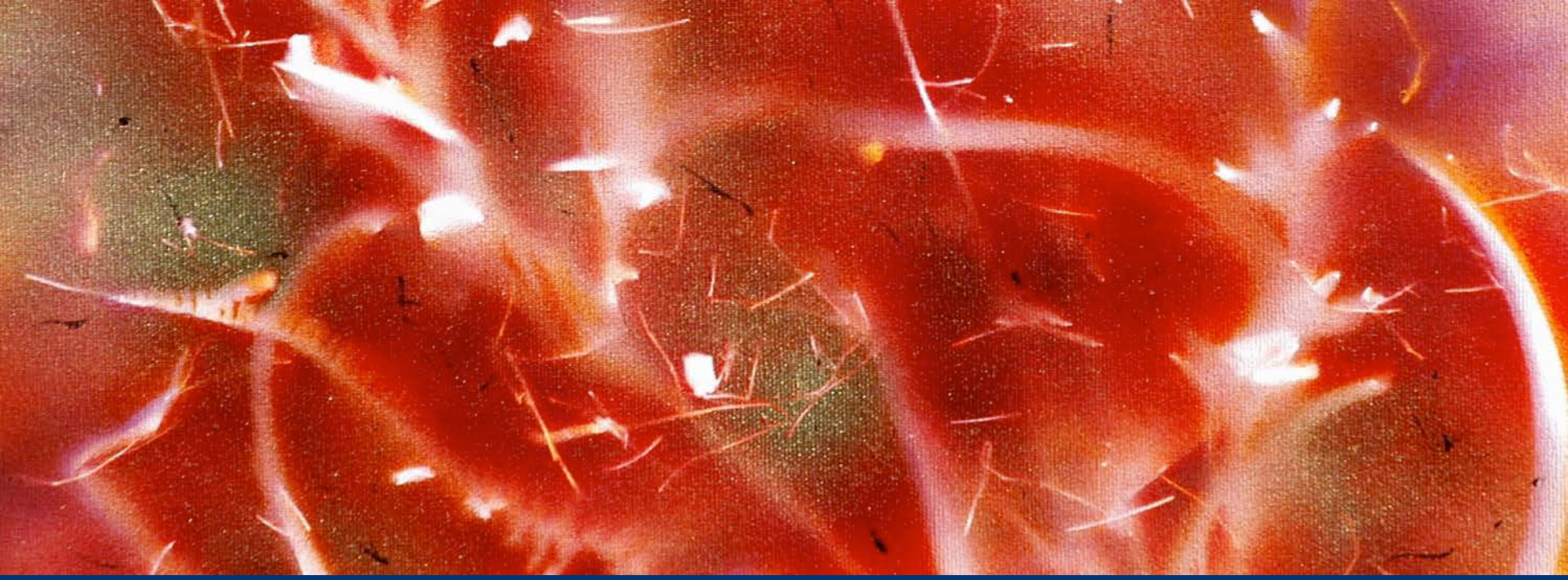


Mechanistic absorption modeling and clinically relevant specifications for enabling formulation technologies

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

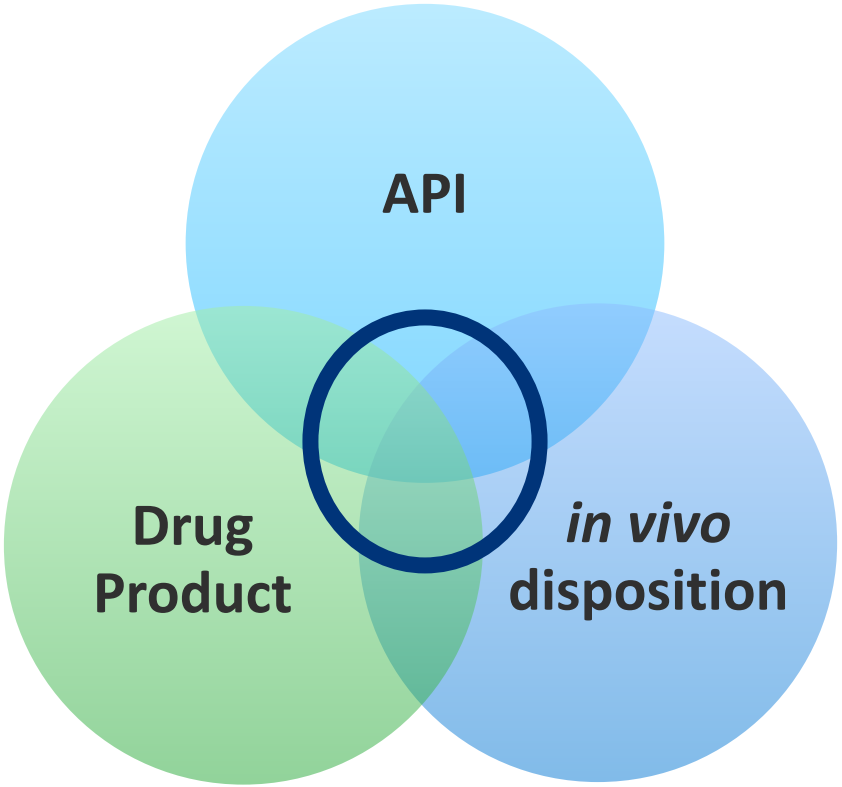
4th PQRI/FDA Conference on Advancing Product Quality
April 9 – 11, 2019
Rockville, Maryland, US

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Outline

- **Introduction**
  - Challenges & solutions in pharmaceutical industry
  - High-throughput screening
  - Mechanistic modeling
  - Example
- **Biopharmaceutics in drug product development**
  - Mechanistic absorption modeling
  - Illustrated workflow for clinically relevant specifications
  - Continuous improvement
- **Closing remarks**

Biopharmaceutics



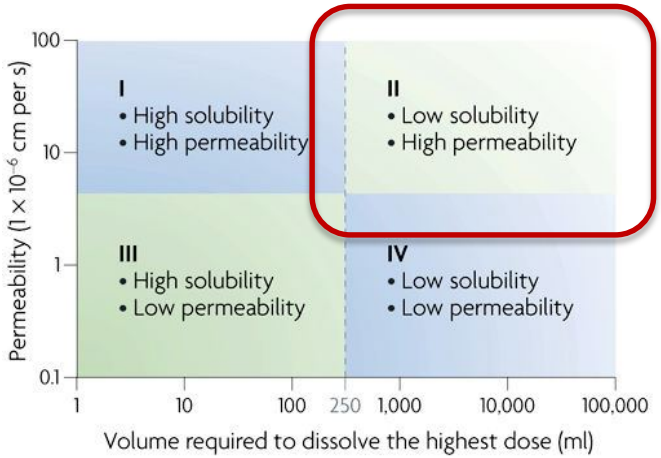
GOAL

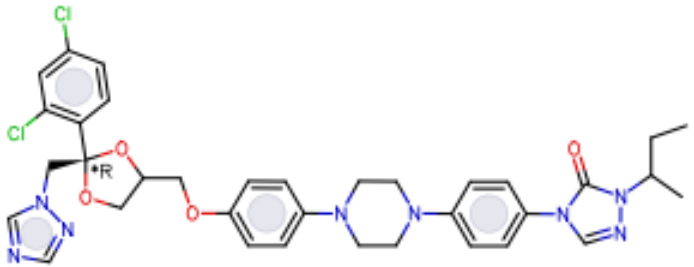
Increase drug product understanding
support clinically relevant specification/control setting

What is our challenge?

