PBBM Case Study 4

EMD Compound A

From Merck Healthcare KGaA, Darmstadt, Germany

Luiza Novaes Borges
Health Surveilance and Regulation Specialist

ANVISA
Agência Nacional de Vigilância Sanitária

Disclamer

This presentation reflects the views of the speaker and should not be construed to represent ANVISA's views or policies.

ANVISA has reviewed EMD Compound A case data (Report, Version 3.0 – Jun, 2022) only under the scope of the PBBM colaborative study.

Data and considerations discussed with company (Nov/2022) were also included as appropriate.

A – Identification of model objective

Q1	**Does the report clearly describe the background and the intended model application/ objective? (i.e.: context of use, question of interest?)**

- EMD Compound A is a hydrochloride salt
- BCS IV (low solubility, low permeability)
- Used for the treatment of certain cancers
- Posology: 500 mg once daily, under fed conditions
- To increase exposure of EMD Compound A, it contains the drug in its micronized form.

REGULATORY QUESTION: "Does the Agency agree that the acceptance criteria for the drug substance particle size distribution (D10, D50, D90) of EMD Compound A can be justified on the basis of the PBBM approach, or does the PBBM only qualify for supportive data?"

A – Identification of model objective

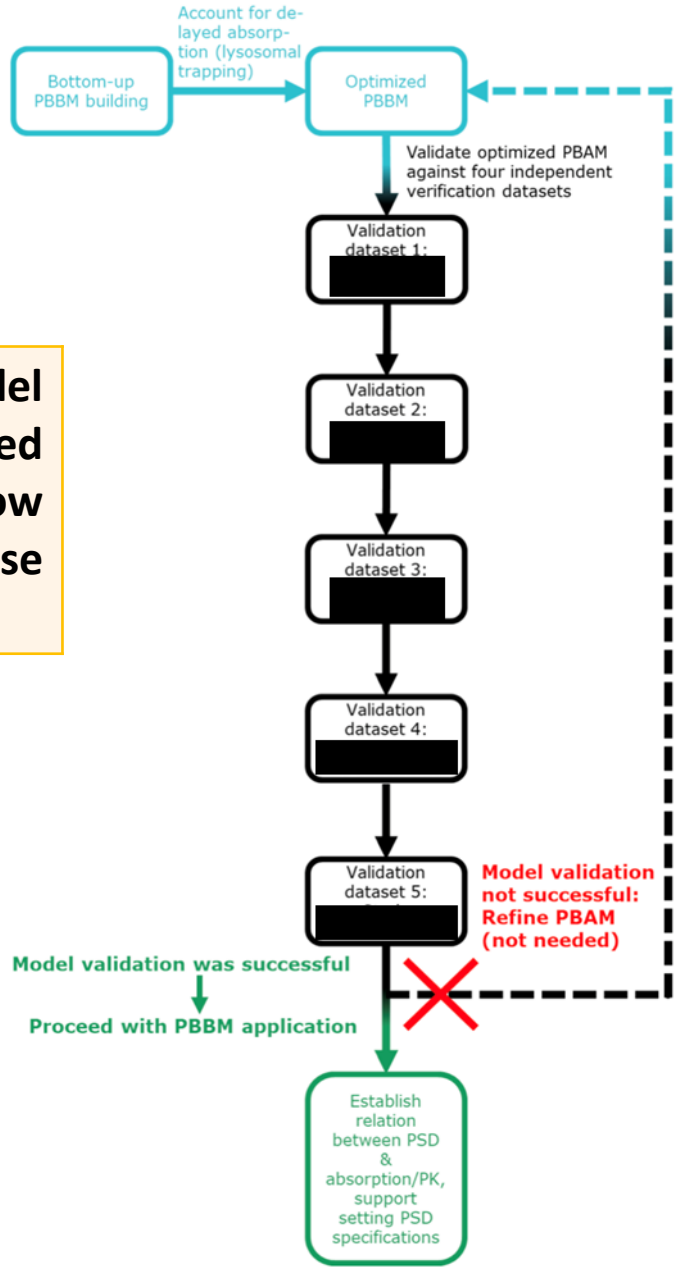
	Proposed specifications based on PBBM*
D10	1.5-6.0µm
D50	6.5-26µm
D90	16-64µm
*Based on 500mg TF2 formulation data	

- Current specs: results of clinical studies, DS batch release data and manufacturability of the drug product
- Formulation used as reference in PBBM: TF2
- Market formulation: TF3
- TF2 and TF3 formulations are bioequivalent (BE study was conducted)
- Manufacturing process: dry granulation, followed by tablet and coating.

Further details on TF2 and TF3 formulations and manufacturing differences would be informative.

B – Model Development

Q2	**Is the strategy on model development described (preferably through flow chart or in step wise write) up?**



Which clinical studies were used for model building?

- IV formulation and solution studies
- Solid formulation (tablet or capsule) were not used for model building (for PSA and validation)

Batches used for parameterizing API and formulation for model building described on the report annex

Figure 2 Overview of modeling strategy. Light blue indicates model building, black indicates model validation, and green indicates model application. The red x indicates that model validation was successful, and that no further refinement was necessary (after initial optimization regarding lysosomal trapping). For more information, please see main text.

B – Model Development

Q4	Is PBBM model structure explained?

Fit-for-purpose model: mechanistic absorption model (ACAT) and 2-compartments disposition

- IV bolus of tracer dose of 14C-labelled EMD Compound A to 6 healthy volunteers with a mean body weight of 81.6Kg

Table 6 Goodness of fit for the two- and the three-compartmental PK model. Based on the Akaike Information Criterion and the Schwarz Criterion, the goodness of fit is slightly better for the two-compartmental model.

