Establishing clinically relevant specifications in pre-approval and post-approval environment

A case study

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Dorethey Gorham, *Day of the Armada*

Dorethey is a joyful, self-taught artist living with arthritis, general anxiety syndrome, and diabetes.

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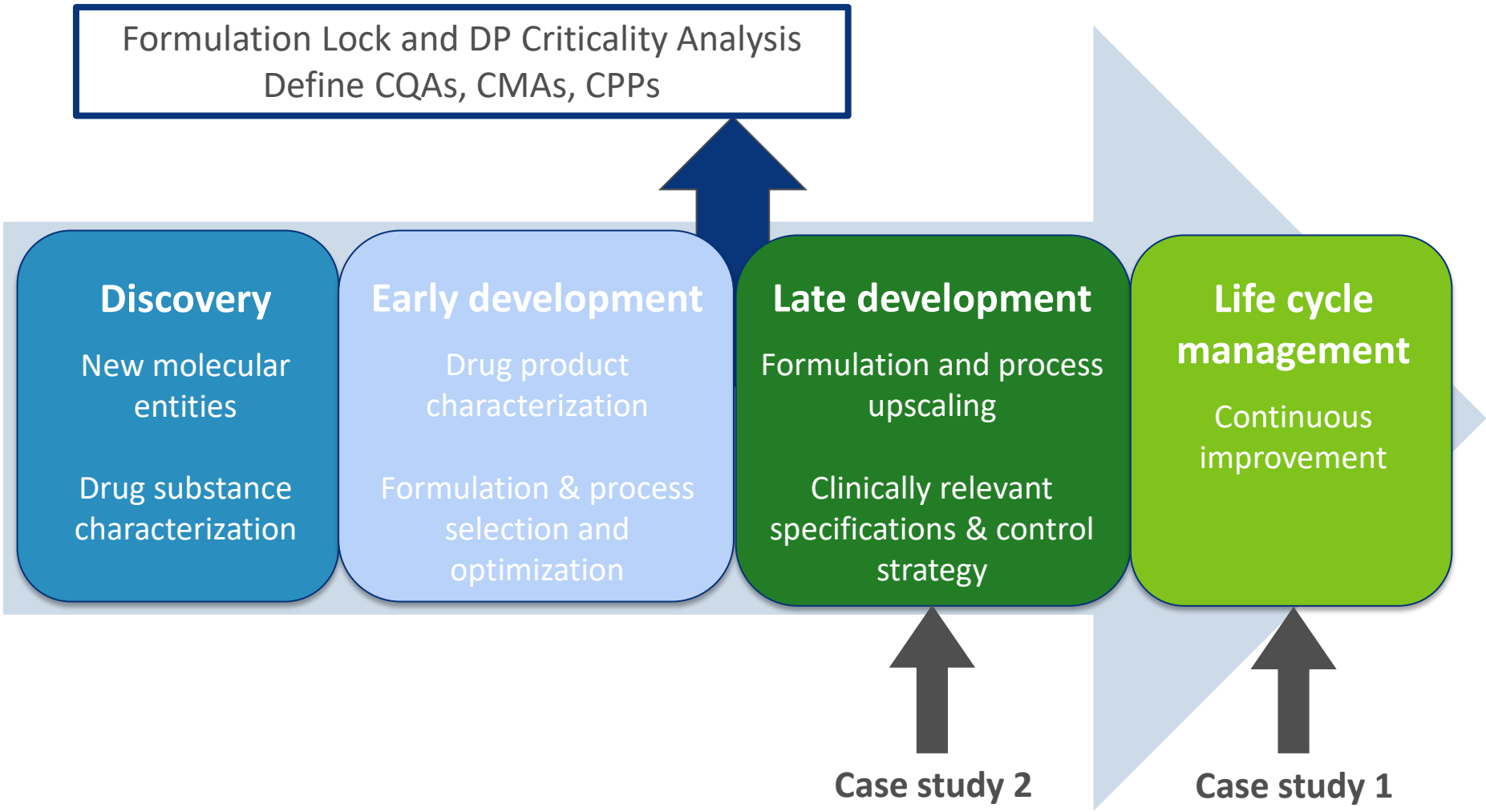
Outline

- **Introduction**
  - Biopharmaceutics in drug product development
  - Clinically relevant specifications
  - Case study background

- **Case studies 1 & 2**
  - Build-up
  - Validation
  - Predictions
  - Confirmation

