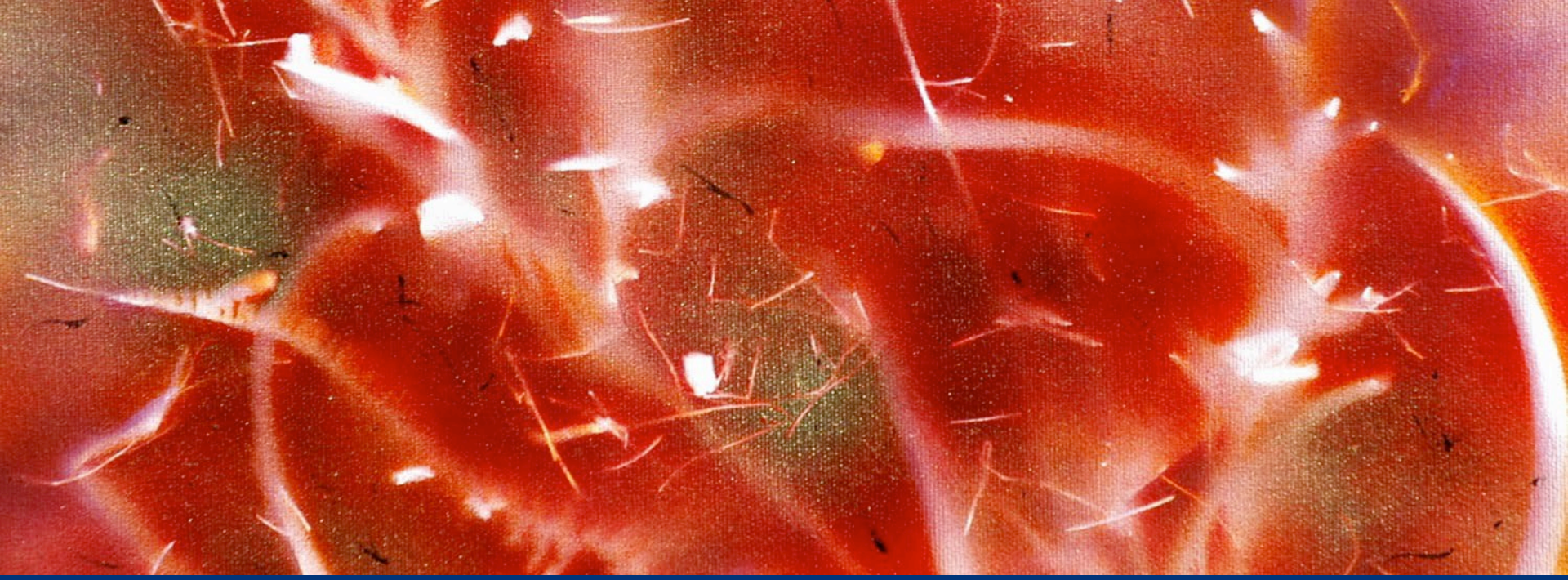


Bridging Physiology-Based Dissolution Testing to QC testing using Physiologically Based Biopharmaceutics Modeling

Donna Williams, *Cheerful*
Donna Williams, an autistic artist, author and renowned autism advocate, was diagnosed with breast cancer in 2011.

Christophe Tistaert
Principal Scientist Biopharmaceutics

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

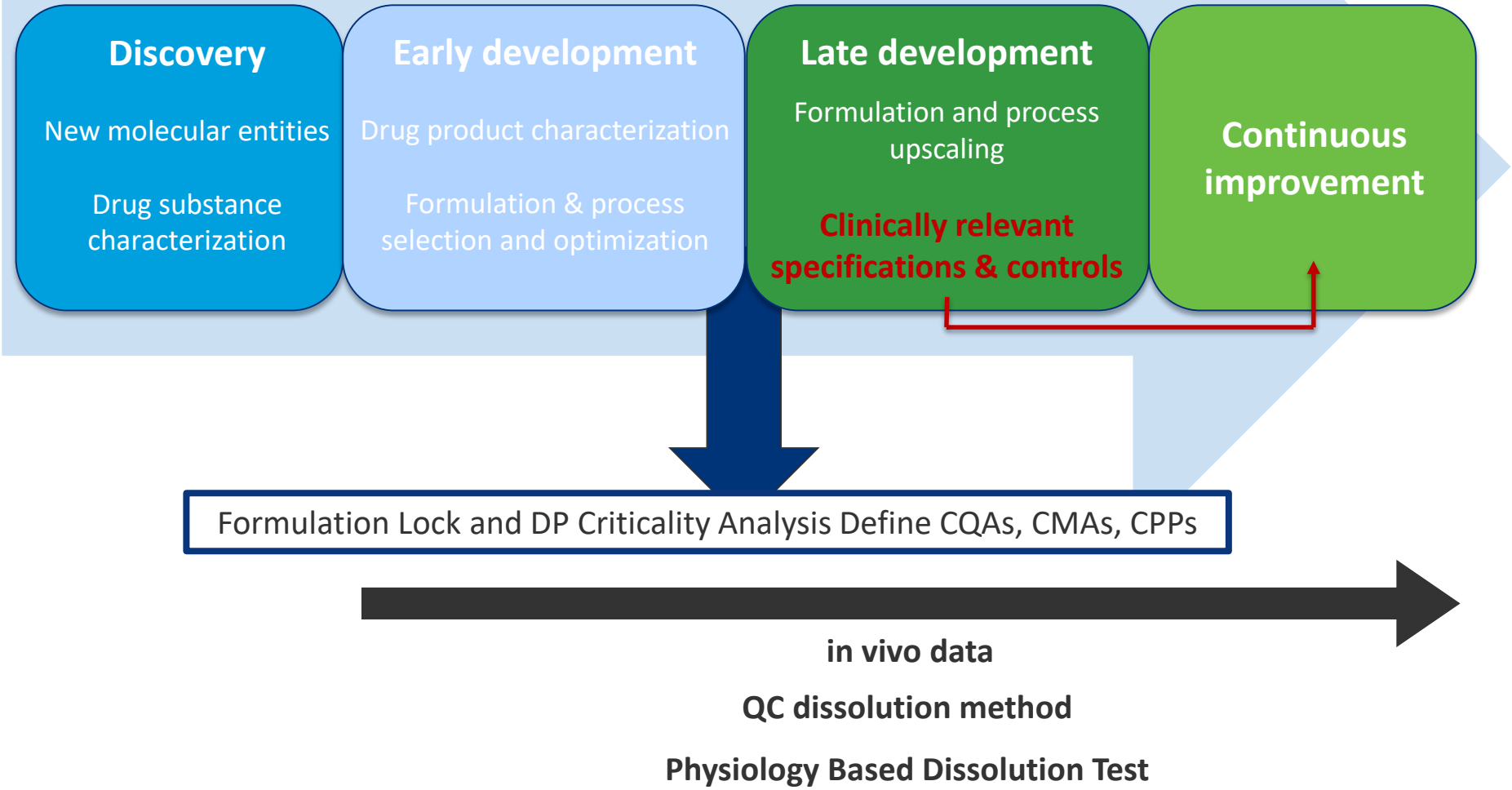
September 23 – 25, 2019
Maryland, US

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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**