	One compartment	Two compartments	Three compartments
Akaike Information Criterion (AIC)	- 12.3662	- 83.0899	- 82.5266
Schwarz Criterion (SC)	- 10.0101	- 78.3776	- 75.4583
R^2	0.4407	0.9949	0.9957

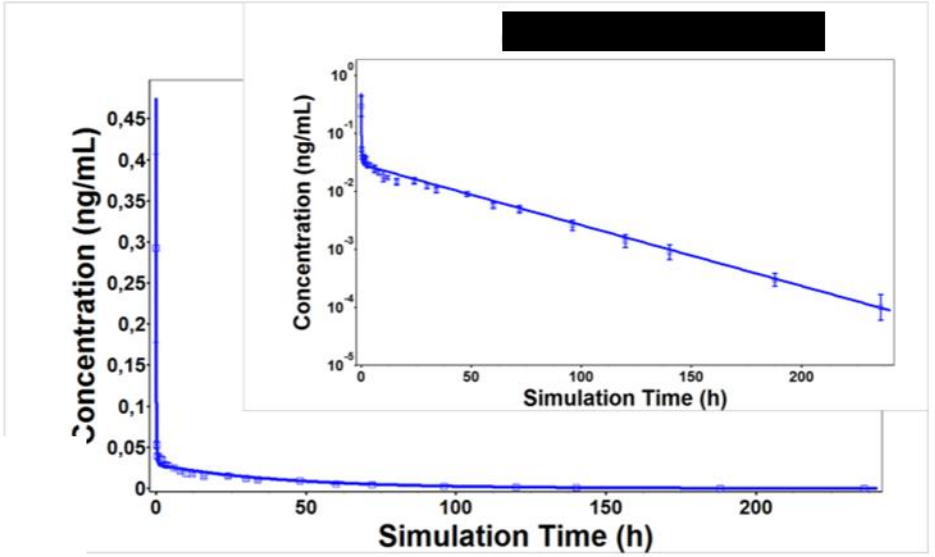


Figure 7 Observed (blue symbols; mean values ± S.D.) [3] *vs.* fitted (solid line) plasma concentration – time profile following intravenous administration of [redacted] to six healthy volunteers. The insert depicts the same plot on a semi-logarithmic scale.

Table 7 Post-absorptive disposition parameters applied to the [redacted] PBBM.

Parameter	Value
CL [L/h/kg]	0.142
Vc [L/kg]	0.376
K12 [1/h]	9.969
K21 [1/h]	0.721
V2 [L/kg]	5.196

CL Clearance; *K* Distribution rate constant; *V* Volume of distribution per compartment

B – Model Development

Q4	Is PBBM model structure explained?	Q9	Are the model assumptions clearly stated?

Pre-systemic metabolism: % of hepatic FPE (obtained based on calculated IV clearance / liver blood flow as system default fed or fasted) + % of intestinal FPE (arbitrarily attributed as half of hepatic FPE).

	Hepatic FPE	Intestinal FPE
Fed	10%	5%
Fasted	12%	6%

Which is known about EMD Compound A elimination and gut metabolism based on *in vitro* data?

- Total clearance can be considered as equal to the hepatic clearance (urinary clearance <14%)
- Mass balance study: Fa 85%, F = 72%. With BA = Fa * Fg * Fh, and assuming a Fg of 95% and Fh of 90%, BA and Fa can be correctly back calculated.
- Limited contribution to CYP3A to EMD Compound A (DDI itraconazol), the 5% gut metabolism are deemed to be reasonable, although arbitrary/ not mechanistic.
- Pgp efflux transport were not considered in the model (expected to be saturated at 500mg and no *in vivo* impact based on DDI results).

Parameter sensitivity analyses (PSA) would be informative.

B – Model Development

Q5	Are all drug model parameters enlisted, referenced, and justified where needed?
Q9	Are the model assumptions clearly stated?

Pharmacokinetics tab		
PK model	Compartmental	See 2.3.2
Body weight [kg]	Various values	See Table 15
B/P ratio	1	GastroPlus default
Plasma Fup [%]	2	[redacted]
Small intestinal FPE [%]	Various values	See Table 15 and 2.3.2
Hepatic FPE [%]	Various values	See Table 15 and 2.3.2
Renal Clearance [L/h/kg]	0	GastroPlus default
CL [L/h/kg]	0.142	See 2.3.2
Vc [L/kg]	0.376	See 2.3.2
T1/2 [h]	[redacted]	Calculated by GastroPlus
K12 [1/h]	9.969	See 2.3.2
K21 [1/h]	0.721	See 2.3.2
V2 [L/kg]	5.196	Calculated by GastroPlus
Enzymes, Vmax SF	1 (gut and liver)	GastroPlus default
Enzymes, Km SF	1 (gut and liver)	GastroPlus default
Gut transporters, influx Vmax SF	1 (apical and basolateral)	GastroPlus default
Gut transporters, influx Km SF	1 (apical and basolateral)	GastroPlus default
Gut transporters, efflux Vmax SF	1 (apical and basolateral)	GastroPlus default
Gut transporters, efflux Km SF	1 (apical and basolateral)	GastroPlus default

Gut physiology tab		
Excrete all un-absorbed drug at the end of transit time	Off	GastroPlus default
Zero-order gastric emptying	Off	GastroPlus default
Physiology	Human – physiological – fasted Human – physiological – fed	Default physiologies
C1	0.06944	GastroPlus default
C2	0.43028	GastroPlus default
C3	0.12147	GastroPlus default
C4	0.46632	GastroPlus default
ASF model	Opt – logD Model SA/V 6.1	GastroPlus default
Qh [L/min]	2 (fed); 1.5 (fasted)	GastroPlus default
Percent fluid in SI	40	GastroPlus default
Percent fluid in colon	10	GastroPlus default

B – Model Development

Table 16 Summary of input parameters used to build the GastroPlus model for [redacted]

Parameter	Value or setting	Comment
Compound tab		
Molecular weight [g/mol]	[redacted]	From molecular structure
Log D (@ pH)	2 – 3 (pH 7.4)	[13]
pK_a (pK_a sub-tab)	Approx. 4 (base)	See 2.3.1.2
Solubility factor (pK_a sub-tab)	2.562	See 2.3.1.2
Human Peff [x 10^{-4} cm/s]	1.74	See 2.3.1.5
Dose volume [mL]	250	Assumed volume of a glass of water
Reference solubility [mg/mL] (@ pH)	0.004 @ pH 6.8 (100 mM NaCl)	See Table 1
pH-dependent solubility [mg/mL]	Various values	See Table 1
Precipitation time [s]	900	GastroPlus default; see 2.3.1.3
lean particle density [g/mL]	1.2	GastroPlus default
Mean particle radius [µm]	Various values	See Table 3 and Table 15
Particle shape factor	1	GastroPlus default
Formulation	IV: Bolus; IR: Solution; IR: Tablet; IR: Capsule	See Table 15
Diffusion coefficient [cm^2/s]	[redacted]	GastroPlus prediction, based on molecular weight
FaSSIF solubility [mg/mL] (Biorelevant solubilities sub-tab)	0.043	See Table 1
FeSSIF solubility [mg/mL] (Biorelevant solubilities sub-tab)	0.319	See Table 1
Bile salt solubilization ratio (Biorelevant solubilities sub-tab)	254000	See 2.3.1.2
Adjust solubility for bile salt effect (Biorelevant solubilities sub-tab)	Yes	GastroPlus default
Adjust diff coeff for bile salt effect (Biorelevant solubilities sub-tab)	Yes	GastroPlus default
Dissolution model (Biorelevant solubilities sub-tab)	Johnson	GastroPlus default
Adjust solubility for nanoparticle effect (Biorelevant solubilities sub-tab)	0.5	GastroPlus default
Interf tension (Biorelevant solubilities sub-tab)	0.013	GastroPlus default
Diffusion layer thickness (Biorelevant solubilities sub-tab)	Adjust with changing radius up to maximum	GastroPlus default
Maximum diff layer thick [µm] (Biorelevant solubilities sub-tab)	30	GastroPlus default
Enzyme table	No entries	Not used
Transporter table	No entries	Not used