Solubility of marble is about 10 µg/ml

Venus de Milo is 10.000 times more soluble than itraconazole





Solublility of itraconazole is about 1 ng/ml

One dose of itraconazole requires **200.000 liters** of water to dissolve

Transition from discovery to early development

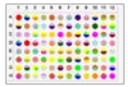
Many options / Many combinations

Organic

Aqueous

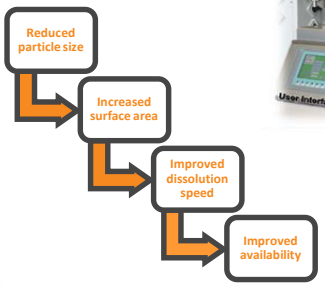
Expand experimental space through miniaturization and automation

DOE

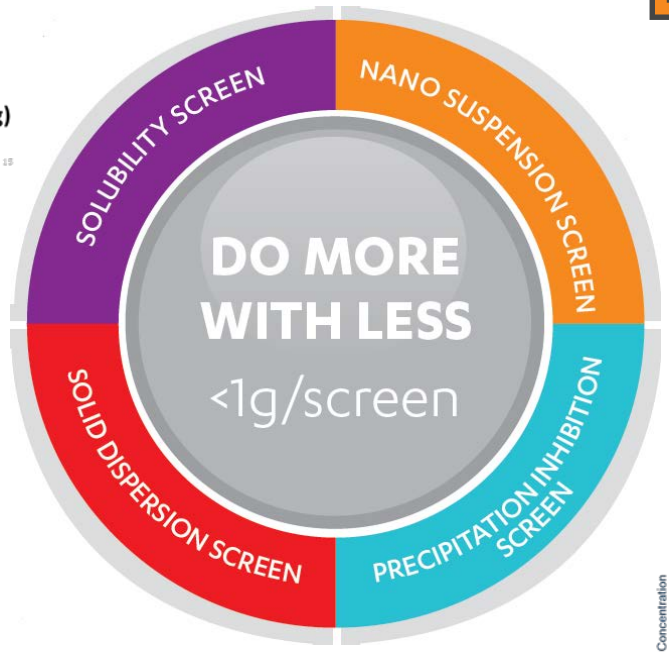


Up to 128 combinations screened (Transmission imaging)