Biopharmaceutics in drug product development



Clinically relevant specifications

Step 1a: CA analysis
API properties
Formulation
Process

Step 1b: Biopharmaceutics
in vitro - in silico - in vivo

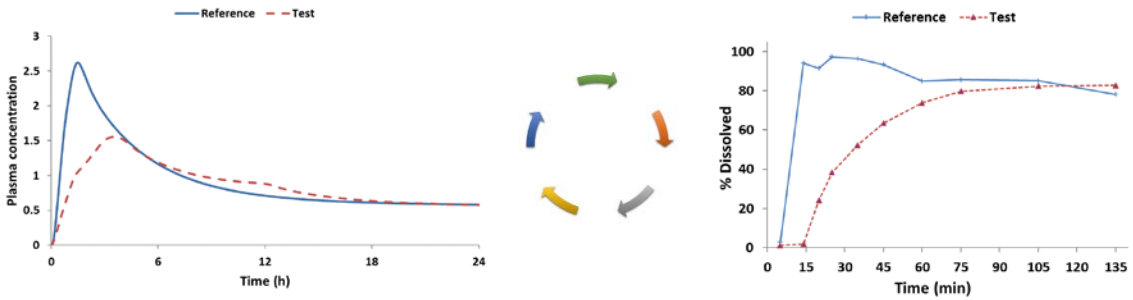
Step 2
Develop CQA analytical methods for drug substance / drug product with highest risk CQA identified

Step 3
understand significance
link *in vitro* experimentation and *in silico* modeling *with in vivo* data
validate *in vitro* and *in silico* approach 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 further develop *in vitro* and *in silico approach* to evaluate additional CQAs



Background

- **BCS class 4 compound**
  - Intermediate lipophilicity
  - Not ionized within physiological pH range
  - Low aqueous solubility
  - Considerable solubilization by bile
  - Intermediate permeability
- **Conventional immediate release formulation**
  - Unit dose strengths 50 – 100 – 150 – 300 mg
  - Broad range for particle size distribution accepted
  - Single Agent and Fixed-Dose Combination Drug Products
- **Dose-dependent PK (linear increase)**
- **No clinically relevant Drug-Drug Interactions within FDCDPs**
- **No significant food effect**

Biopharmaceutics history

- **Over a decade of clinical information available**
  - Low dose / high dose
  - Particle size
  - Prandial state
  - Different formulations
  - Polymorphism

- **PBBM models for internal decision taking and regulatory support**
  - Formulation selection
  - Particle size specifications
  - **Polymorphism**
  - **Dissolution specification**
  - Continuous Manufacturing
  - Real Time Release

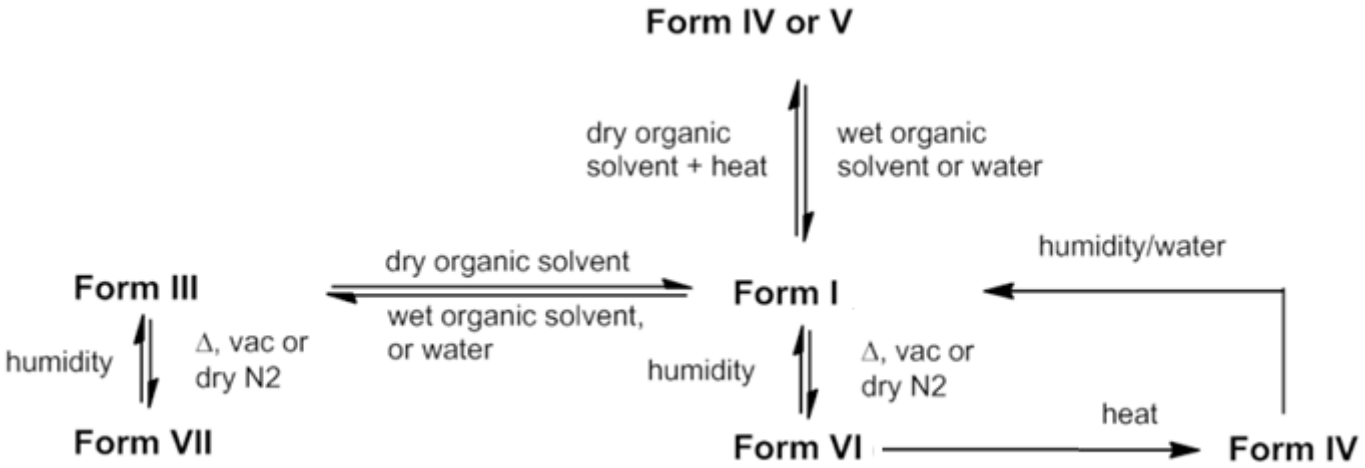
Case study 1

Problem statement

Investigations on new crystal forms

- Commercial product contains form I
- Proces is no longer able to exclusively produce form I
- Forms III, IV and V may be present

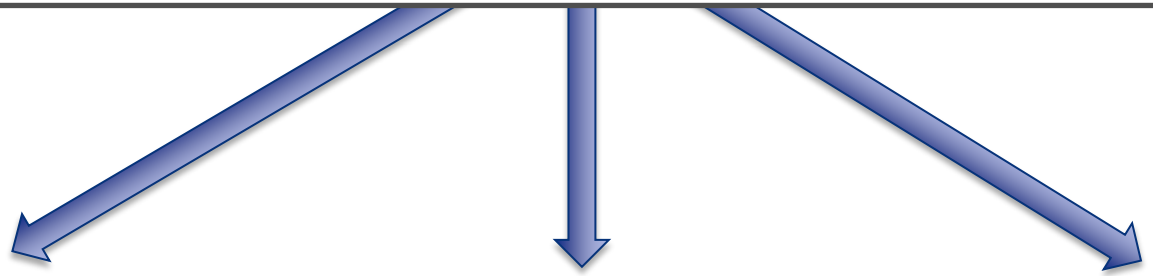
In vivo relevance?