B – Model Development

SOLUBILITY:

- Hydrochloride hydrate salt: decreased solubility in the presence of chloride ion.
- Chloride ions ubiquitous in human body, concentration approximately 90mM and 180mM in jejunal fluids*
- Deemed more biorelevant to directly apply solubility values measured in presence with 100mM NaCl

* Fuchs, A., & Dressman, J. B. (2014). doi:10.1002/jps.24183

Media without chloride: EMD Compound A is a low-solubility drug and has pH-dependent solubility (slightly soluble at a pH 4.5 and practically insoluble at pH 1.2 and 7.4

Table 1 Biorelevant and pH-dependent solubility (24 h measurements) of [redacted] in the presence of chloride ions [7]. The solubility in media devoid of chloride ions is approximately 0.87 mg/mL (phosphoric acid pH 1.0), 0.77 mg/mL (acetate buffer pH 4.5), and 0.038 mg/mL (SIF pH 6.8) [7] and thus markedly higher compared to media containing physiological amounts of chloride ions.

Medium, *pH*	Chloride concentration* [mM]	Solubility [mg/mL]
HCl pH 1.0	100	0.011
Acetate buffer pH 4.5	100	0.006
SIF pH 6.8	100	0.004
FaSSIF	106	0.043
FeSSIF	203	0.319

FaSSIF Fasted State Simulated Intestinal Fluid; *FeSSIF* Fed State Simulated Intestinal Fluid; *SIF* Simulated Intestinal Fluid

The approach for modeling common ion effect is appropriate/ justified?

B – Model Development

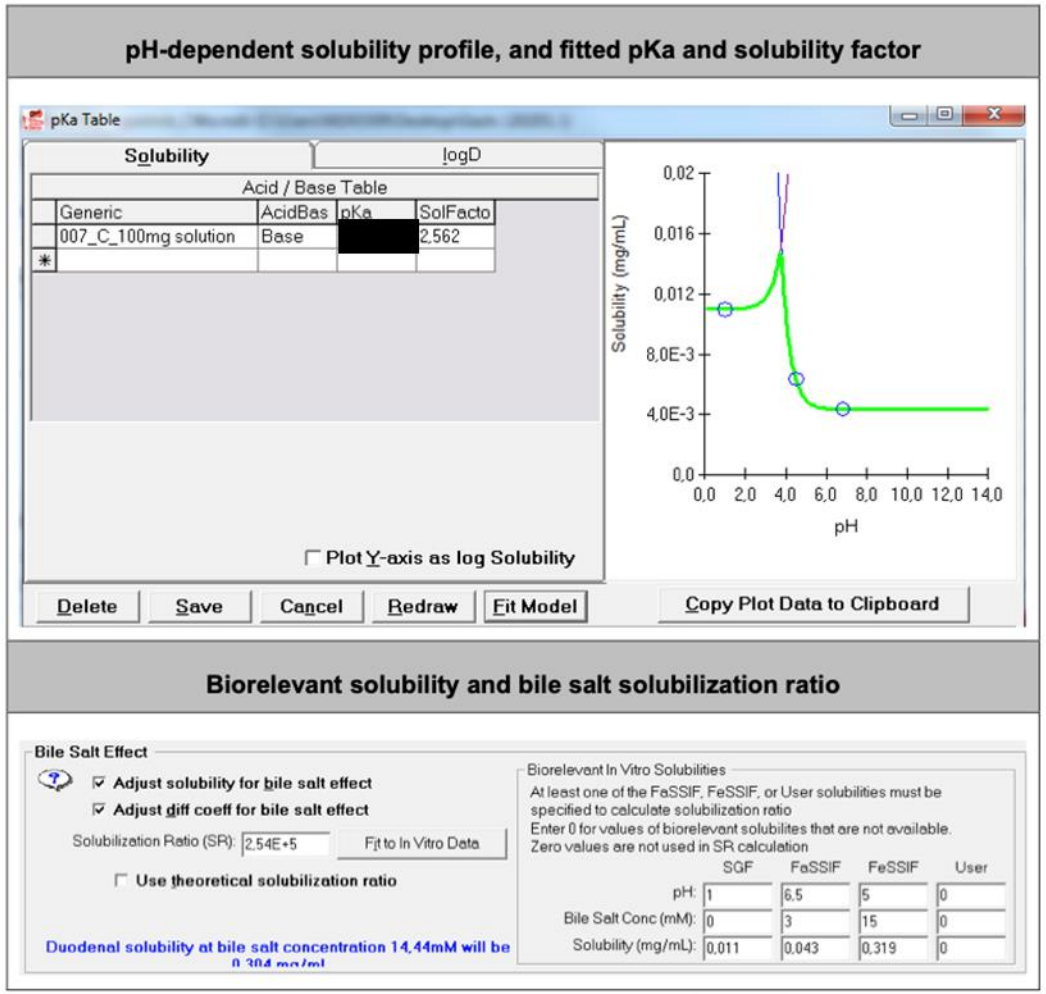


Figure 3 Upper panel: pH-dependent solubility profile of [redacted]. The calculated profile (green curve) was derived by fitting the pK_a and the solubility factor to the measured solubility of [redacted] (blue symbols), using GastroPlus' "fit model" functionality within the pK_a table set-up. Lower panel: Calculation of the bile salt solubilization ratio, based on the drug's FaSSIF and FeSSIF solubility.

PKA AND SOLUBILITY FACTOR:

- pKa value **was not obtained experimentally**, instead it was fitted to match the measured in vitro solubility in the pH range between pH 1.0 and 6.8
- The resulting pKa value **was approx. 4** and solubility factor 2.562
- pKa predicted by ADMET predictor **was approx. 9**

Would experimentally measured pKa be necessary?