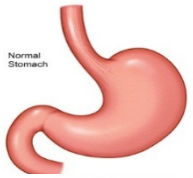
Biopharmaceutics in drug product development



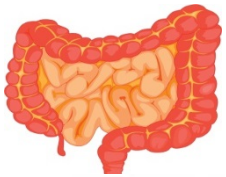
Physiology Based Dissolution Test

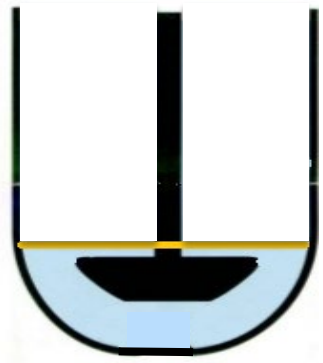
Gastric Phase

Intestinal Phase



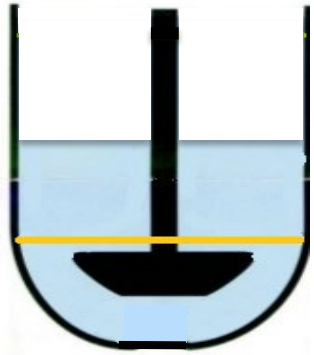
75 rpm
37°C





250 mL

+ 250 mL
cFaSSIFv1



500 mL

250 mL FaSGF (pH 1.6)
30 min

500 mL FaSSIF (pH 6.5)
120 min

https://doi.org/10.1021/acs.molpharmaceut.7b00198

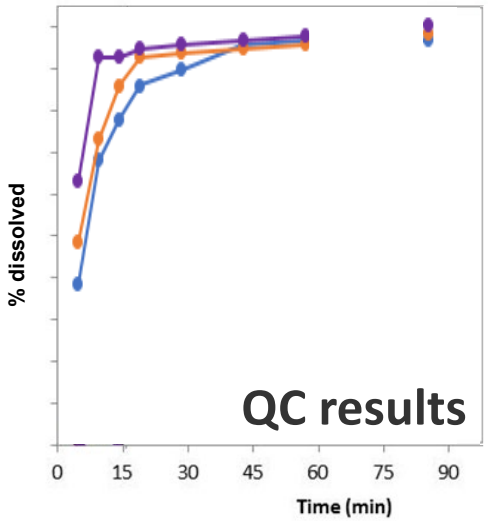
PBDT method

- **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?



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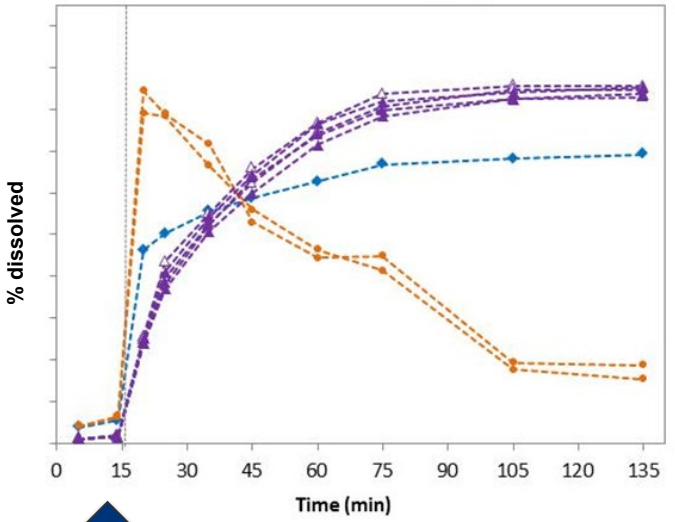
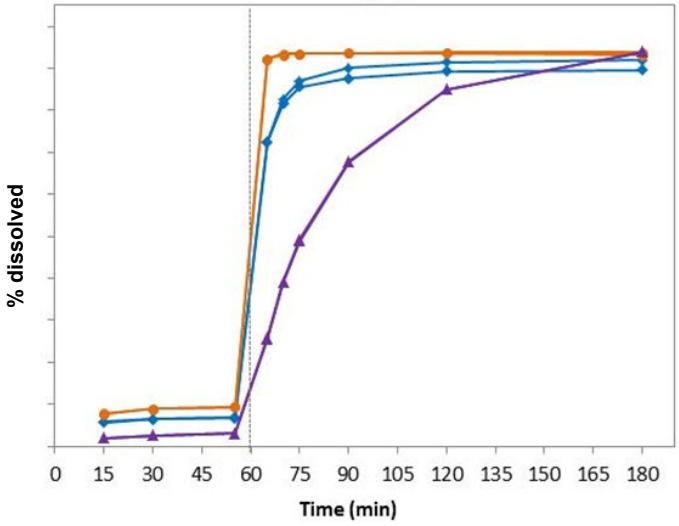
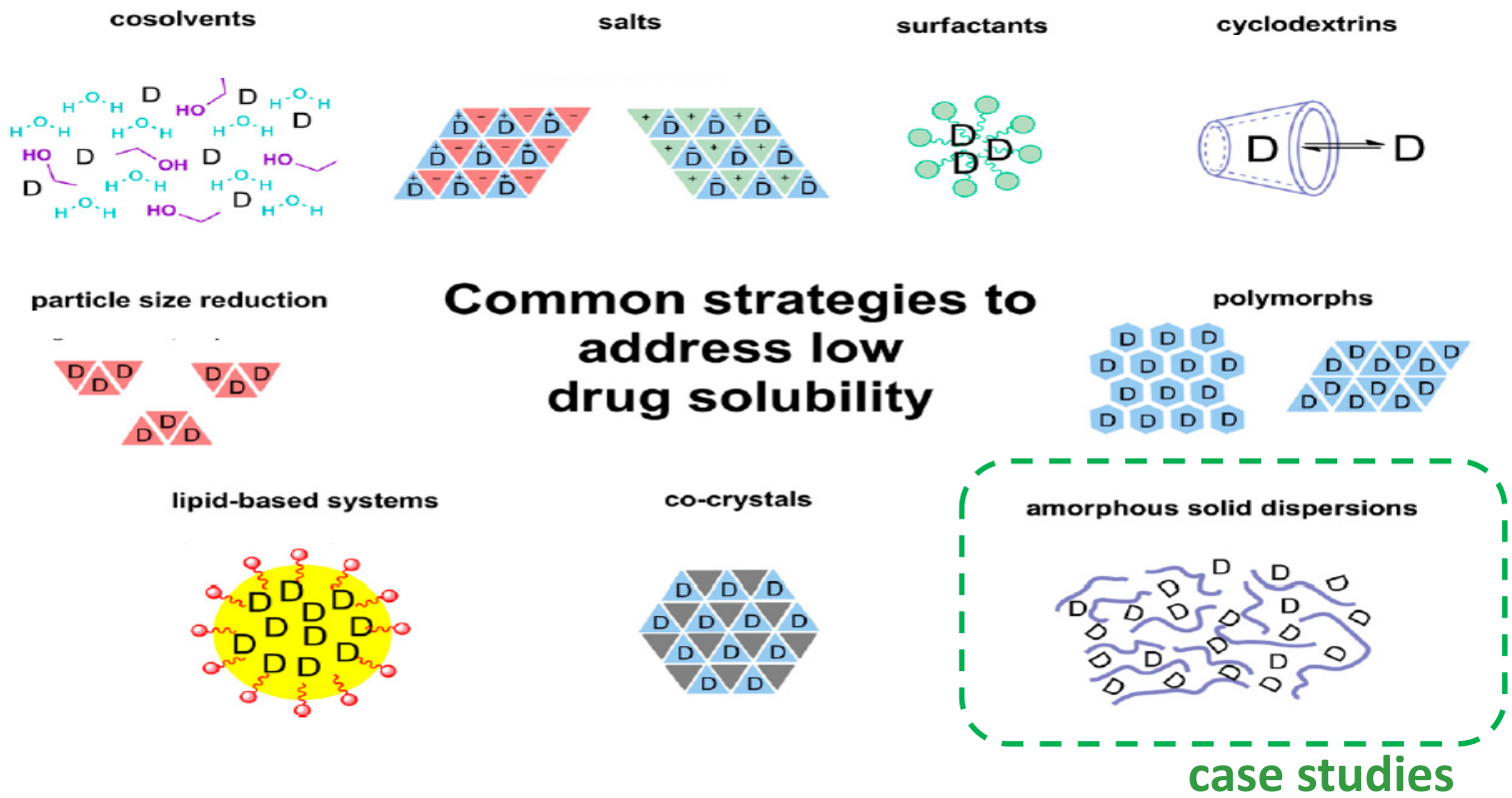


