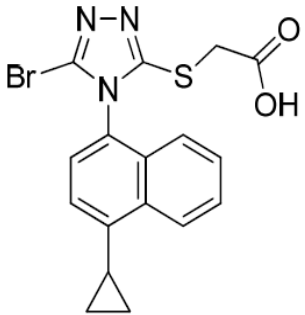
M-CERSI - Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development
May 15-17, 2017, Maryland

in silico PBPK modelling in support of drug product dissolution and drug substance particle size specifications

Priadel® 200 mg

Li_2CO_3

ZURAMPIC™
lesinurad tablets



Xavier Pepin
16th May 2017

Priadel®

Post approval change support of dissolution specifications using PBPK and historical PK data on formulations with different release rates

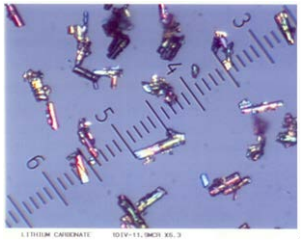
Priadel 200 mg
Justification for a dissolution specification change

- Lithium carbonate 200 mg –Priadel ®
  - Issues of dissolution testing at end of product shelf life
  - Formulation with magnesium stearate
  - Maturation process during storage
  - Old data in the dossier
  - Current large specifications for dissolution with no issue of safety
    But :
  - Approx. 3 batches per year were destroyed (since not meeting dissolution specs) leading to annual losses of 70 k€ for the manufacturing plant

- Question to BioPharm
  - Post Approval Change dossier was prepared with proposed new dissolution specs @ end of shelf life
  - Can you help justify a proposed change in dissolution specifications to avoid those losses ?

Priadel 200 mg
Biopharmaceutical properties of Li2+

- Lithium carbonate $Li_2CO_3 \rightarrow 2Li^+ + CO_3^{2-}$



D_{50} 30-50µm

- Solubility
- In water at 37°C = 12 mg/mL

$$CO_3^{2-} + 2H^+ \rightarrow H_2CO_3$$

$$H_2CO_3 + H^+ \rightarrow H_3O^+ + \overuparrow{CO_2}$$

- Dissolution not pH dependent . Existence of CO_2 bubbles which can reduce dissolution rate (isolation of the tablet)

Need to increase HCL molarity to 0.025M to buffer carbonates

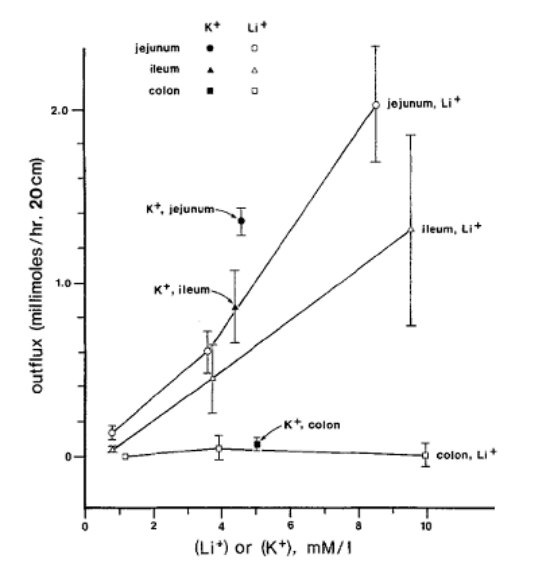
Priadel 200 mg
Biopharmaceutical properties of Li^{2+}

- Permeability
- Was measured in man 30 years ago !

$$\frac{dM}{dt} = SP_{eff}C$$

Fluxes transformed in P_{eff} using radii from ICRP89 & lengths perfused in vivo

J.M Diamond et al. J. Membrane Biol. 72, 153-159 (1983)



	Flux/Concentration (cm3/h)[a]	radius cm	length cm	Peff x 10^4 cm/s
Jejunum	228.7	1.38	20	3.66
Ileum	134.5	0.98	20	3.03
Colon	14.7	2.41	20	0.13