Problem statement

Key question

How can we evaluate the **impact on the bioavailability** of a drug product containing **drug substance** that may consist of **mixtures** of the marketed solid state form with other solid state forms that **may / may not be thermodynamically more stable**?



in vitro

Solubility

Intrinsic dissolution rate

Particle characterization

Dissolution

in silico

PBBM

Exposure prediction

in vivo

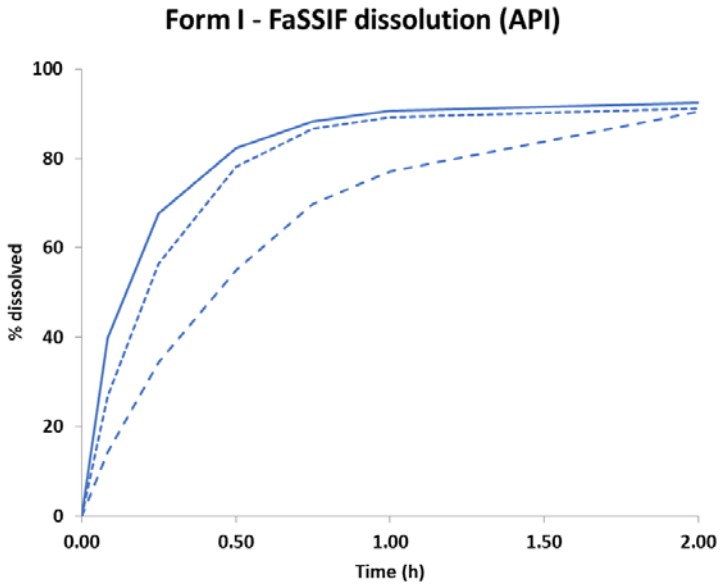
Preclinical study

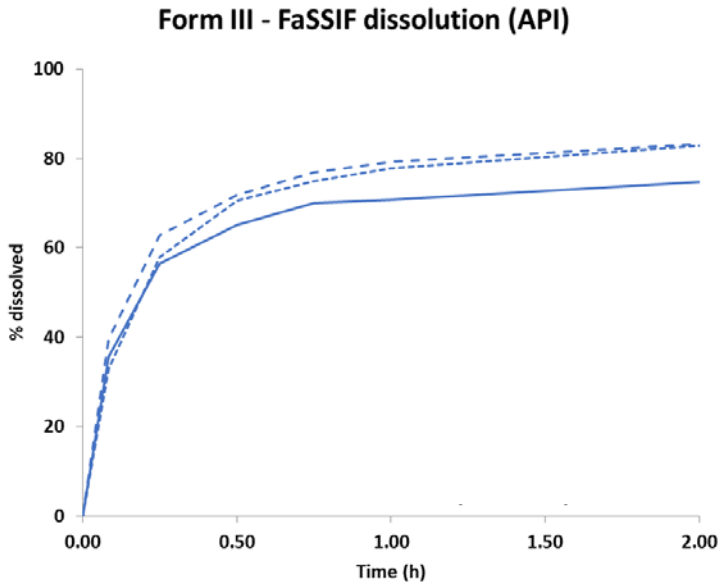
Clinical study

In vitro characterization

Translate differences between form I and form III

- Solubility: form III 40% less soluble (form I = sink)
- IDR: form III 40% slower
- API characterization: different morphology, PSD and SSA





***in vitro* data not conclusive – start *in silico* evaluation using PBPK**

PBBM model

Legacy PBBM model available

2012: Clinically relevant specifications for **particle size distribution**

2015: Clinically relevant specifications for **polymorphic purity**

Changes introduced

- GastroPlus v7.0 → **GastroPlus v8.6**
- **Johnson dissolution model** → **Takano dissolution model** (z-factor)
  - Same solvent system
  - Similar particle size
  - Differences in morphology
  - Differences in SSA
- Physico-chemical properties (solubility, pKa, logP)
- Compartmental PK based on oral data → **IV data**
- Fed state → **Fasted / Fed Food effect**
- In silico permeability → **In vitro permeability**