2-phase FaSSIF



2-phase FeSSIF

Focus on BCS II / IV compounds



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

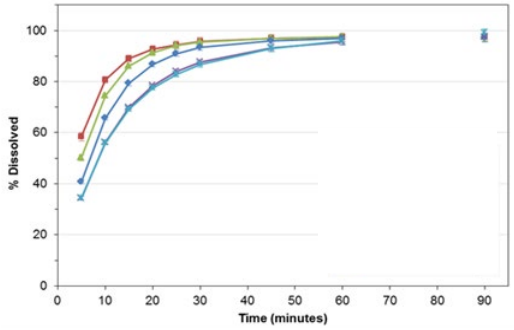
- Facilitate choice of enabling platform
- Guide formulation concept selection and development
- **Establish clinically relevant specifications**

CRC strategy workflow

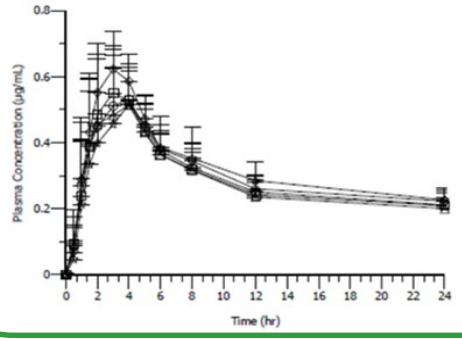
Step 1a: CA analysis
API properties
Formulation
Process

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

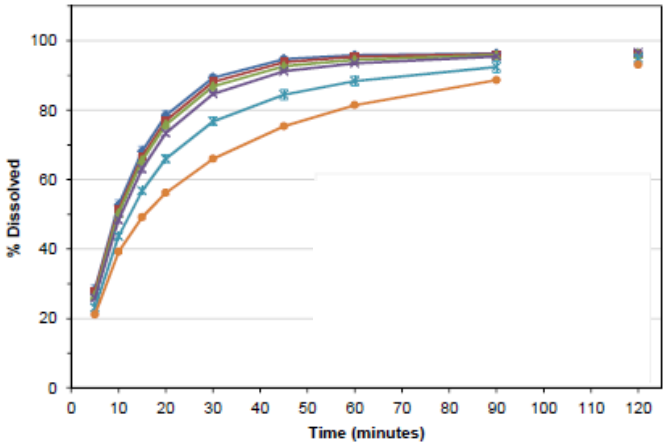
Step 5: Define design space/spec to ensure CQAs are always met

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

Limited in vivo testing e.g. crystallization

QC method development

Method A

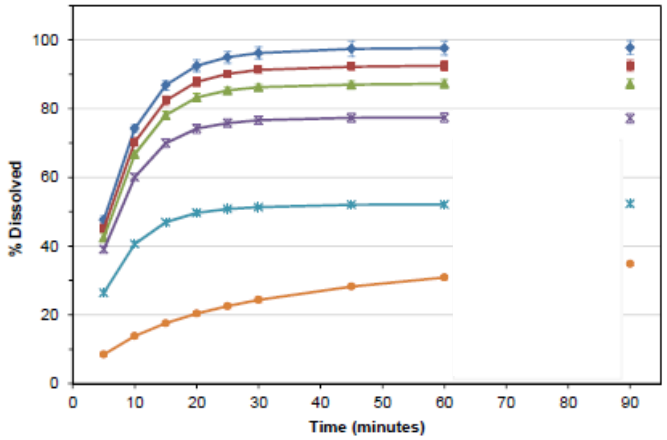


?