Could a PSA be supportive?

B – Model Development

PERMEABILITY:

- Papp from Caco2 experiment (using cyclosporine A, Pgp inhibitor)
- GastroPlus built-in Papp-Peff conversion tool was used
- Peff estimated: **1.74 x 10^{-4}cm/s**

Table 4 Apparent permeability of [redacted] and reference compounds in Caco2 cells in the presence of the p-glycoprotein inhibitor cyclosporine A [13].

Compound	Permeability classification	Papp [x 10^{-6} cm/s] A → B	Papp [x 10^{-6} cm/s] B → A	Geometric mean [x 10^{-6} cm/s]
[redacted]	N.c.	[redacted]		
Atenolol	Low	0.17	0.28	0.22
Pindolol	High	20.9	16.7	18.7
Propranolol	High	33.9	18.3	24.9

A Apical; *B* Basolateral; *N.c.* Not classified; *Papp* Apparent permeability

Table 5 Parameter sensitivity analysis (PSA) for Peff. The PSA was conducted on the 100 mg oral solution (90 mg free base equivalents) administered in study [redacted] [3] and does not yet account for lysosomal trapping (see below).

Peff [x	AUC(0-144) [ng*h/mL]		Cmax [ng/mL]			Tmax [h]			% absorbed	
		io	Pred	Obs[1]	Ratio	Pred	Obs[1]	Ratio	Pred	Obs
3.38	6621		1.29	173		1.43	1.7		0.28	100	
1.74[2]	6611		1.29	158		1.31	2.5		0.42	100	
1.0	6325	5117	1.24	140	121	1.16	3.4	6	0.56	96	N.a., yet complete absorption assumed
0.5	4992		0.98	105		0.87	4.3		0.72	76	
0.1	1606		0.31	32		0.26	7		1.17	24	

Estimated Peff is adequate or would PSA support adopting a lower value?

B – Model Development

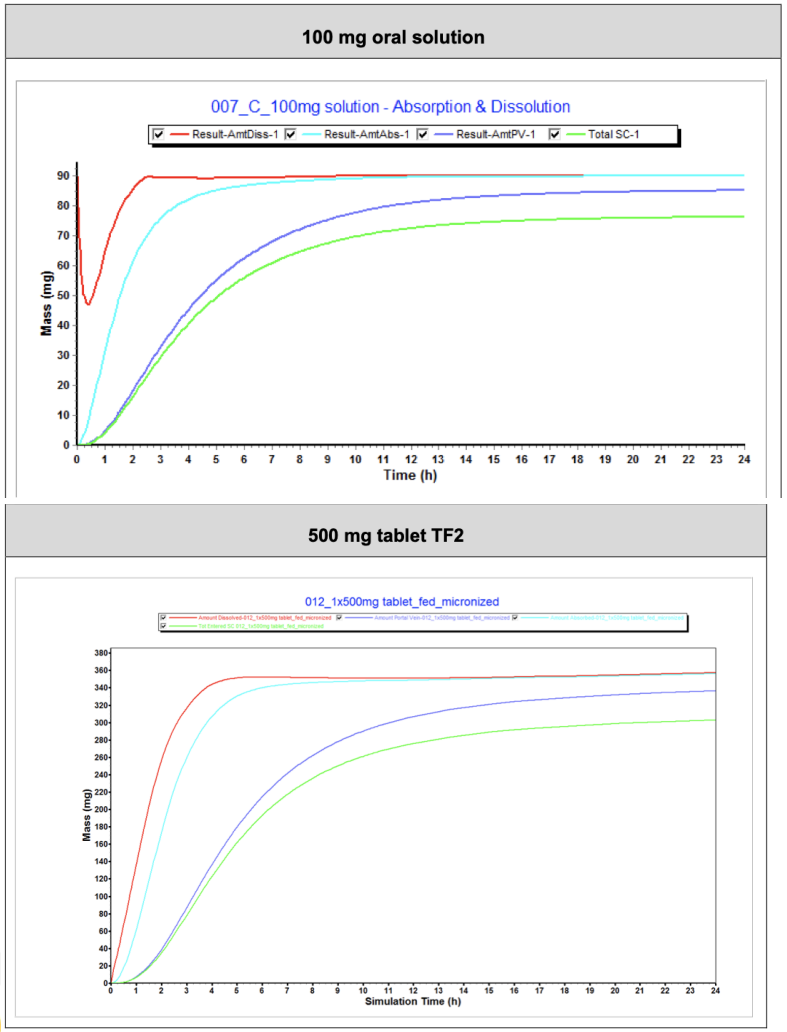


Figure 4 Predicted luminal dissolution (red line), absorption into enterocytes (light blue line), absorption into portal vein (dark blue line), and total systemic availability (green line) for the 100 mg oral solution (upper panel) and the 500 mg TF2 (lower panel) in fed state humans. Please note that, with a salt factor of 0.9004,

PRECIPITATION:

predictions in fed state with precipitation time default (900s) for OS 100mg and TF2 tablet 500mg

PSA varing precipitation time

Based on drug properties, experimental precipitation results would be informative.

Table 2 Predicted absorption, absolute bioavailability, AUC(inf), Cmax, and tmax of [redacted] when administered as 100 mg (90 mg free base equivalents) oral solution (upper part) and 500 mg (450 mg free base equivalents) TF2 (lower part) to fed humans. The precipitation time was varied between 90 s and 9000 s.

Predicted PK parameter, 100 mg oral solution					
Precipitation time [s]	AUC(inf) [ng*h/mL]	Cmax [ng/mL]	Tmax [h]	% absorbed	% bioavailable
90	6823	131	9.4	100	86
900	6824	131	9.4	100	86
9000	6826	132	9.1	100	86

Predicted PK parameter, 500 mg TF2					
Precipitation time [s]	AUC(inf) [ng*h/mL]	Cmax [ng/mL]	Tmax [h]	% absorbed	% bioavailable
90	27120	490	10.6	80	69
900	27500	498	10.6	81	70
9000	28580	522	10.5	85	72

AUC Area under the plasma concentration – time curve; *Cmax* Maximum plasma concentration; *Inf* Infinity; *TF2* Tablet formulation 2; *tmax* Time to reach the maximum plasma concentration

B – Model Development

LYSOSSOMAL TRAPPING:

For 100mg oral solution:

- Observed $T_{máx}$ for OS: 6h
- Predicted with bottom-up PBBM: 2-3h
- Dissolution, precipitation and low passive permeability excluded as root causes
- Fraction unbound in enterocytes: fitted from 100% to 3% (fed simulations)

Based on drug properties (LogP and pKa), lysosomal trapping is expected.

