Define design space/spec to ensure CQAs are always met

**Step 6:** If applicable develop PBPK model further to evaluate additional CQAs

Limited in vivo testing e.g. crystallization
QC method development

Method A

Method B

Method C

Clinical relevance
PBDT profiles

Formulation Lock and DP Criticality Analysis Define CQAs, CMAs, CPPs
In vivo data – Simulate by PBBM

PBDT profiles as input for PBBM

Can we simulate the in vivo results?
No in vivo data – Predict by PBBM

Mean simulations

Population simulations
Include variability and uncertainty
Cross-over design
Multiple trials
Include intra-subject variability
Statistics

Safe space approach
QC method selection

Method A

Method C

Method B

Stack ranking
discriminative properties
Similar to PBDT
CRC workflow in practice

Critical Quality Attribute 1

Human BA Trial

Polymorphic purity

Validated PBPK Model

In vivo bioequivalent with target formulation

In silico bioequivalent with target formulation

In silico non-bioequivalent with target formulation
CRC workflow in practice

Proposed Clinically Relevant Specification

Time point and Q value where
non-BE batches are below Q-value
(most) BE-batches are above Q-value

In silico non-BE
In silico BE
In vivo BE
In silico non-BE

Scope of clinically relevant specifications not limited to QC dissolution
clinically relevant acceptance criteria for polymorphic purity
(opposed to acceptance criteria based on LOD/LOQ of analytical techniques)
Case study 2

BCS class IV compound
pKa = 2.85 (base) and 5.24 (acid)
LogD (pH 4) > 5
Formulated as amorphous sodium salt
  - Solubility crystalline API in FeSSIF = 0.001 mg/ml
  - Solubility amorphous salt in FeSSIF = 0.140 mg/ml

Biopharmaceutics assessment
- Low QC dissolution results during site stability testing
- Determine main drivers in absorption process
- Clinical relevance of the current spec / support spec broadening?

https://doi.org/10.1208/s12248-019-0292-3
Complex PK

Non-linear pharmacokinetics
- Liver metabolism
- Gut metabolism
- Hepatic transporters
- Active intestinal efflux transporters

Supportive information
- IV dosing
- Mass balance
- Metabolic profiling
- Different dose levels
- Interaction studies

PBPK model
PK elucidation and DDI evaluation
Include dissolution based mechanistic absorption model

https://doi.org/10.1208/s12248-019-0292-3
https://doi.org/10.1002/cpt.206
Oral dose predictions

Plasma concentration-time profiles

50 mg

1000

100

10

1

0 20 40 60 80

Time (h)

Concentration (ng/ml)

150 mg

10000

1000

100

10

0 20 40 60 80

Time (h)

Concentration (ng/ml)

In silico PK

in vivo PK

Absorption and dissolution curves

Amount of drug dissolved in function of time versus amount absorbed in function of time

Relative importance of permeation rate

Amount dissolved

Amount absorbed

Amount entering portal vein

Amount entering systemic circulation

https://doi.org/10.1208/s12248-019-0292-3
Validation

Can the model differentiate between a bioequivalent and non-bioequivalent formulation?

150mg biorelevant dissolution profiles

- crystalline drug substance
- amorphous sodium salt

Concentration (ng/ml) vs. Time (h)
Parameter sensitivity analysis

PSA on the dissolution rate of biorelevant dissolution profiles from:

- Reference formulations (---)
- Formulations demonstrating slower QC dissolution profiles (---)

Large toleration window for dissolution rate towards changes in bioavailability
All observed profiles well within the acceptable range
Overdiscriminative QC dissolution method

Supportive information for QC dissolution spec change
Closing remarks

• There is added value for biorelevant dissolution testing besides traditional QC testing.

• However!
  • Time consuming
  • Resource intensive
  • When to start?

• Two cases studies for bridging PBDT and QC using PBBM
  • QC method selection and clinically relevant specifications
  • CRC during continuous improvement
Acknowledgements
Donna Williams, an autistic artist, author and renowned autism advocate, was diagnosed with breast cancer in 2011.

More info?
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