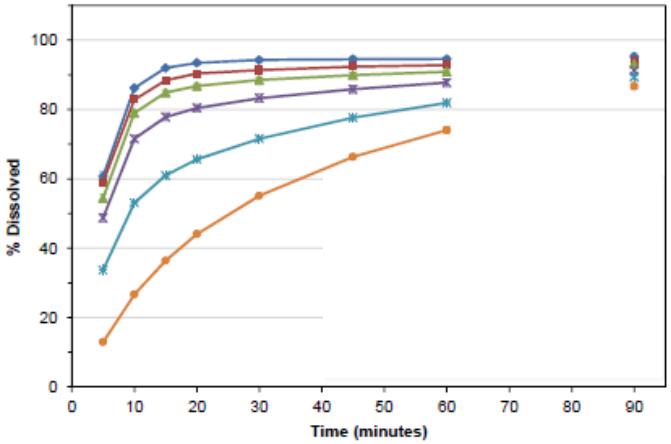
Clinical relevance

?

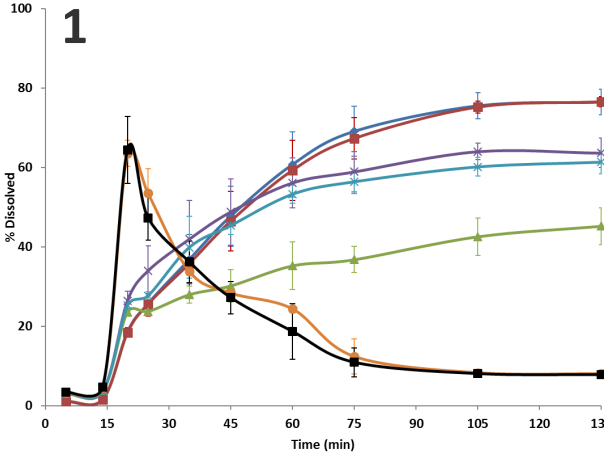
Method B

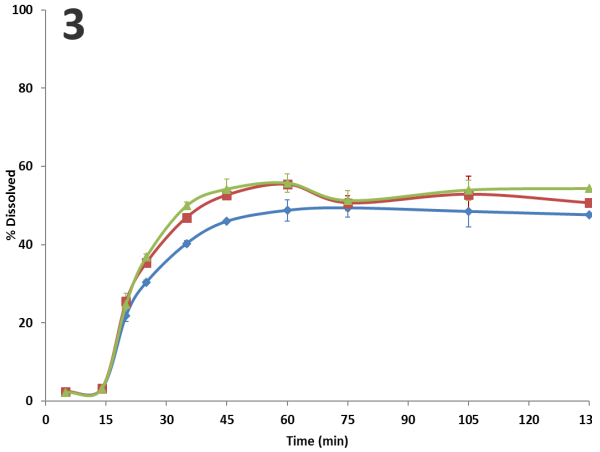


Method C

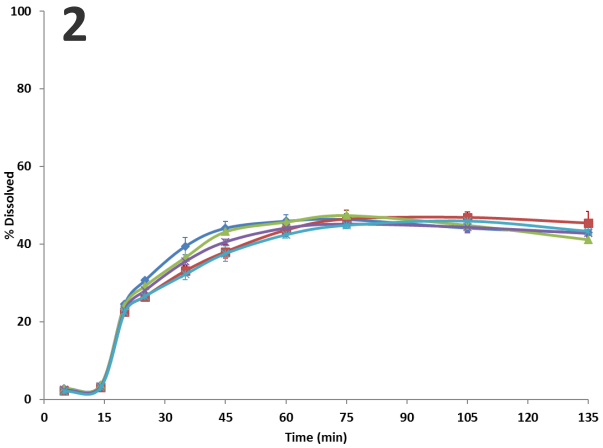


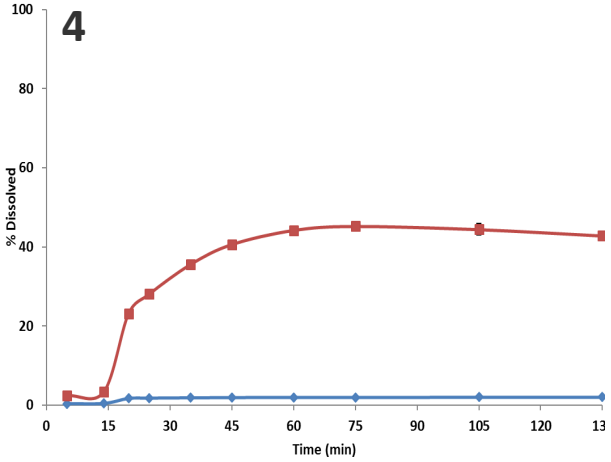
PBDT profiles





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

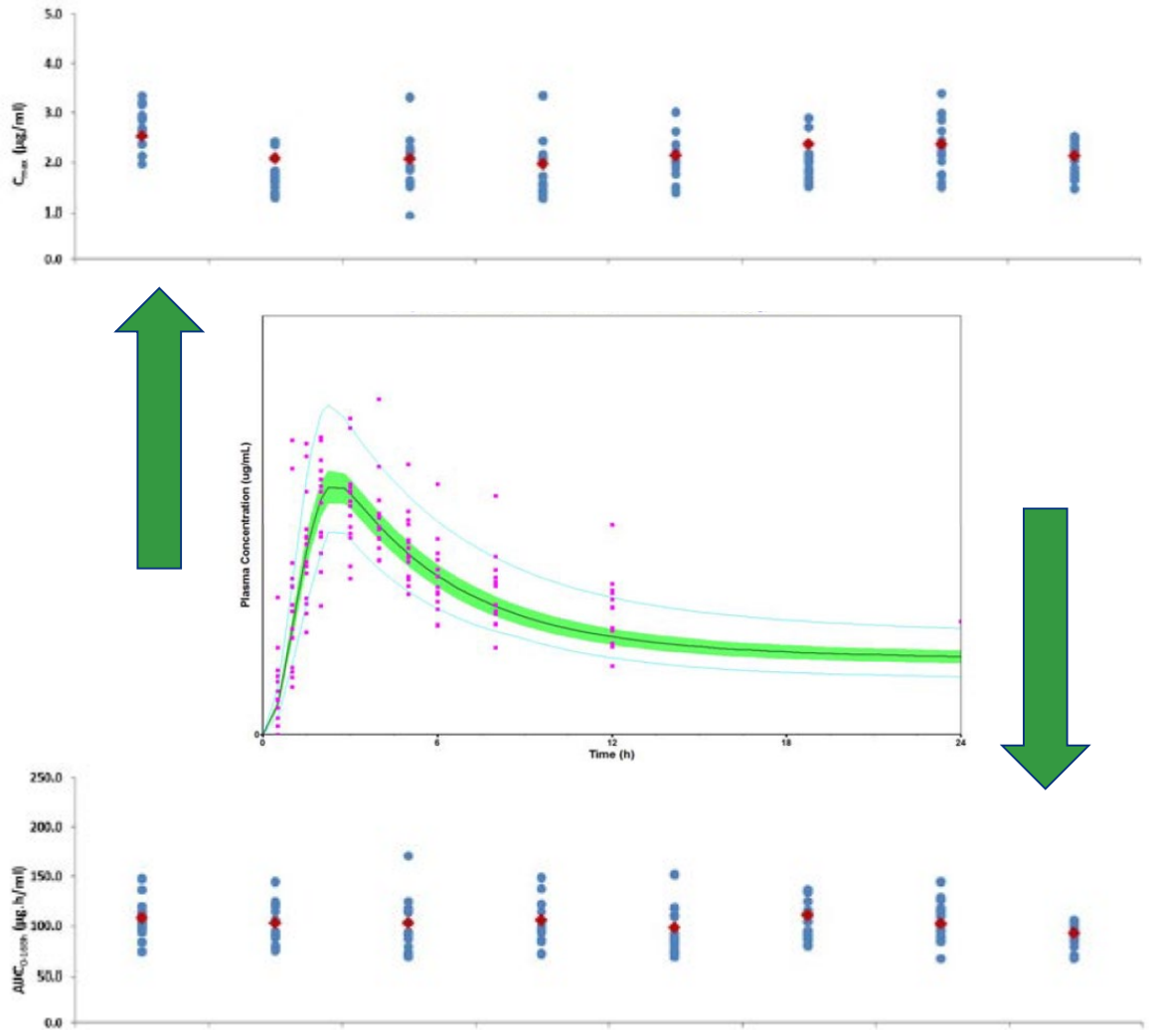




In vivo data – Simulate by PBBM

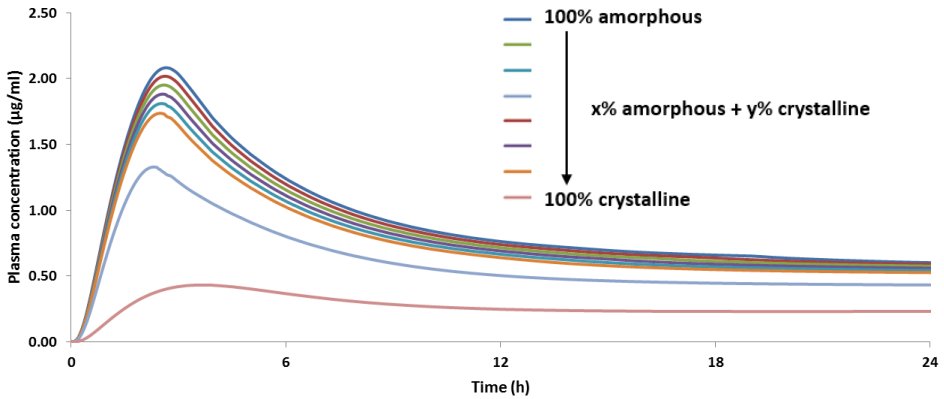
PBDT profiles as input for PBBM

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

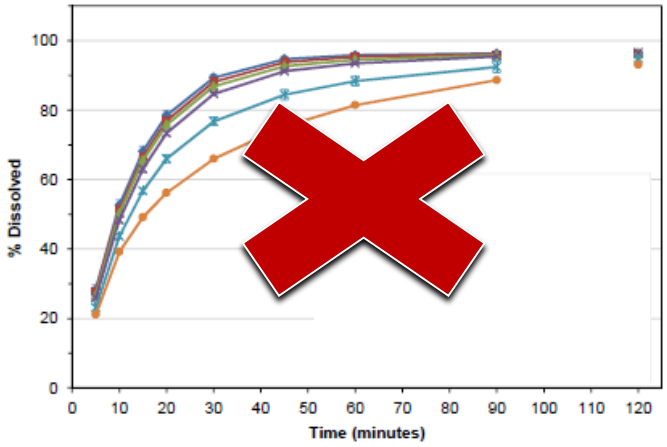
Statistics

Virtual bioequivalence trials																
Virtual Trial Number	w % crystallinity				x % crystallinity				y % crystallinity				z % crystallinity			
	C_{max}		AUC_{0-168h}		C_{max}		AUC_{0-168h}		C_{max}		AUC_{0-168h}		C_{max}		AUC_{0-168h}	
	90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI	
	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL