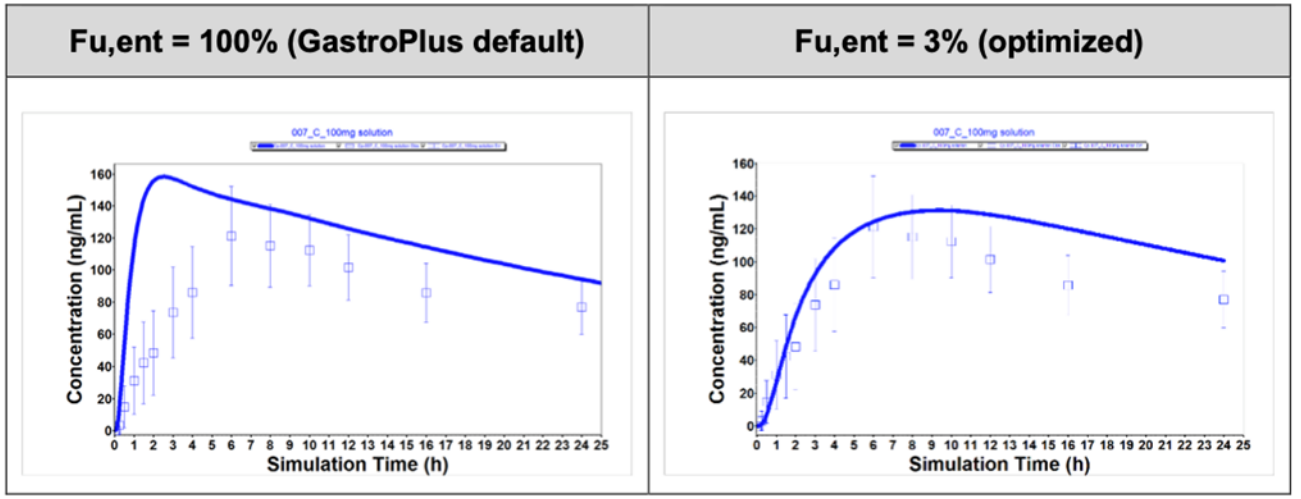


Figure 6 Predicted (solid line) and observed (symbols mean ± S.D., n = 15) [3] plasma concentration – time profile of [redacted] 100 mg oral solution (90 mg free base equivalents), assuming 100% (left panel) and 3% (right panel) unbound drug in the enterocytes.

Would a PSA of $f_{u,ent}$ be needed to justify the % chosen?

Which other factors could (partially) explain the late T_{max}?

B – Model Development

Q5	Are all drug model parameters enlisted, referenced, and justified where needed?
Q7	Is there acceptable justification for the approach selected for inputting dissolution data into the model (direct input vs. Z factor vs. P-PSD, etc.)
Q9	Are the model assumptions clearly stated?

Luminal dissolution:

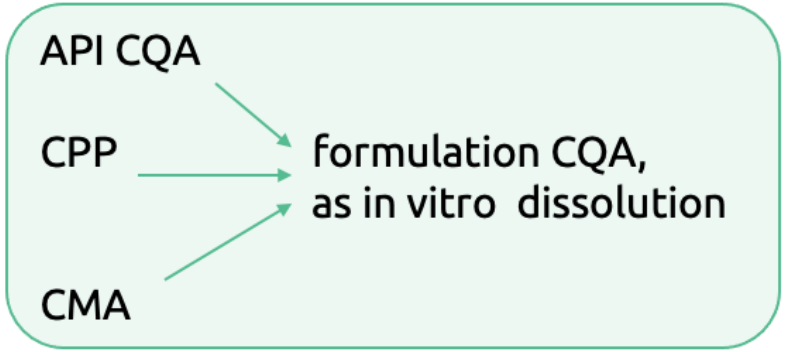
Johnson dissolution model (for oral solution used in model building)

and

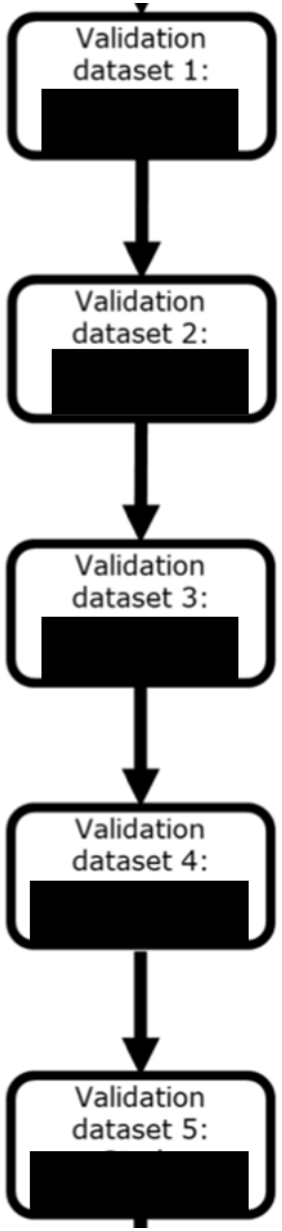
API PSD (d10, d50 and d90 values for tablets and capsules, used in model validation and application).

***In vitro* dissolution data of drug product were not incorporated in PBBM for solid oral formulations.**

Is this an acceptable approach?



C – Model Validation



First in human:
- Fed state, capsule, micronized, 30mg, 60mg, 100mg,130mg , 145mg, 175mg, 215mg, 300mg, 315mg, 400mg, 500mg, 700mg, 100mg, 1400mg
- Fed state, tablet, micronized, 500mg
- Fasted state, capsule, non-micronized, 30mg, 60mg, 115mg, 230mg

Food effect and relative BA:
- Fed and fasted state, both capsule and tablet, micronized, 30mg

Absolute and relative BA and mass balance:
-Fed state, tablet, fine micronized, 100mg
-Fed state, tablet, micronized, 100mg, 5x100mg
- Fed state, capsule, micronized, 500mg

Relative BA:
-Fed state, tablet, micronized, 5x100mg
-Fed state, tablet, micronized, 500mg (TF2)

BE TF3 vs. TF2 and food effect TF3 and TF2:
- Fed state, tablet, micronized, 500mg (TF2)
- Fasted, tablet, micronized, 500mg (TF2)
- Fed state, tablet, micronized, 2x250mg (TF3)

Q10	Is the virtual clinical trial or single simulation appropriate and does model analysis provide simulation design details?