Modeling approach

Model validated with clinical data

- Different dose levels
- Fasted and fed conditions
- Food effect
- Steady state

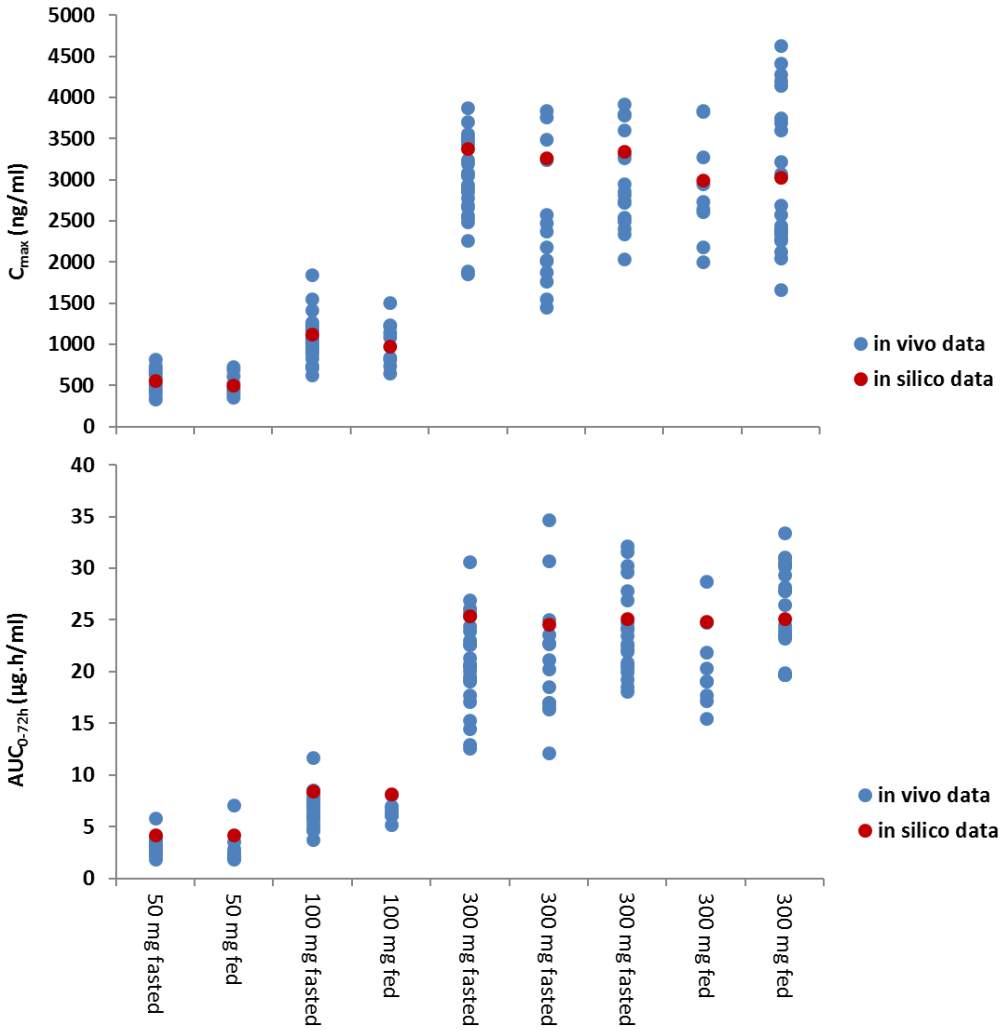
Mean values

Virtual (BE) trials

Model based on *in vitro* approach form I

Calculate required theoretical *in vitro* dissolution profiles in FaSSIF and FeSSIF corresponding with the boundaries towards no risks in safety and efficacy