1	84.90	94.66	93.17	99.29	86.87	96.85	92.41	98.47	82.94	92.47	87.82	93.59	80.05	89.25	87.05	92.76
2	89.30	98.31	91.44	94.65	83.36	91.77	92.89	96.15	83.78	92.24	87.32	90.39	77.01	84.78	87.38	90.45
3	88.92	97.69	92.95	97.81	86.04	94.53	89.36	94.03	85.54	93.98	87.18	91.73	79.47	87.31	84.32	88.72
4	92.12	102.28	93.60	97.80	88.14	97.85	91.23	95.32	83.10	92.25	88.76	92.74	81.51	90.49	86.00	89.86
5	82.95	93.92	93.45	97.58	84.24	95.38	91.07	95.10	80.11	90.71	87.49	91.36	77.78	88.07	85.76	89.54
6	89.65	100.59	91.64	95.68	81.94	91.94	91.03	95.04	81.75	91.72	89.42	93.36	75.72	84.96	85.87	89.66
7	86.92	95.32	93.56	97.62	86.15	94.47	90.34	94.26	83.78	91.88	86.89	90.66	79.43	87.11	85.20	88.90
8	85.04	97.65	94.02	98.22	84.04	96.50	90.38	94.42	83.46	95.83	88.32	92.27	77.65	89.16	85.14	88.95
9	89.99	100.13	92.61	97.81	88.61	98.60	90.58	95.66	81.95	91.18	88.47	93.43	81.74	90.95	85.39	90.18
10	86.58	97.90	92.31	96.20	80.18	90.66	89.06	92.82	83.10	93.96	88.84	92.59	74.06	83.73	83.93	87.47