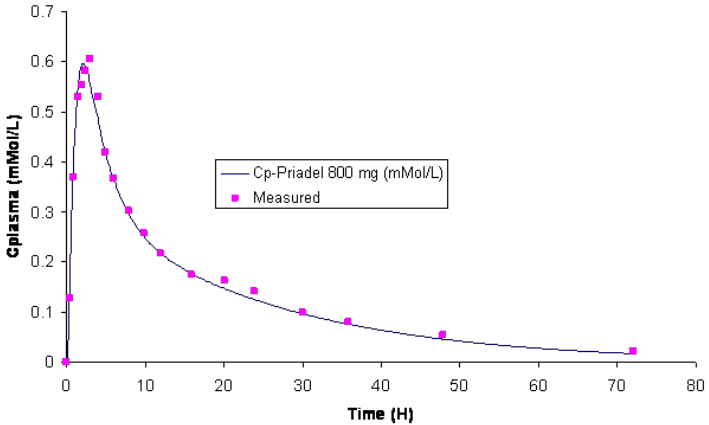
Good solubility and good permeability except in the colon

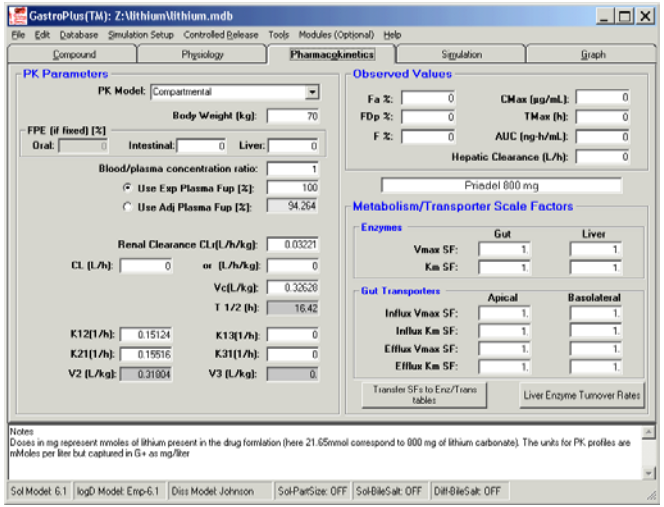
http://www.icrp.org/publication.asp?id=ICRP%20Publication%20110

Priadel 200 mg
GastroPlus model building

Priadel 2 x 400 mg profile used to set up the PK model

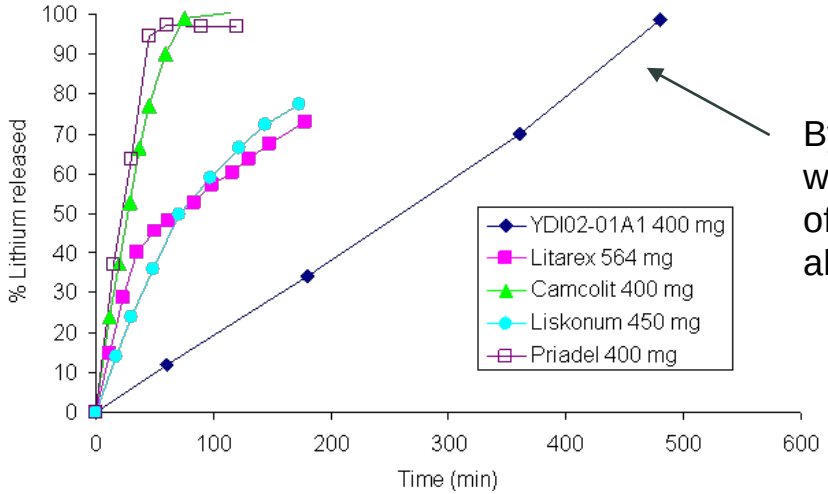
- GastroPlus™ V7, ASF model 6.1, Human fasted physiology
- Lithium is excreted by the kidneys with no metabolism
- Fit of V_d, k_{12}, k_{21} & CL_R to observed PK profile





Priadel 200 mg
GastroPlus model validation

Use of historical data and « new » slow release internal lithium carbonate formulation

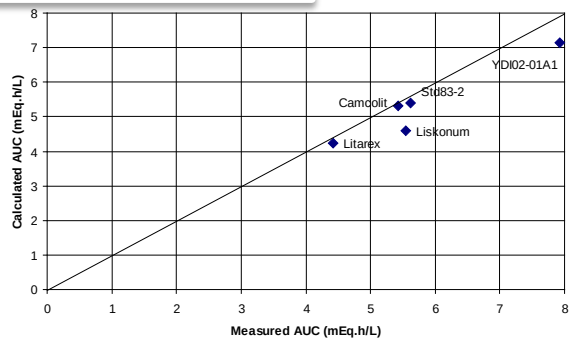


By chance we had worked on a formulation of lithium that was abandoned…in 2001 !