Mean simulations – single dose



Different dose strengths

fasted / fed state data

Mean simulations within *in vivo* observed values

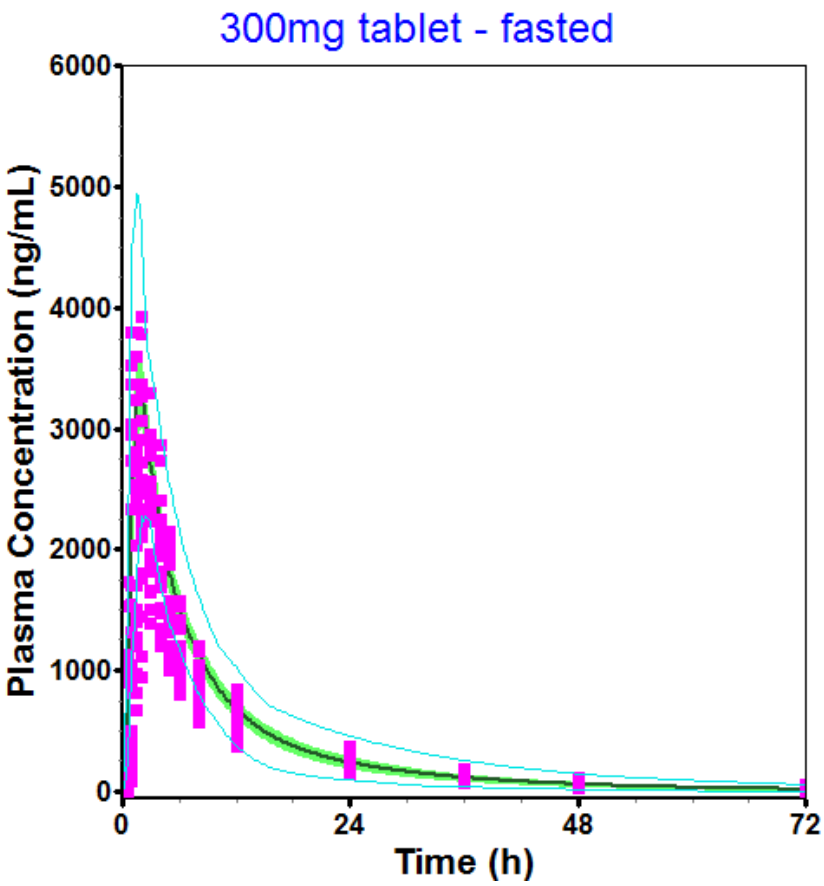
Virtual trial simulations

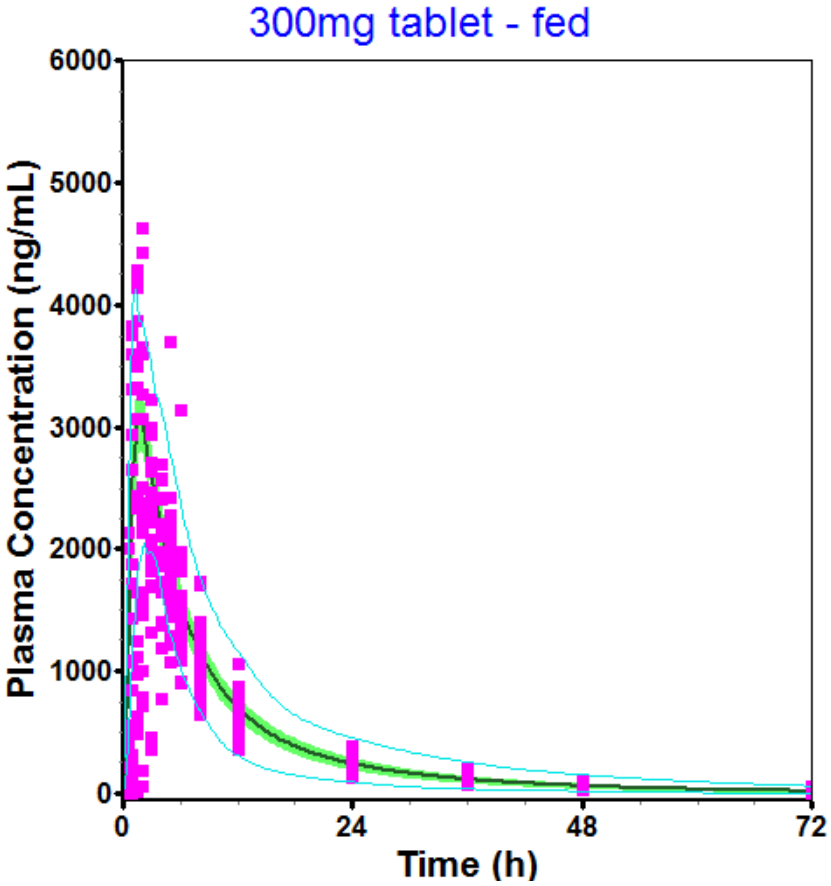
Parameter
Clearance
FPE liver
Vc/kg
K12
K21
K13
K31
Body weight
Permeability
Length SI
Stomach transit time
Bile concentration
Fluid volume SI
Transit time SI
Caecum transit time
Colon transit time

PK
(clinical data)

Absorption
(reference standards, in-house data, literature…)

Virtual trials





Risk assessment – form III

Excercise under most discriminative conditions

(highest dose / fasted state)

Parameter sensitivity analysis

Z-factor

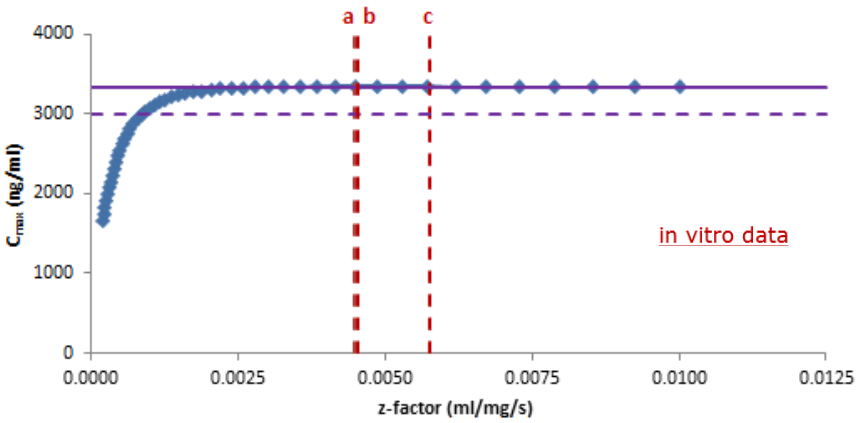
Compare *in silico* results form III with exposure data form I

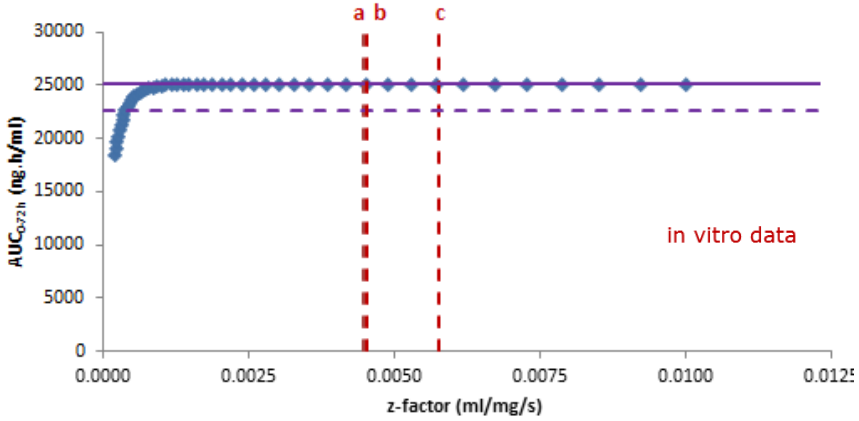
Define ‘no impact on bioavailability’