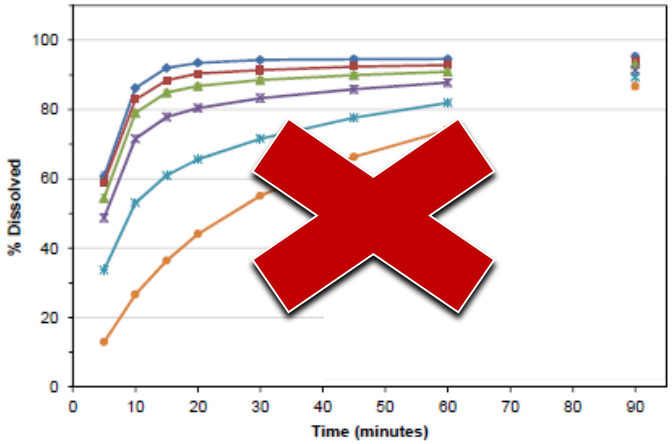
Safe space approach

QC method selection

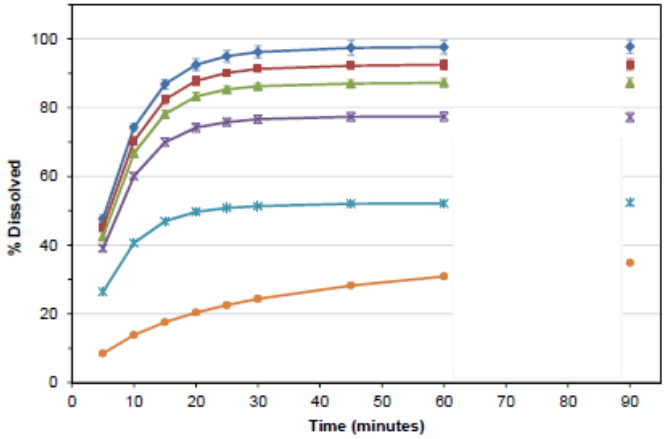
Method A



Method C



Stack ranking discriminative properties Similar to PBDT

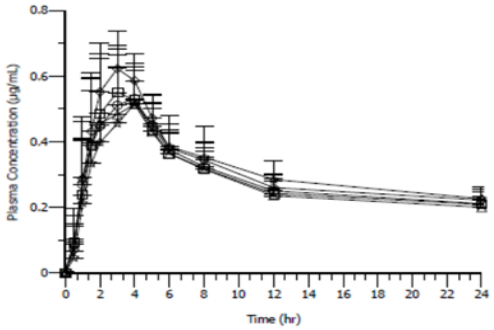


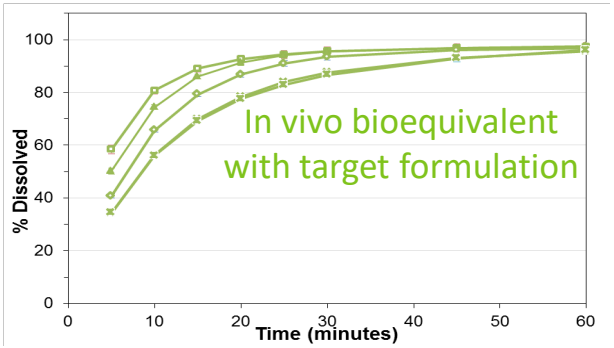
Method B

CRC workflow in practice

Critical Quality Attribute 1

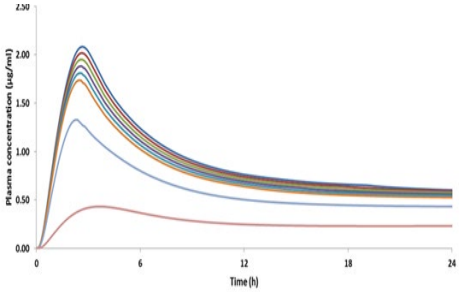
Human BA Trial



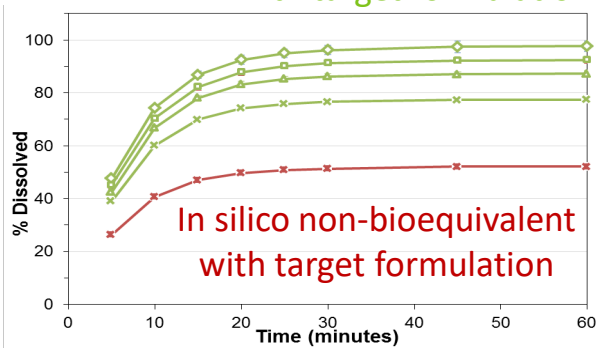


Polymorphic purity

Validated PBPK Model



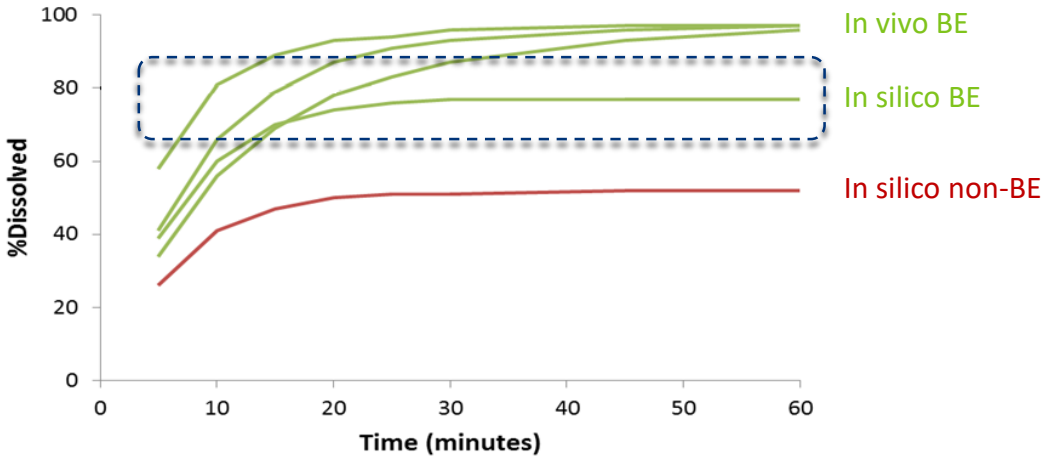
In silico bioequivalent
with target formulation



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

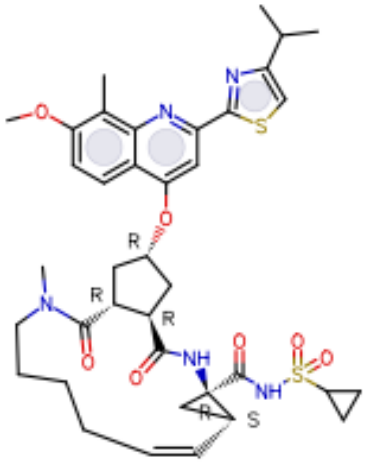


Scope of clinically relevant specifications not limited to QC dissolution

clinically relevant acceptance criteria for polymorphic purity

(opposed to acceptance criteria based on LOD/LOQ of analytical techniques)

Case study 2



simeprevir

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 proces
- 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