Miniaturization



$$\frac{dm}{dt} = A\frac{D}{d}(C_s - C_b)$$

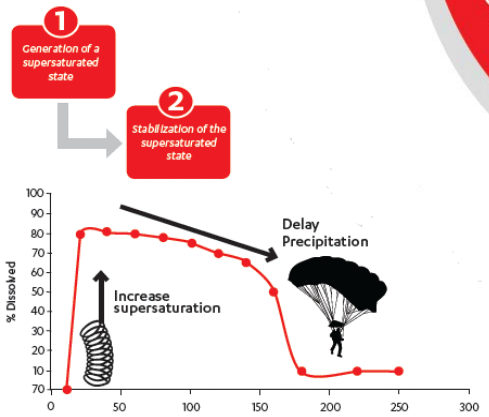


Preformulation

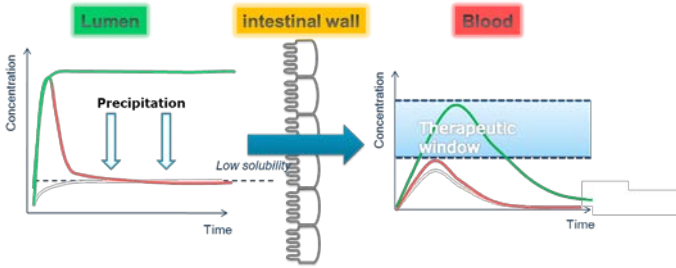
Multiple polymers

Different ratios

In Triplicate



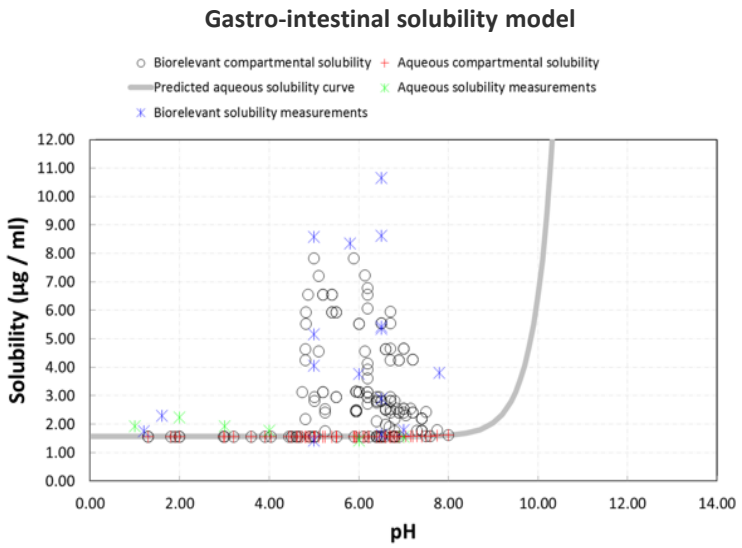
Automation

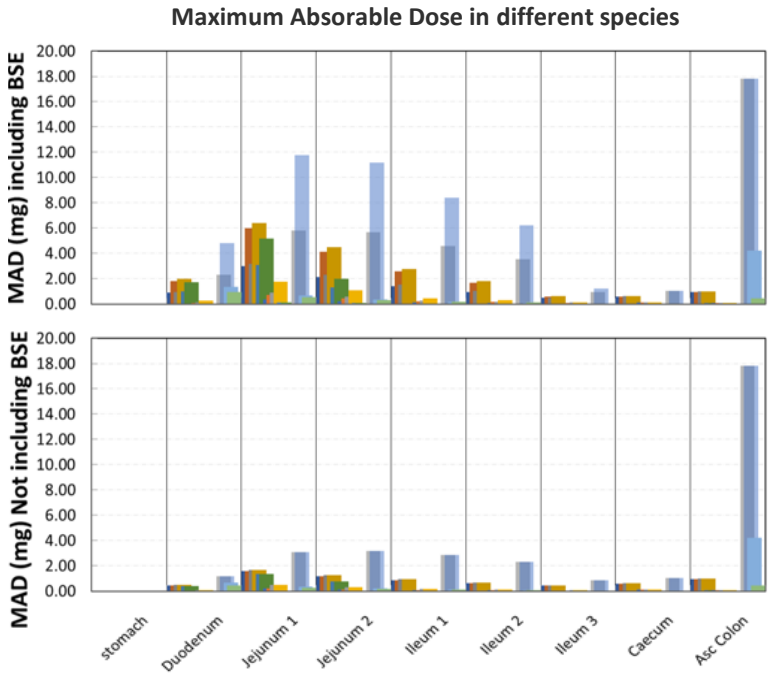


Supersaturation driven absorption

Translating the information

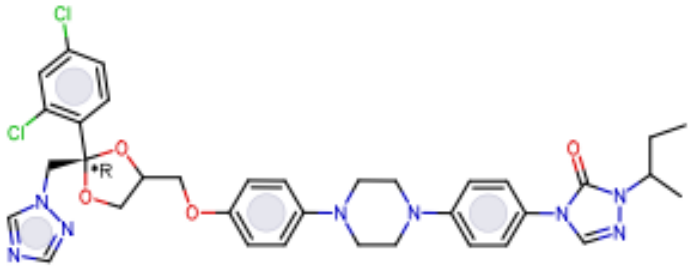
PhysioMAD





- Virtual physiology
- Descriptive and mechanistic algorithms
- Differential framework

Itraconazole

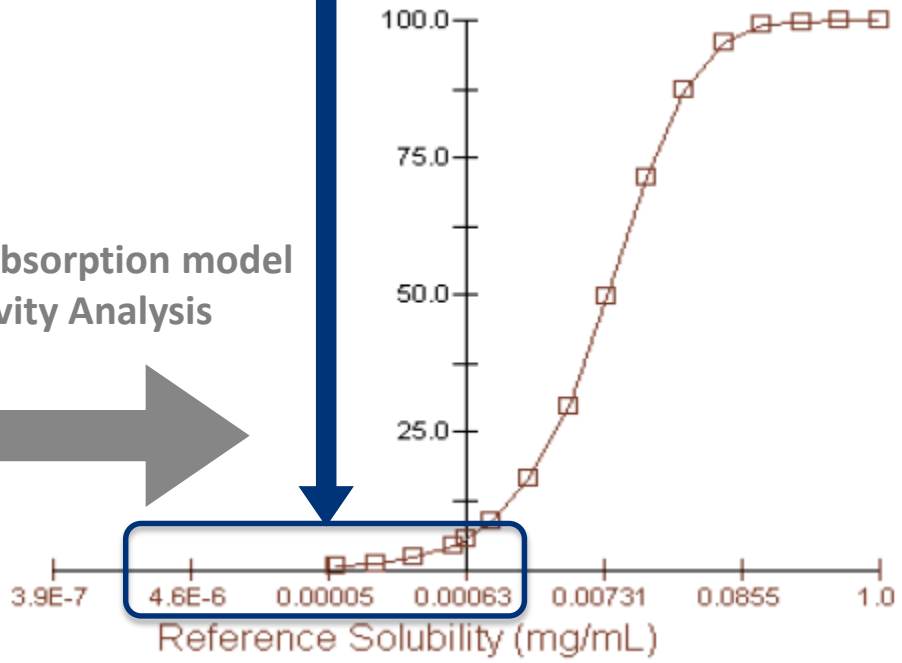


itraconazole

Estimated fraction absorbed
< 10%

Baseline mechanistic absorption model
Parameter Sensitivity Analysis

LogP > 5
pKa = 4
Aqueous solubility pH 7 = 1 ng/ml
Solubility in SGF = 4 µg/ml
High permeability

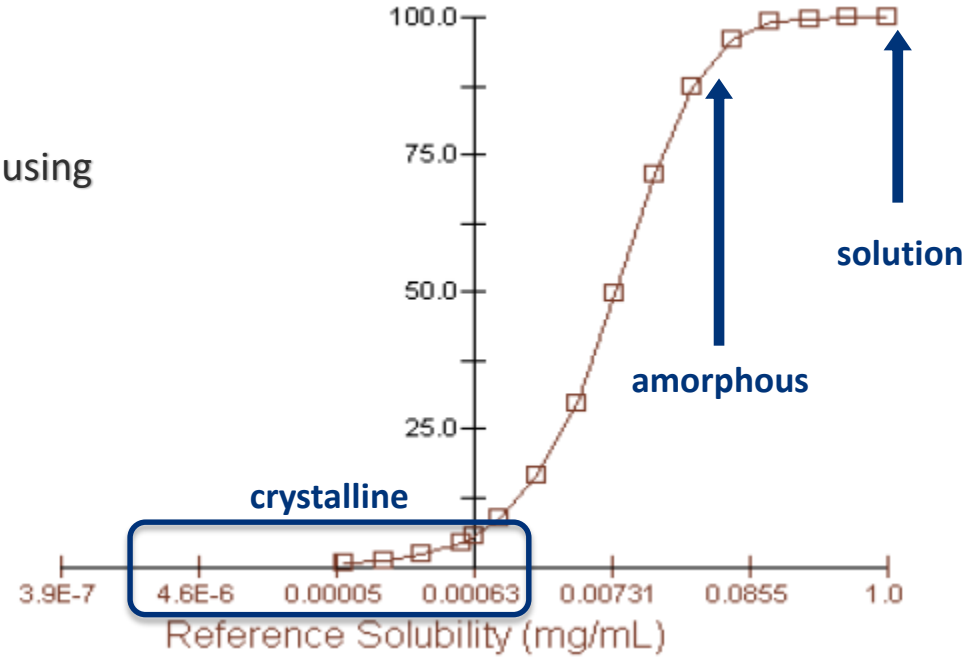


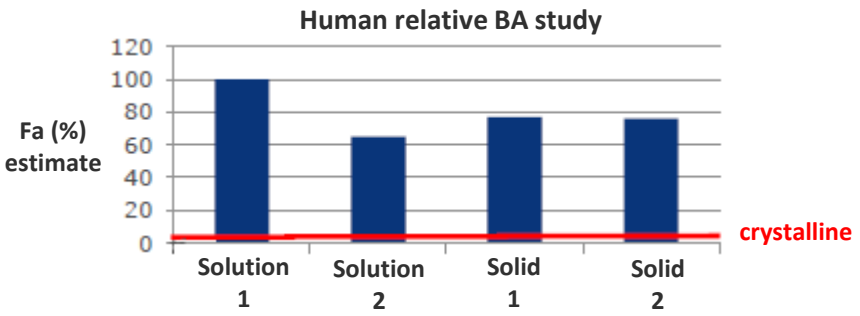
Itraconazole

- Aqueous and non-aqueous solubility screen
- Theoretical amorphous solubility enhancement using thermodynamic descriptors*

Itraconazole		
MW	705.64	g/mol
ΔHf	84.5	J/g
ΔCpTg	0.43	J/gK
Tm	440.3	K
Tg	332.4	K
T	310	K