Cutoff of 10 % change compared to form I

Relate to z-factor of available batches form III

Risk assessment – form III





Current form III API batches not at risk

Highest dose / fasted conditions

Safety – no increase in C_{max} / AUC

(permeation limited)

(>99% absorbed)

Efficacy – no decrease in C_{max} / AUC

(Sufficient dissolution speed and solubility)

Risk assessment – form III

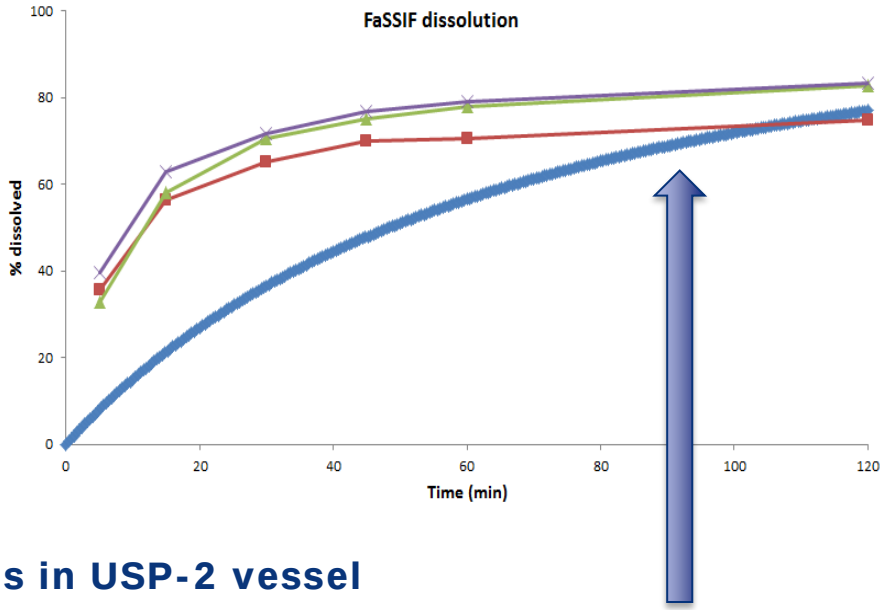
100% form III predicted to be bioequivalent compared to form I

No need to model intermediates

Z-factor corresponding to ± 10% change calculated using PSA

All current API batches well above threshold

- Future batches?
- Changes in crystallization solvent?
- Changes in morphology?
- Particle size distribution?
- SSA?



Modified ACAT model to simulate conditions in USP-2 vessel

Use treshold z-factor to establish minimum required dissolution profile in PBDT

in vivo confirmation

Confirmatory study performed after approvals on polymorphic purity

Bridge M&S with *in vivo* data

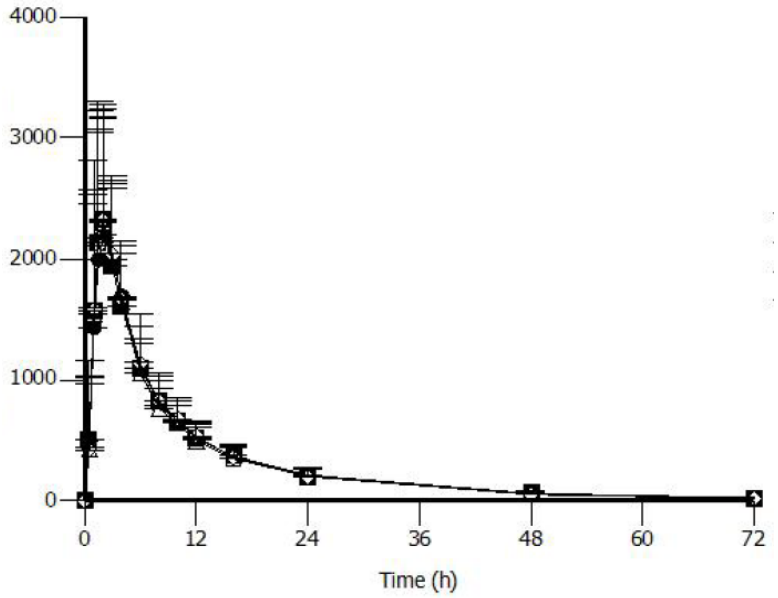
Validate approach for potential future use

- NDA/MAA
- Life cycle management

4-way crossover

- 100% form I
- 90% form I – 10% form III
- 50% form I – 50% form III
- 100% form III