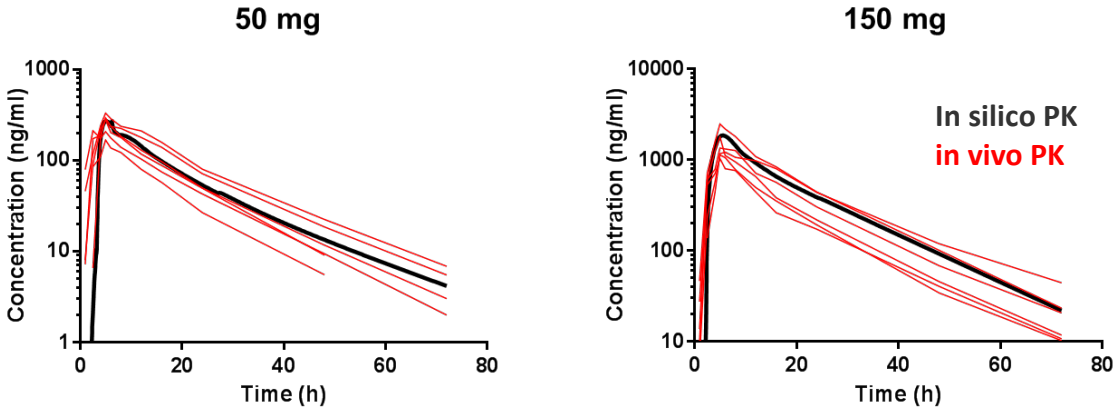
PK elucidation and DDI evaluation

Include dissolution based mechanistic absorption model

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

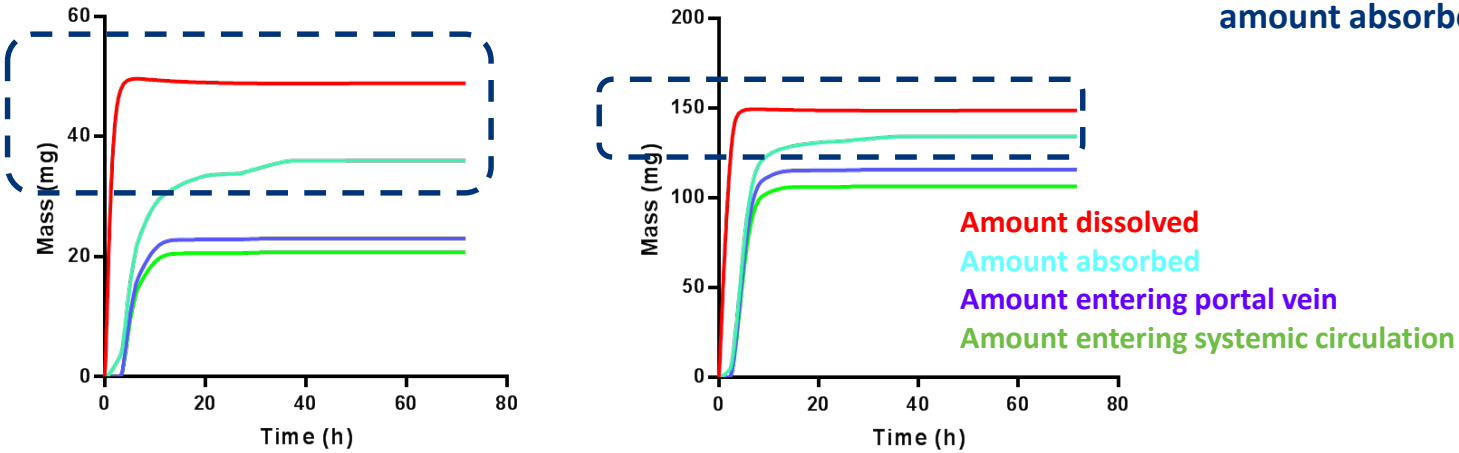
Oral dose predictions

Plasma concentration-time profiles



Relative importance of permeation rate

Absorption and dissolution curves

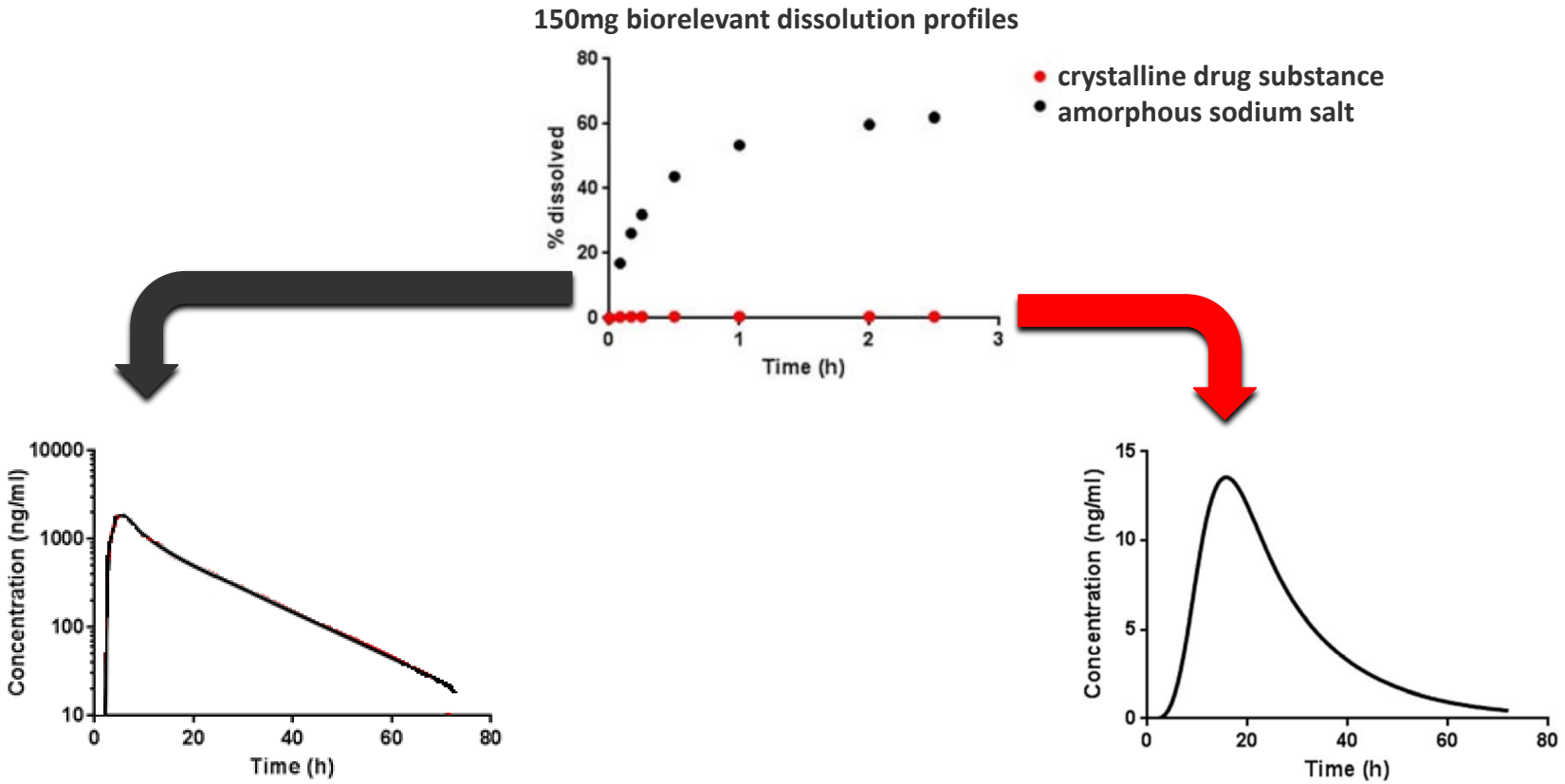


Amount of drug dissolved in function of time versus amount absorbed in function of time

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

Validation