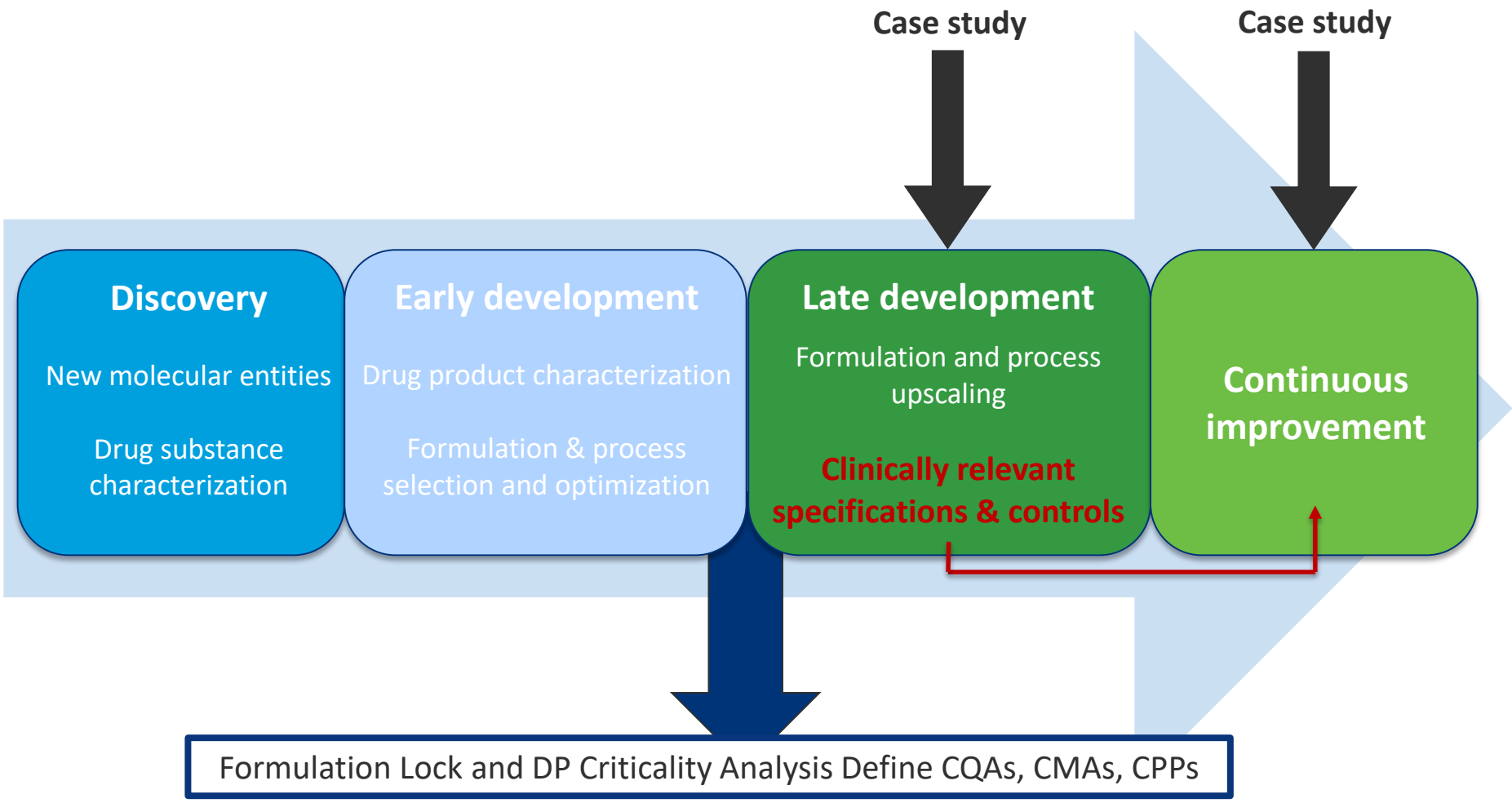
ΔH_T	38.1030	J/g
ΔS_T	0.0710	J/gK
ΔG_T	16.0824	J/g
amorphous/crystalline	81.8803	