Simulation set-up:

- Single individual: no population simulations or vBE studies conducted
- Simulation length: matched the respective clinical study (24h-504h, long t1/2)
- Prandial state: fed or fasted using default Gastroplus physiologies

Population simulations and vBE comparison to the reference PK dataset (500 mg TF2) would be necessary to support intended model application.

A non-BE study/ arm would be needed?

C – Model Validation

Table 11 Model validation: Predicted *vs.* observed PK parameters (study [redacted] Observed data is geometric mean (AUC, Cmax) and median (tmax), respectively. Color code: Prediction is within ± 25% (dark green) or 2-fold (light green) of the respective observed PK parameter.

Dose [mg]	AUC(0-inf)[1] [ng*h/mL]			Cmax [ng/mL]			Tmax [h]			Pred % absorbed	Pred % bioavailable
	Pred	Obs	Ratio	Pred	Obs	Ratio	Pred	Obs	Ratio		
500[2], T,*,+	27500	25710	1.07	498	463	1.08	10.6	8	1.33	81	70
5 x 100, T,*,+	28420	26990	1.05	516	486	1.06	10.5	8	1.31	84	72

Company conclusion on validation:

Validation dataset covered relevant doses (100mg, 250mg and 500mg), particle size (micronized) and prandial state (fed).

PK of the commercial formulation TF3 was predicted well.

Table 12 Model validation: Predicted vs. observed PK parameters (study [redacted] [5]. Observed data is geometric mean (AUC, Cmax) and median (tmax), respectively. Color code: Prediction is within ± 25% (dark green) or 2-fold (light green) of the respective observed PK parameter.

Dose [mg]	AUC(0-inf)[1] [ng*h/mL]			Cmax [ng/mL]			Tmax [h]			Pred % absorbed	Pred % bioavailable
	Pred	Obs	Ratio	Pred	Obs	Ratio	Pred	Obs	Ratio		
500[2], T,*,-	9366	16728	0.56	146	253	0.58	12.2	14.1	0.87	29	24
2 x 250[3], T,*,-	10074	19316	0.52	159	288	0.52	12.1	12	1.01	31	26
500[4], T,*,+	27690	24443	1.13	502	476	1.05	10.6	12	0.88	82	70
500[4], T,*,-	9366	13037	0.72	146	199	0.73	12.2	24	0.51	29	24
2 x 250[5], T,*,+	29656	30118	0.99	542	559	0.97	10.4	8	1.30	75	88
2 x 250[5], T,*,-	10074	18447	0.55	159	280	0.57	12.1	12	1.01	31	26

T Tablet; + Fed; - Fasted; * Micronized drug

AUC Area under the plasma concentration – time curve; *Cmax* Maximum plasma concentration; *Inf* Infinity; *Obs* Observed; *Pred* Predicted; *tmax* Time to reach the maximum plasma concentration

[1] Table 15 in the Appendix provides more information about the respective simulation setups, incl. runtime of simulations

C – Model Validation

Q11	Does the analysis demonstrate that the proposed PBBM is appropriate for the modelling purpose or question asked for the drug product and study population and is robust enought to respond to perturbations in uncertain parameters?

Table 8 Model validation: Predicted *vs.* observed PK parameters (study [redacted]. Observed data is geometric mean (AUC, Cmax) and median (tmax), respectively. Color code: Prediction is within ± 25% (dark green), 2-fold (light green), or outside 2-fold (yellow) of the respective observed PK parameter.

Dose [mg]	AUC(0-t)[1] [ng*h/mL]			Cmax [ng/mL]			Tmax [h]			Pred % absorbed	Pred % bioavailable
	Pred	Obs	Ratio	Pred	Obs	Ratio	Pred	Obs	Ratio		
30, C,#,-	472	207	2.28	12	6	2.00	24.6	10	2.46	43	35
60, C,#,-	793	311	2.55	19	11	1.73	21.6	17	1.27	37	30
115, C,#,-	1230	745	1.65	30	22	1.36	17.8	33	0.54	30	24
115, C,#,+	2807	1324	2.12	76	37	2.05	12.7	24	0.53	59	51
230, C,#,-	929	517	1.80	46	29	1.59	15.5	8	1.93	19	15

C Capsule; *T* Tablet; + Fed; - Fasted; * Micronized drug; # Non-micronized drug

AUC Area under the plasma concentration – time curve; *Cmax* Maximum plasma concentration; *Obs* Observed; *Pred* Predicted; *tmax* Time to reach the maximum plasma concentration

[1] Table 15 in the Appendix provides more information about the respective simulation setups, incl. runtime of simulations

Graphical results of validation would be desired to all datasets.

Are the validation metrics and acceptance criteria adequate?

Should all validation datasets results comply with the more stringent acceptance criteria?

E – Model application

Q13	Does model analysis presente the results using the validated PBPK/PBBM to address the study question using tables, graphs, and text where appropriate?

Table 13 Particle size input (d_{10}, d_{50}, and d_{90}) used for the sensitivity analysis of [redacted] particle size. The measured particle size distribution from batch [redacted] served as input for the "baseline simulation" [10].

Condition	d_{10} [µm]	d_{50} [µm]	d_{90} [µm]
0.1 x [redacted]	0.3	1.3	3.2
0.3 x [redacted]	0.9	3.9	9.6
0.5 x [redacted]	1.5	6.5	16
0.75 x [redacted]	2.25	9.75	24
[redacted] (baseline simulation)	3	13	32
1.25 x [redacted]	3.75	16.25	40
1.5 x [redacted]	4.5	19.5	48
1.75 x [redacted]	5.25	22.75	56
2.0 x [redacted]	6	26	64