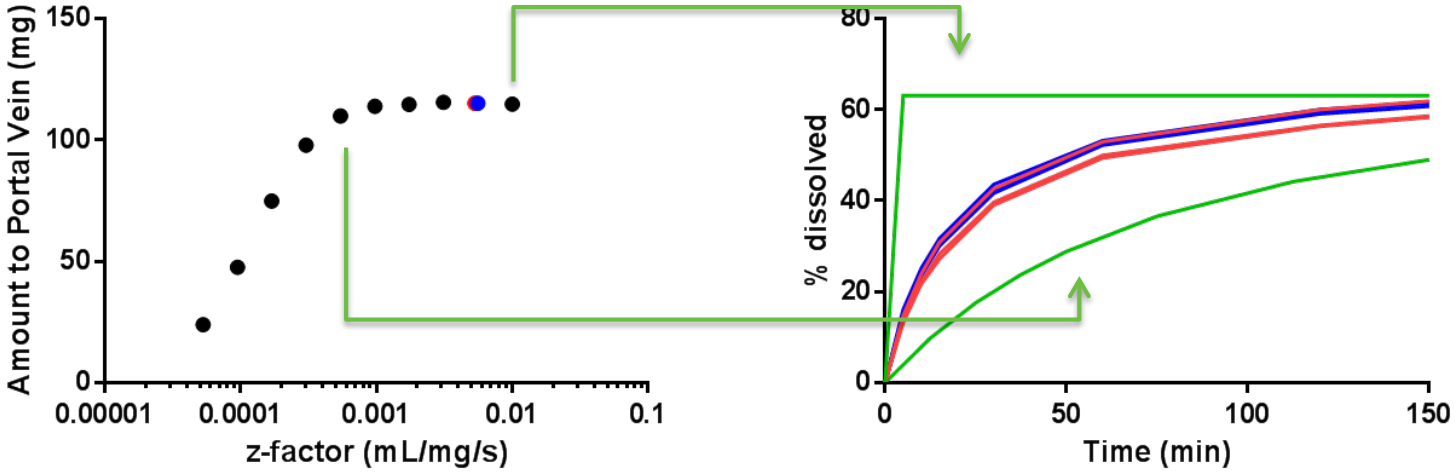
Can the model differentiate between a bioequivalent and non-bioequivalent formulation?



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

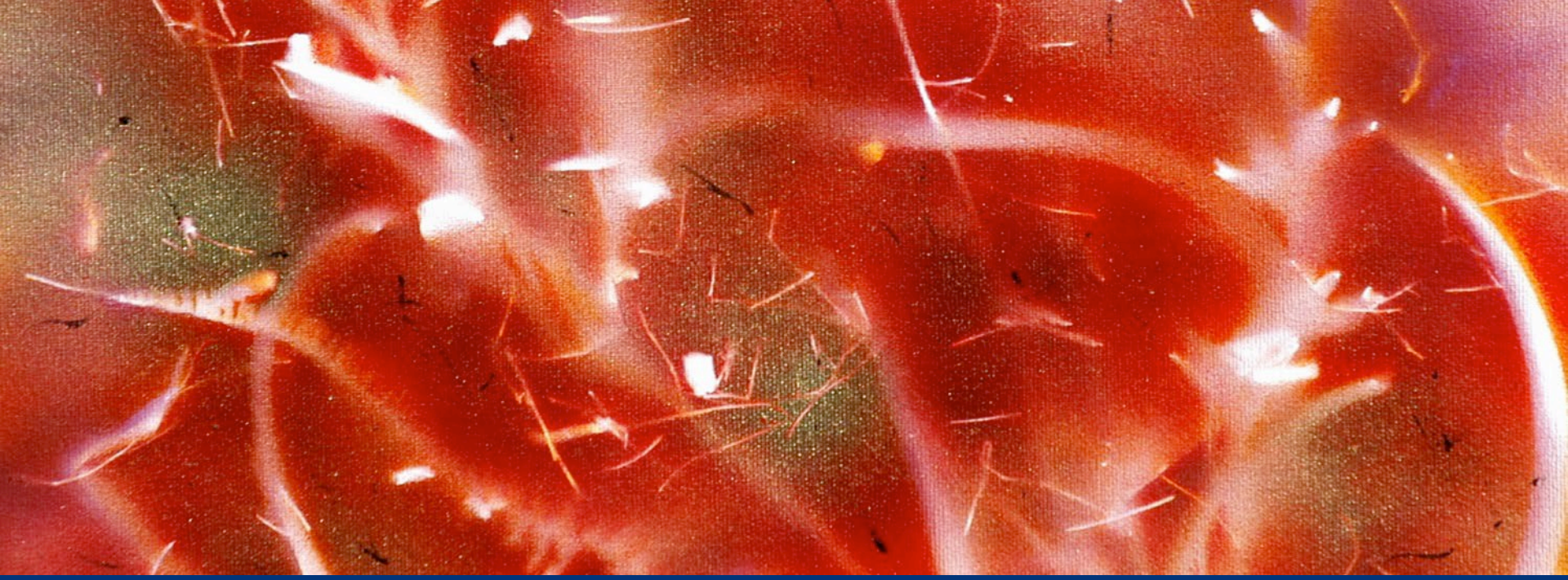
Closing remarks

- **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



Thank you

More info?

Contact @ ctistaer@its.jnj.com

Donna Williams, *Cheerful*
Donna Williams, an autistic artist, author and renowned autism advocate, was diagnosed with breast cancer in 2011.

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