* https://doi.org/10.1023/A:1007516718048

Biopharmaceutics in drug product development



Case study late development

BCS class II compound

Neutral species in physiological pH range

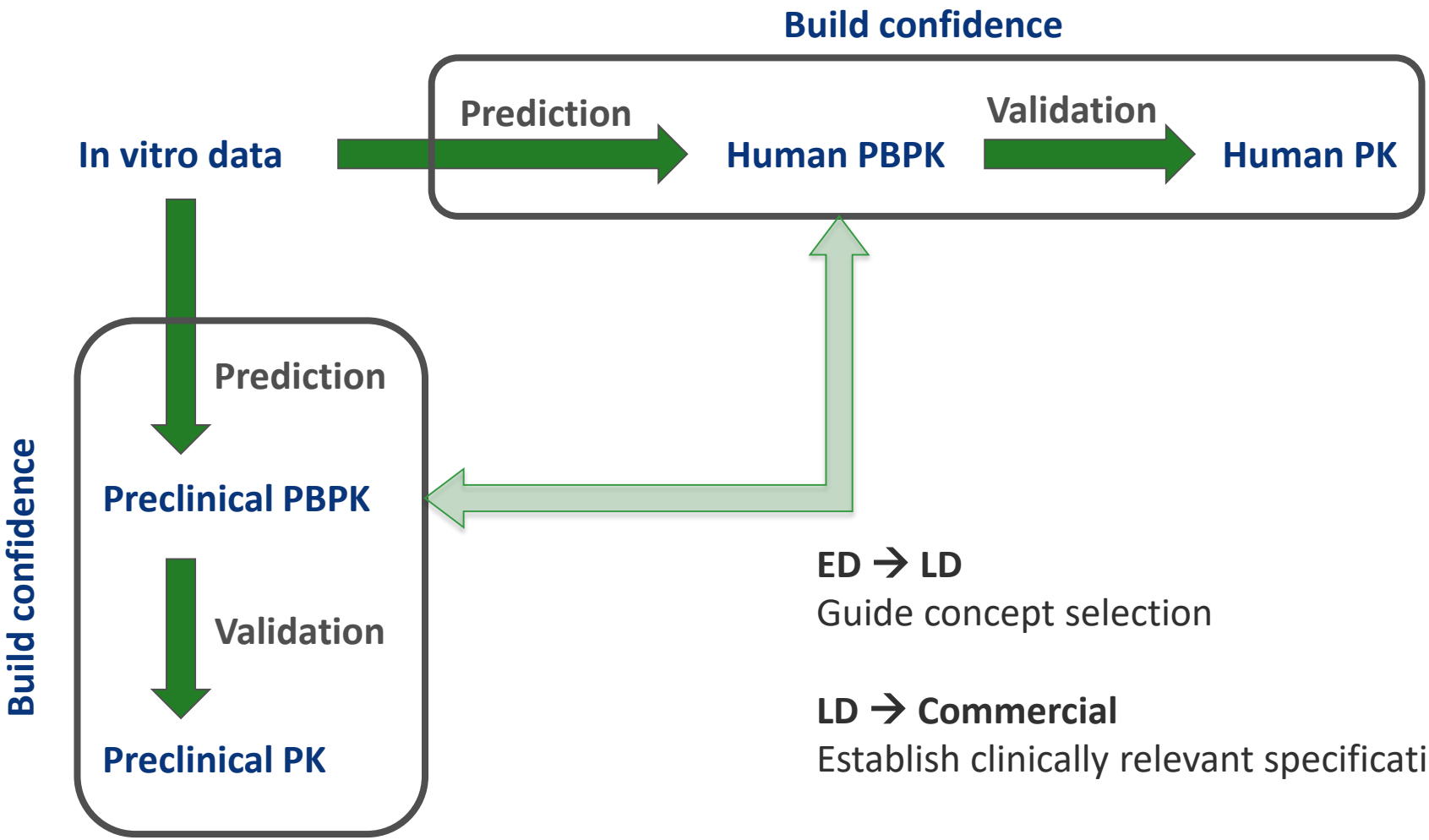
Oral solid development

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

Biopharmaceutics approach

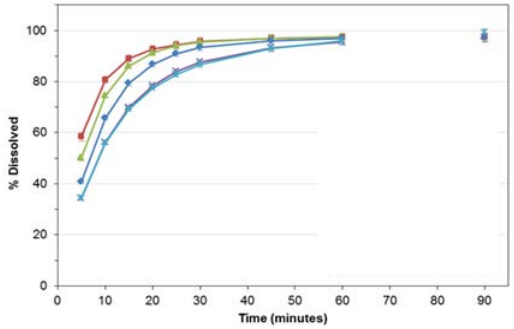


ED → LD
Guide concept selection

LD → Commercial
Establish clinically relevant specifications

CRC strategy workflow

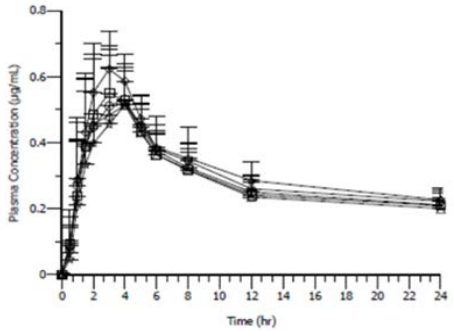
Step 2: Develop CQA Dissolution Test(s) using tablets with highest risk CQA identified in step 1



Step 1a: CA analysis
API properties
Formulation
Process

Step 1b: Build PBPK Model

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

Defining model parameters

- All input parameters considered to be key
  - ✓ Experimentally determined
    - ✓ pKa + LogP
    - ✓ Solubility + biorelevant solubility
  - ✓ Derived from analytical data
    - ✓ **Z-factor**
    - ✓ **Precipitation time**
    - ✓ **Disposition parameters**
    - ✓ **Permeability**

PARAMETER SENSITIVITY ANALYSIS (PSA)

uncertainty assessment

population simulations

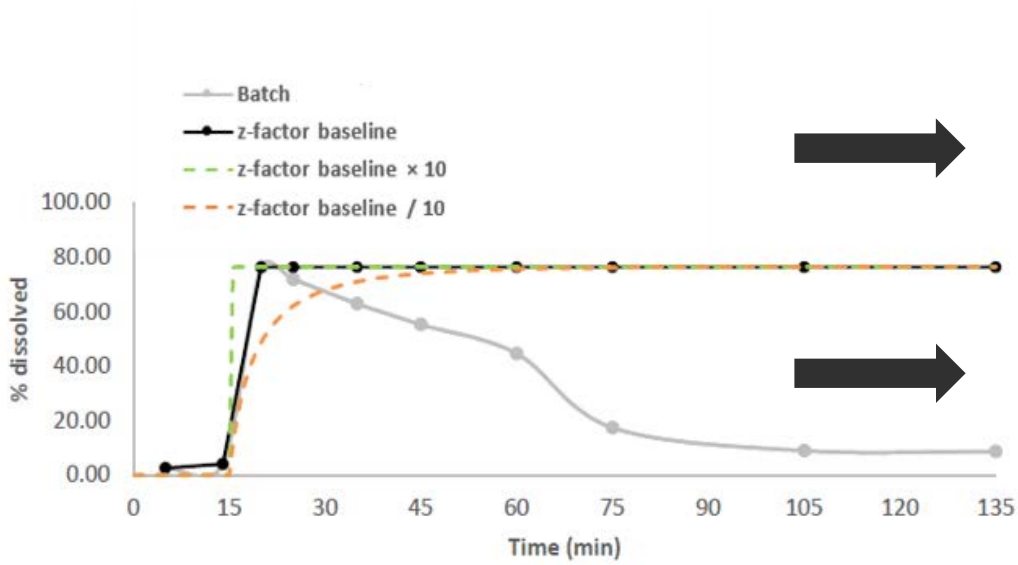
- Avoid parameter estimation
- Avoid optimization to improve fit