All formulations bioequivalent

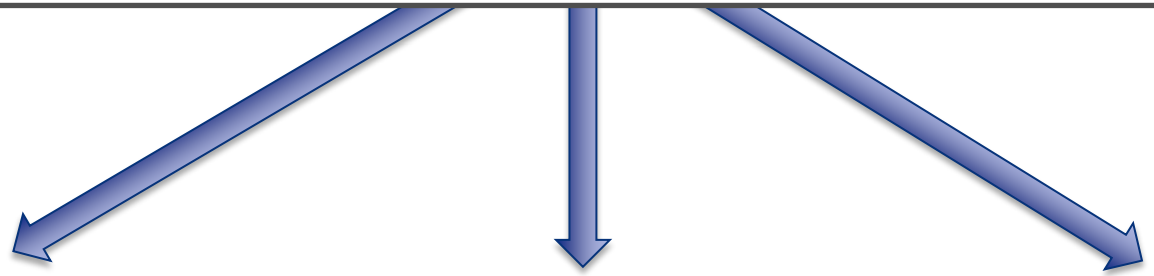


Case study 2

Problem statement

Key question

A newly developed FDCDP was bioequivalent with the co-administered single agent formulations used during phase 3. However, setting and justification of the dissolution specification based on solely the pivotal batches was at risk of rejecting tablet batches manufactured with drug substance batches at the boundaries of the API particle size distribution of the production process.



in vitro

Solubility

Particle characterization

Dissolution

in silico

PBBM

Exposure prediction

in vivo

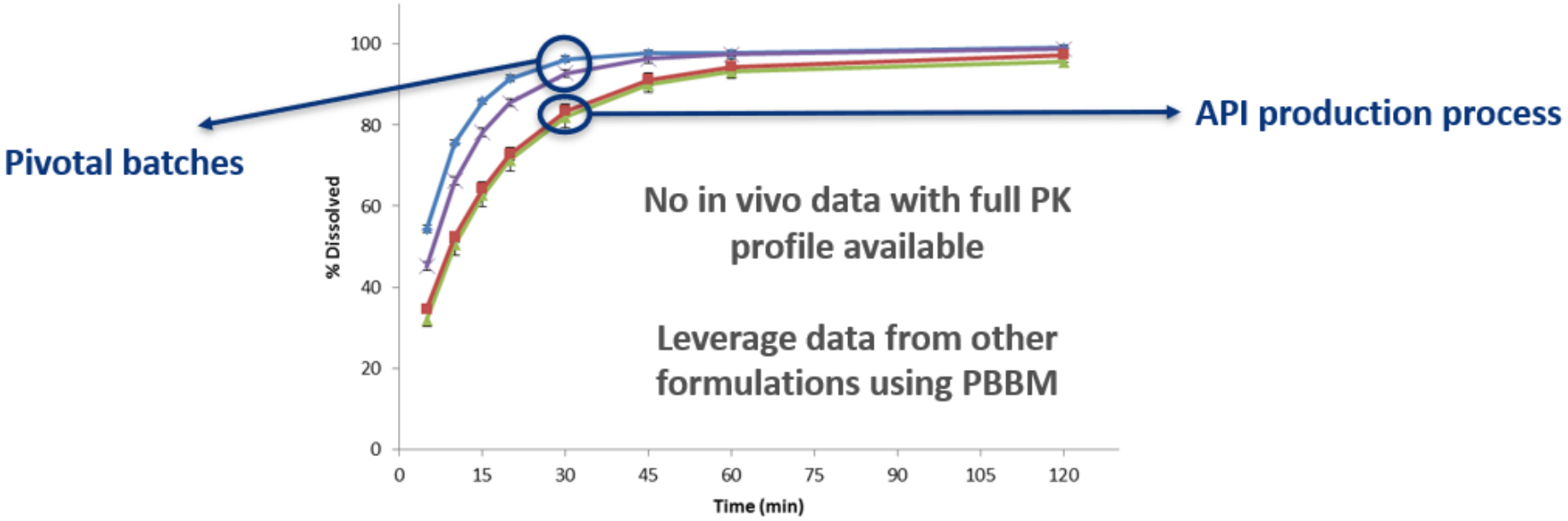
Preclinical study

Clinical study

Problem statement

In vivo relevance of QC dissolution

- Method is sensitive to **API particle size**
- Setting and justification based on **pivotal batches** may be at risk of rejecting tablet batches manufactured with API batches at the lower/higher end of the API particle size specifications



PBBM model

Legacy PBBM model available

2012: Clinically relevant specifications for **particle size distribution**

2015: Clinically relevant specifications for **polymorphic purity**

2016: Clinically relevant specifications for **QC dissolution** of a FDCDP

Changes introduced

- GastroPlus v8.6
- **Z-factor model**
- Single agent

GastroPlus v9.0

FDCDP

Takano dissolution model
(z-factor)

Same API

Different formulation

Different QC method

Modeling approach

Model validated with clinical data

- Different dose levels
- Fasted and fed conditions
- Food effect
- Steady state
- **Multiple different formulations**