D Diameter

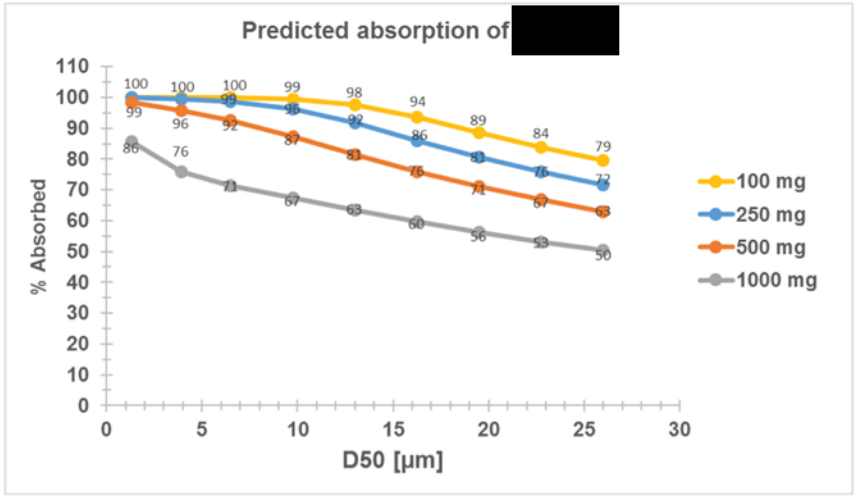
Applying 0.1-fold to 2-fold varied d10,d50, d90 of TF2 reference batch

Keeping the constant d10/d50/d90 ratio

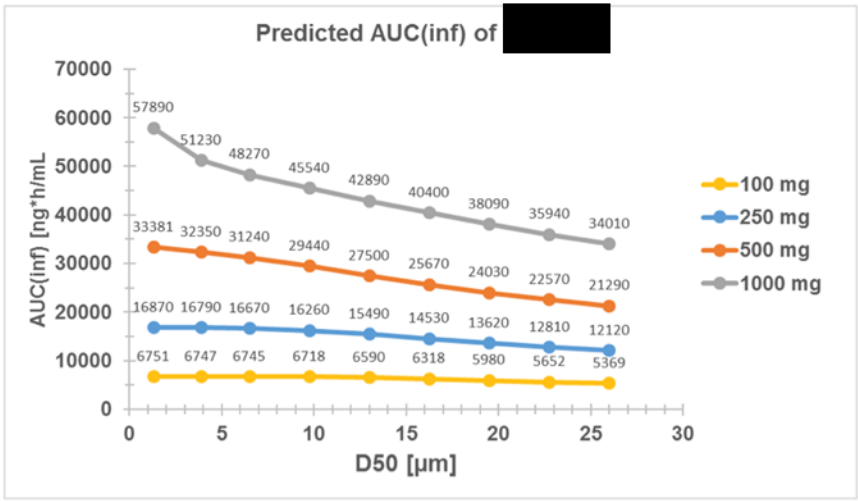
	d10	**d50**	**d90**
TF2: study of Dataset 4	3	13	32
TF2: study of Dataset 5	4.8	14	31
TF3: study of Dataset 5	3.8	11	23

E – Model application

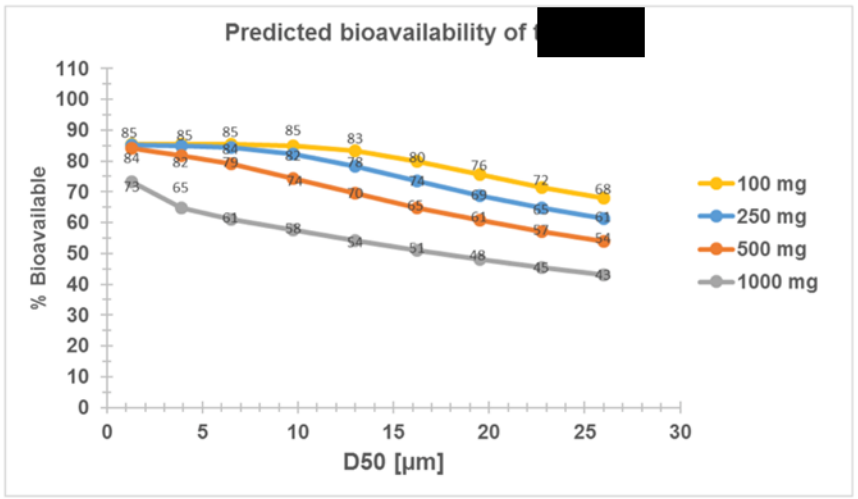
Predicted impact of particle size on the absorption of [redacted] in fed humans



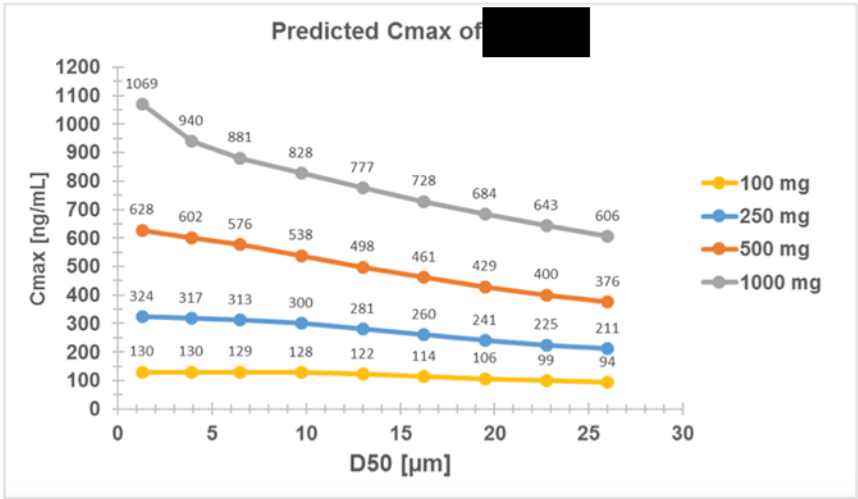
Predicted impact of particle size on the AUC(inf) of [redacted] in fed humans



Predicted impact of particle size on the bioavailability of [redacted] in fed humans