Uncertainty assessment

- Key biopharmaceutical parameters
- Fitted to experimental results

→ **z-factor**

→ **Precipitation time**

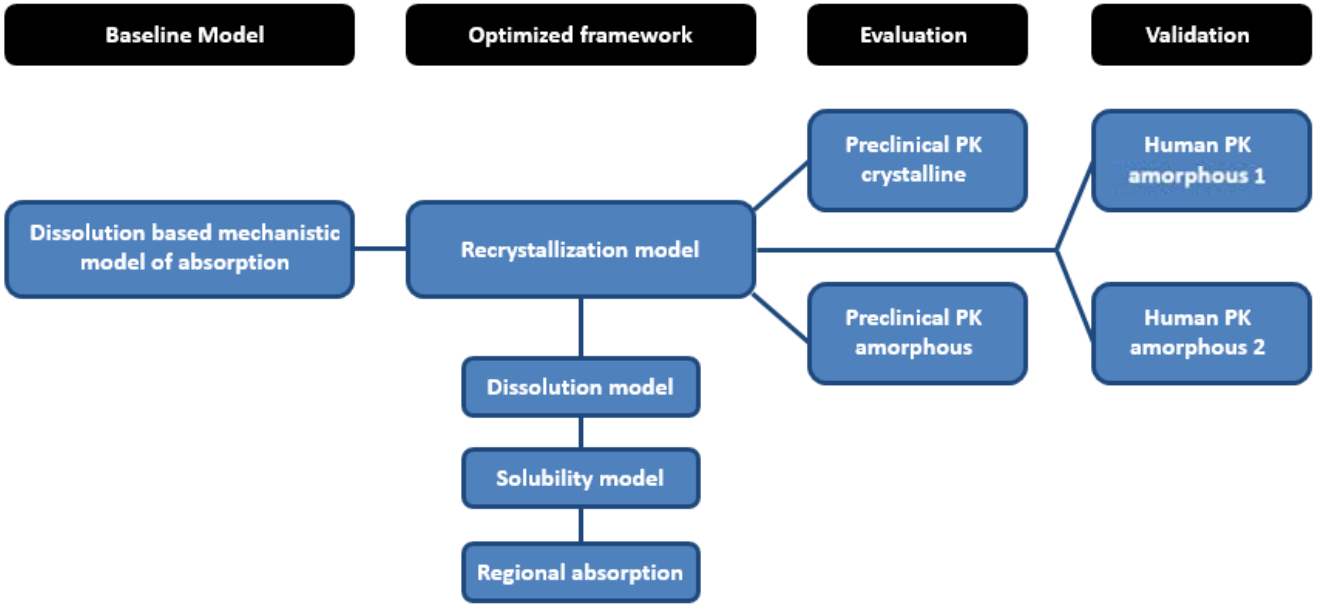


→ **PSA on 10-fold range in z-factor**

→ **PSA from instant to no precipitation**

Both PSA result in less than 5% influence on C_{max} / $AUC_{0\text{-}168h}$

Mechanistic understanding



Understand the mechanism
In vitro experiments
In vivo data
In silico algorithms

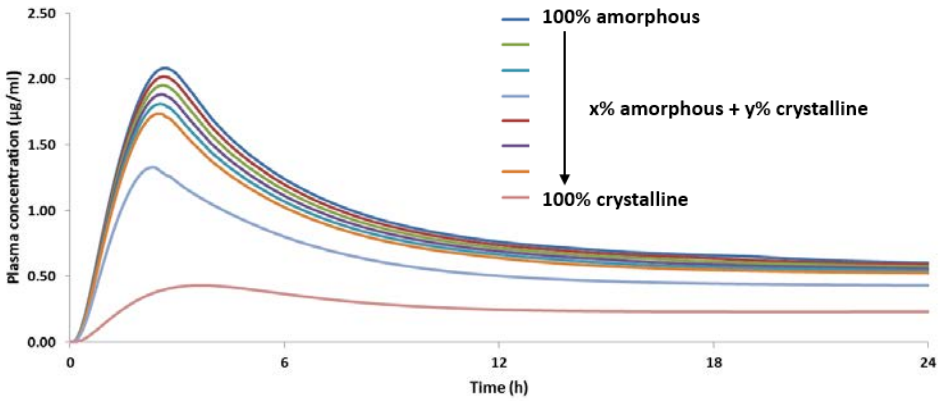
Implement the mechanism
Clever use of
existing framework

Evaluate the approach
Does it work for
the intended purpose?

Validate the approach
Is it predictive for the
in vivo data available

Increase confidence in results

Mean simulations



Population simulations

Include variability and uncertainty

Cross-over design

Multiple trials

Include intra-subject variability

Statistics

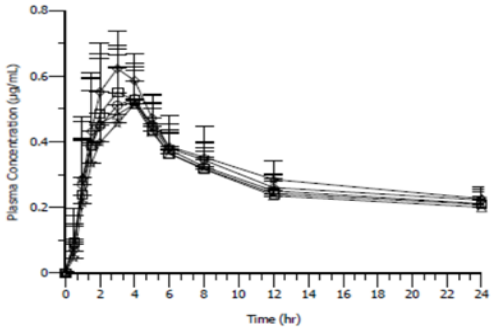
Virtual bioequivalence trials																
Virtual Trial Number	w % crystallinity				x % crystallinity				y % crystallinity				z % crystallinity			
	C_{max}		AUC_{0-168h}		C_{max}		AUC_{0-168h}		C_{max}		AUC_{0-168h}		C_{max}		AUC_{0-168h}	
	90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		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

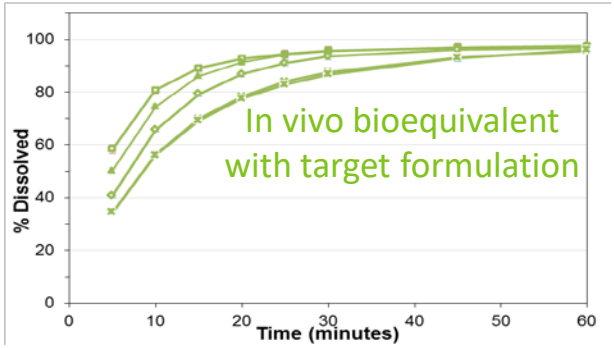
Safe space approach

CRC workflow in practice

Critical Quality Attribute 1

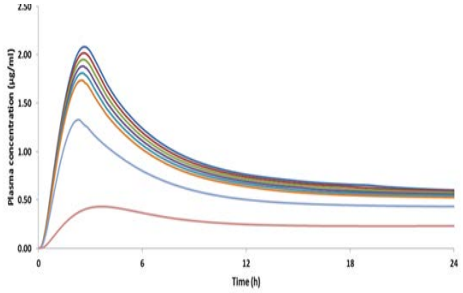
Human BA Trial



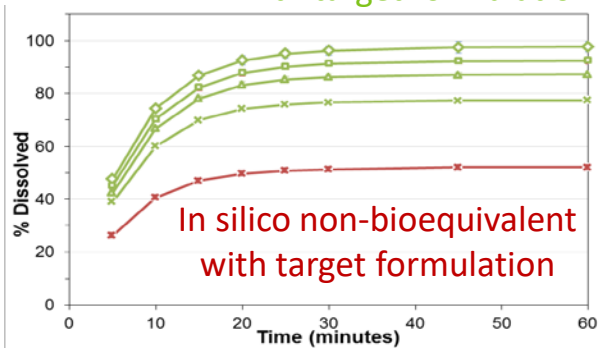


Polymorphic purity

Validated PBPK Model



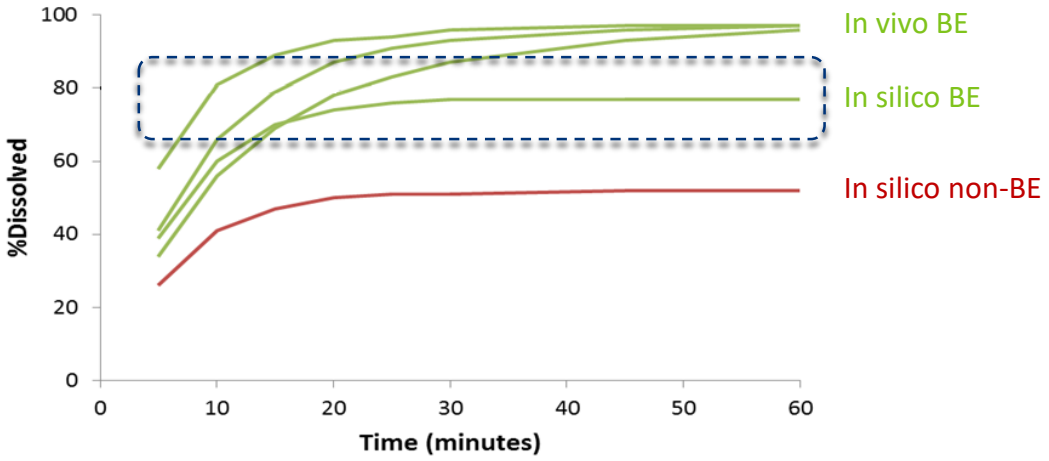
In silico bioequivalent
with target formulation