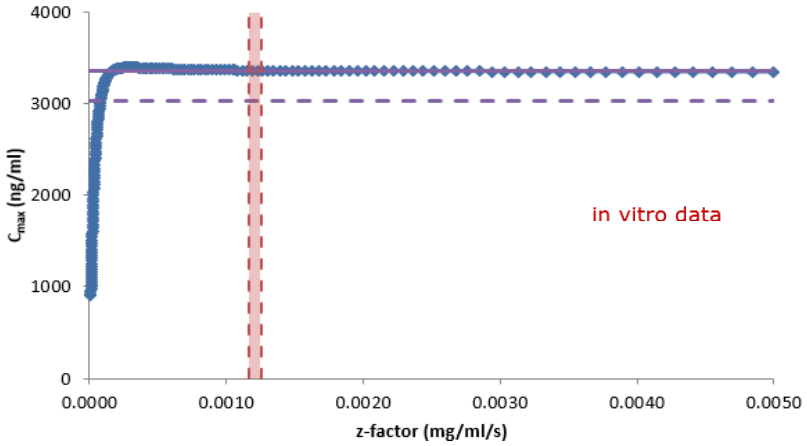
Mean values

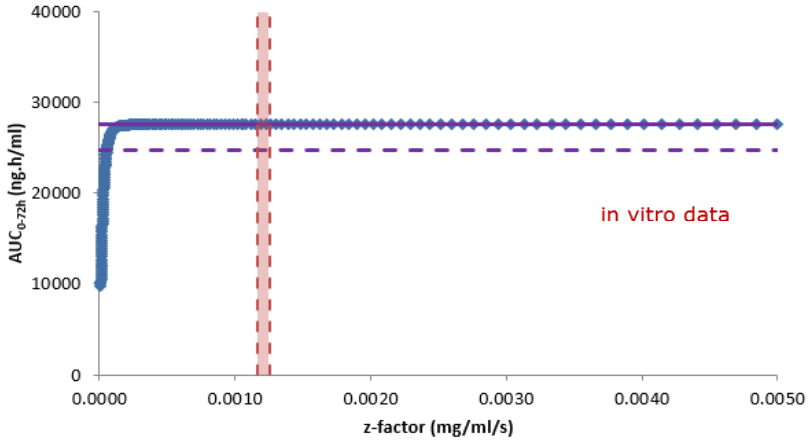
Virtual (BE) trials

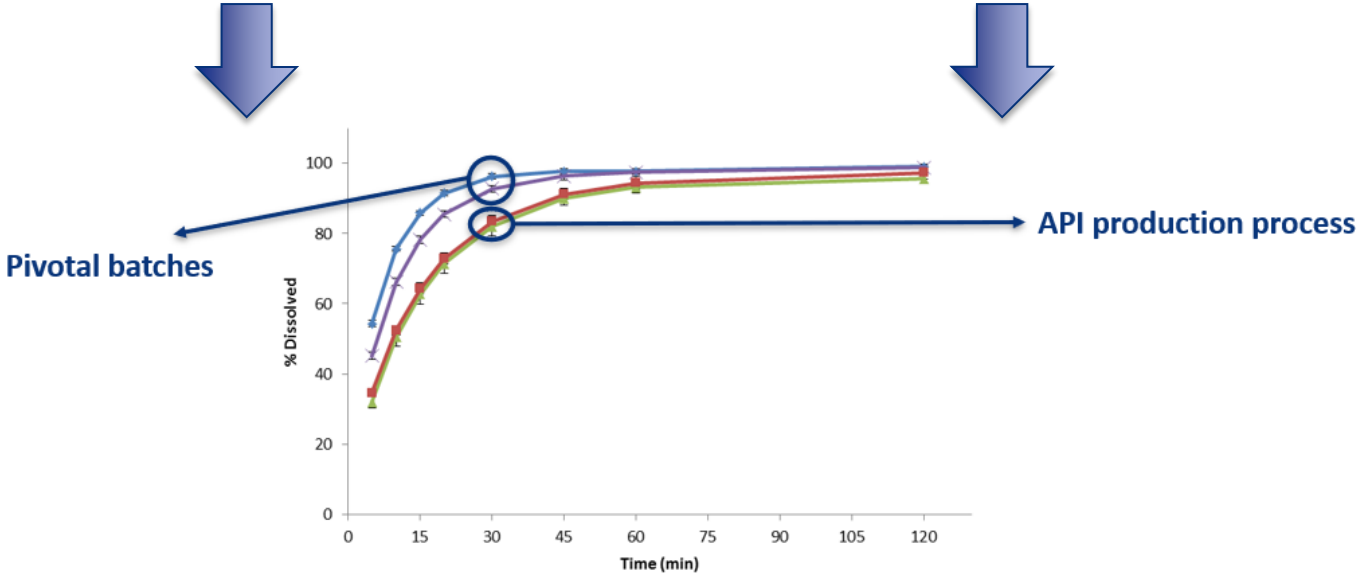
Model based on *in vitro* approach using biorelevant dissolution

Calculate boundaries towards no risks in safety and efficacy + bridge towards the QC dissolution method

Risk assessment – FDCDP







Acknowledgements

Q&A?

Thank you

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