Predicted impact of particle size on the Cmax of [redacted] in fed humans



Model application aimed only for 500mg dose

Fed state

540h

E – Model application

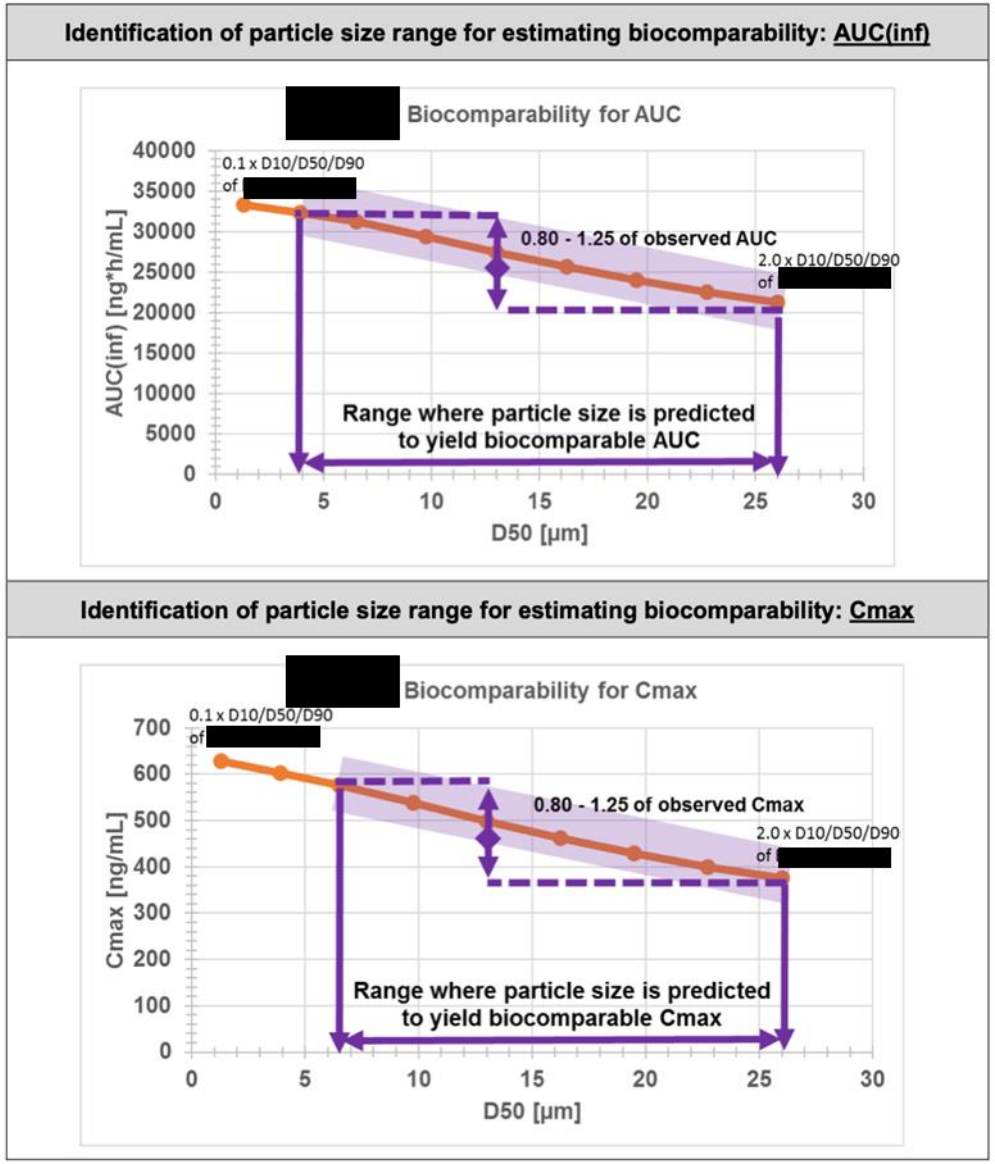


Figure 10 Identification of particle size range for estimating "biocomparability"

Table 14 Identification of particle size range for estimating biocomparability between a test and a reference product [4]. The upper and lower limits for d_{10}, d_{50}, and d_{90} were identified based on Figure 10.

	d_{10} [µm]		d_{50} [µm]		d_{90} [µm]	
	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit
AUC	0.9 (0.3 x [redacted])	6 (2.0 x [redacted])	3.9 (0.3 x [redacted])	26 (2.0 x [redacted])	9.6 (0.3 x [redacted])	64 (2.0 x [redacted])
Cmax	1.5 (0.5 x [redacted])	6 (2.0 x [redacted])	6.5 (0.5 x [redacted])	26 (2.0 x [redacted])	16 (0.5 x [redacted])	64 (2.0 x [redacted])
Overall	1.5 (0.5 x [redacted])	6 (2.0 x [redacted])	6.5 (0.5 x [redacted])	26 (2.0 x [redacted])	16 (0.5 x [redacted])	64 (2.0 x [redacted])

AUC Area under the plasma concentration – time curve; *Cmax* Maximum plasma concentration; *D* Diameter

Are results valid for TF3 formulation?

Or application is limited to reference TF2 formulation?

Summary & Conclusions

Q14	**For the intended application of PBBM, is there a need to define safe space and if yes, is safe space adequately demarcated?**
Q15	**Do the results support the intended model application and arguments (e.g., dissolution specification, biowaiver, etc) as proposed by the modelers?**

- Relevant uncertainties on key input parameters (mainly pKa, solubility, lysosomal trapping);
- Major concern on model development strategy (direct incorporation of API PSD instead of formulation attribute);
- Lack of variability on results due the use of single simulations during model validation and application;
- Results directly applicable only to TF2 PK results in study [10] and d10,d50, d90 ratio of that API batch

REGULATORY QUESTION: "Does the Agency agree that the acceptance criteria for the drug substance particle size distribution (D10, D50, D90) of EMD compound A can be justified on the basis of the PBBM approach, or does the PBBM only qualify for supportive data?"

SUPORTIVE DATA

Possible approaches

For considering this PBBM **as conclusive evidence** for setting **clinically relevant API PSD specifications**, which refinements would be necessary in model building and validation steps?

- Obtaining **experimental results for pKa, solubility** on the physiological pH range without NaCl or with varied amounts of NaCl
- Build a link **(IVIVR/IVIVC)** between API PSD and drug product *in vitro* dissolution data
- Appropriately include ***in vitro* dissolution data** as model input data for drug product
- Ideally, validate the model with clinical PK data of a **non-bioequivalent** drug product batch (preferentially due to variation in API PSD)
- Include **population simulations** in the validation and application steps of the model, with adequate **representation of WSV/ BSV**, instead of using only average simulations
- Define **safe space for API PSD**

Thank you for the attention!

luiza.borges@anvisa.gov.br

Anvisa

SIA Trecho 5 - Área especial 57 - Lote 200 -

CEP: 71205-050 - Brasília - DF

www.gov.br/anvisa

ACKNOWLEDGEMENTS

Reviewers from CETER (Therapeutic Equivalence) and GQMED (Quality Assessment) – Working Group on PBBM

Profa. Andrea Diniz – University State of Maringá (UEM) - Brazil

Prof. Marcelo Dutra Duque - Universidade Federal de São Paulo (Unifesp) - Brazil

Profa. Natália Valadares de Moraes - University of Florida - USA

Profa. Sandra Elisa Haas – Federal University of Pampa (Unipampa) - Brazil

ANVISA
Agência Nacional de Vigilância Sanitária