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

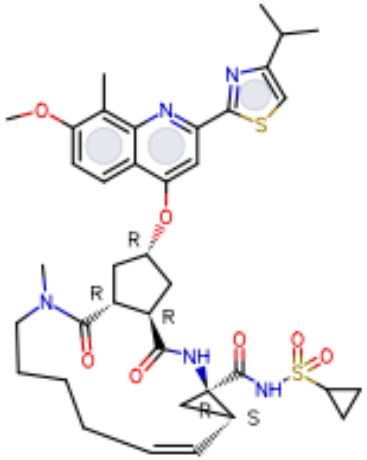


Scope of clinically relevant specifications not limited to QC dissolution

clinically relevant acceptance criteria for polymorphic purity

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

Case study continuous improvement



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

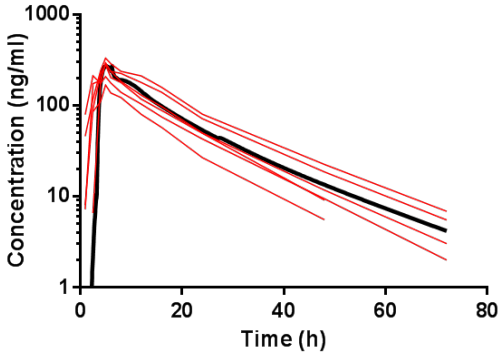
Include dissolution based mechanistic absorption model

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

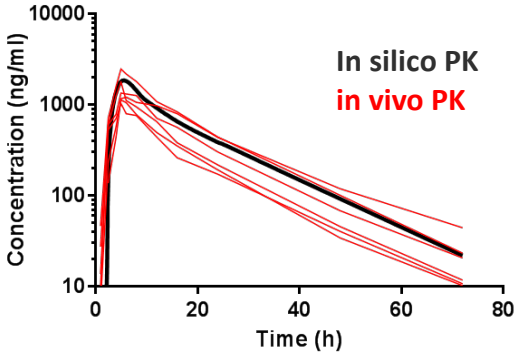
Oral dose predictions

Plasma concentration-time profiles

50 mg



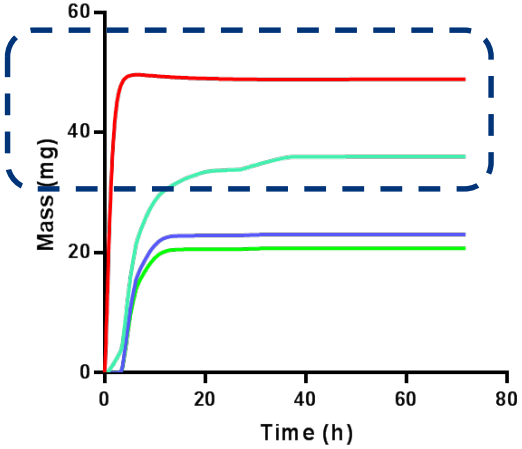
150 mg

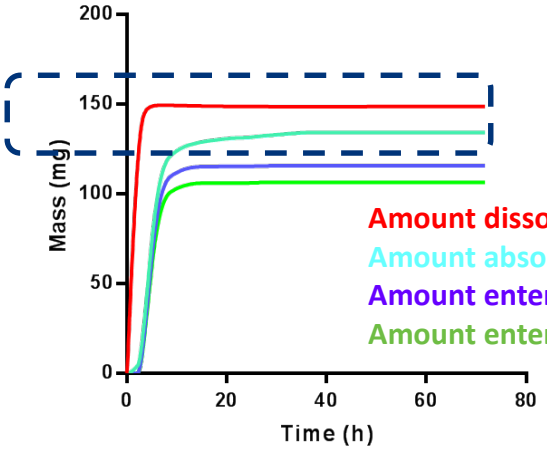


Relative importance of permeation rate

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

Absorption and dissolution curves

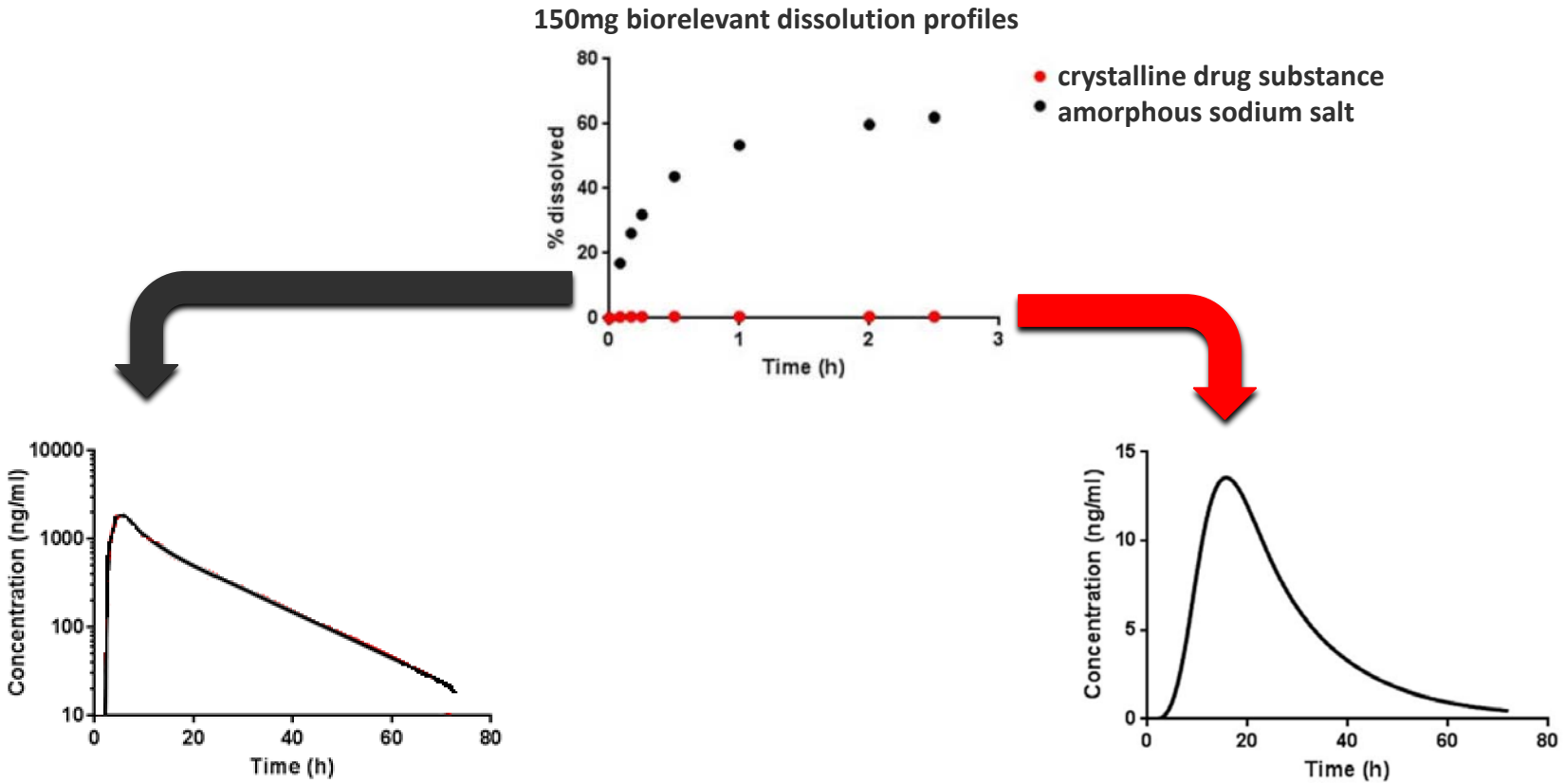




https://doi.org/10.1208/s12248-019-0292-3

Validation

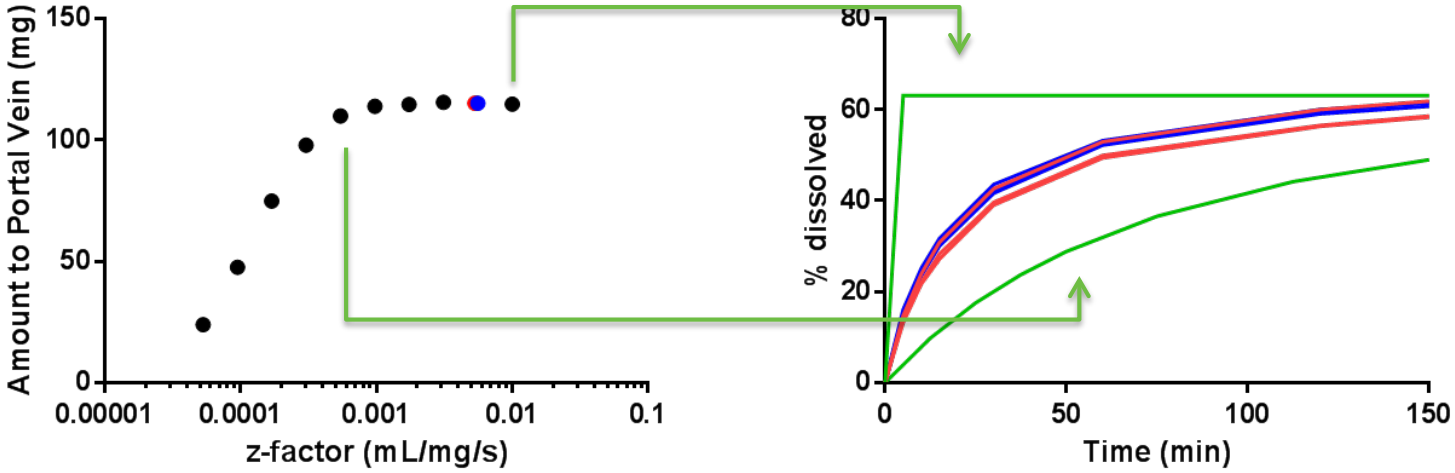
Can the model differentiate between a bioequivalent and non-bioequivalent formulation?



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

Biopharmaceutics / MAM to understand in vivo behavior

- Absorption rate limiting steps
- Guidance in the formulation development process
- Derisk BA/BE trials
- Criticallity assessment of CQA's / CPP's / CMA's
- Polymorphic purity
- Quality Control Dissolution specification
- ...

Clinically Relevant Specifications

Major progress in the last years

- Science (OrBiTo, UNGAP, User groups, publications, algorithm qualification...)
- Regulators (Guidelines, acceptability...)

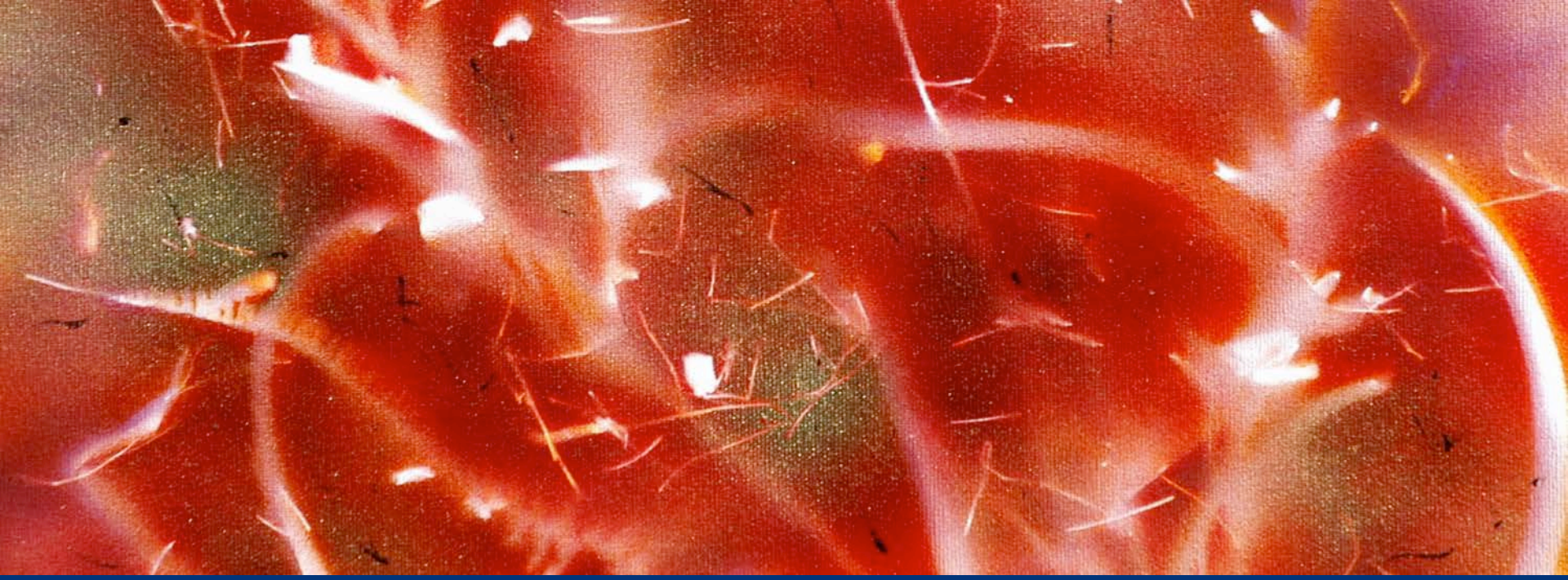
Room for improvement

- In vitro / in silico tools
- In vivo characterization
- Complexity...

Acknowledgements

An Van Den Bergh

Johannes Moes



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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