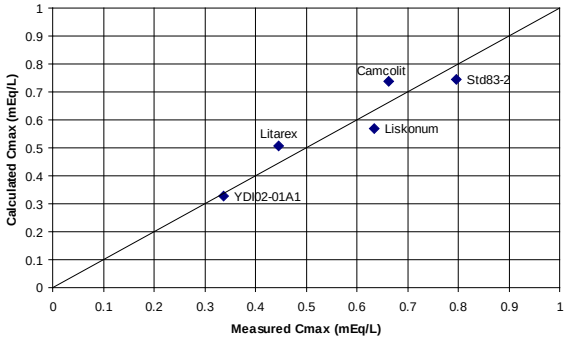
Priadel 200 mg
GastroPlus model validation

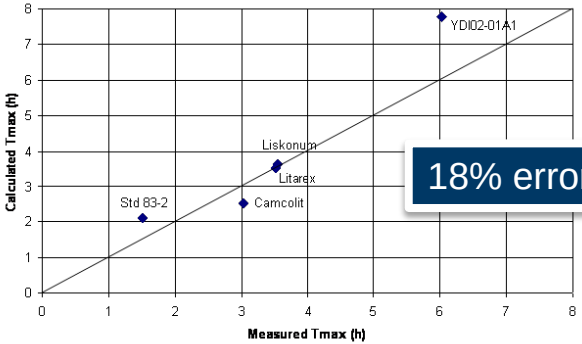
Prediction errors were good

7% error on AUC



9% error on C_{max}

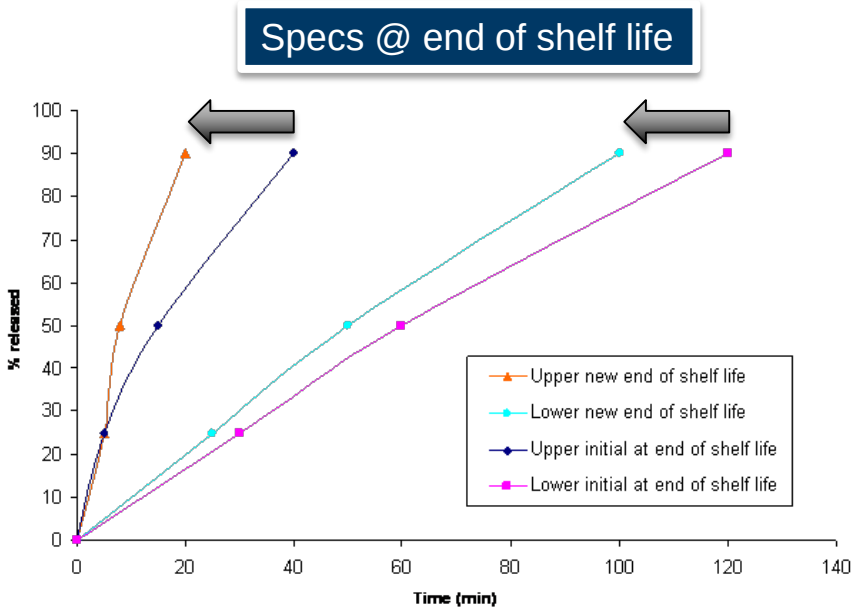




18% error on t_{max}

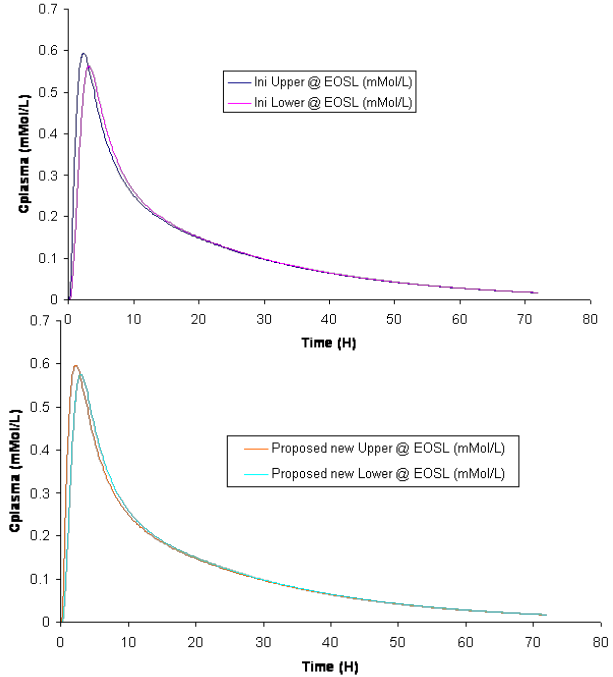
Priadel 200 mg
GastroPlus model use

Evaluation of old and new proposed specifications



Priadel 200 mg
GastroPlus model use

Evaluation of old and new proposed specifications at end of shelf life



With new proposed specs, DP at end of shelf life are bioequivalent to one another and ratios are closer to 1

PK parameter	Upper/lower	Lower/upper
AUC ratio	1.01	0.99
C_{max} ratio	1.05	0.95
T_{max} ratio	0.73	1.36

PK parameter	Upper/lower	Lower/upper
AUC ratio	1.01	0.99
C_{max} ratio	1.04	0.96
T_{max} ratio	0.75	1.33

New proposed specs, are actually more restrictive !

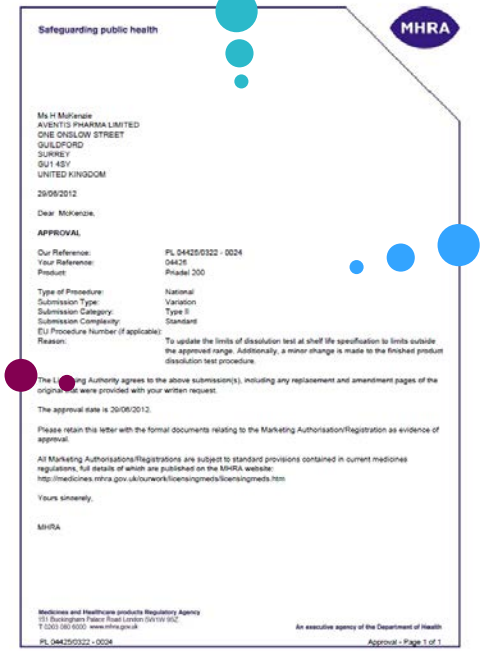
Priadel 200 mg
Conclusion

Variation dossiers submitted to UK and Irish authorities
Positive reply in spring 2012

Significant savings

Easier production, storage, release management

No batch is discarded



Safeguarding public health

MHRA

Ms H McKenzie
AVENTIS PHARMA LIMITED
ONE ONSLOW STREET
GUILDFORD
SURREY
GU1 4SY
UNITED KINGDOM

29/06/2012

Dear McKenzie,

APPROVAL

Our Reference:	PL 04425/0322 - 0024
Your Reference:	04426
Product:	Priadel 200
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	
Reason:	To update the limits of dissolution test at shelf life specification to limits outside the approved range. Additionally, a minor change is made to the finished product dissolution test procedure.

The Licensing Authority agrees to the above submission(s), including any replacement and amendment pages of the original that were provided with your written request.

The approval date is 29/06/2012.

Please retain this letter with the formal documents relating to the Marketing Authorisation/Registration as evidence of approval.

All Marketing Authorisations/Registrations are subject to standard provisions contained in current medicines regulations, full details of which are published on the MHRA website:
http://medicines.mhra.gov.uk/ourwork/licensingmeds/licensingmeds.htm

Yours sincerely,

MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

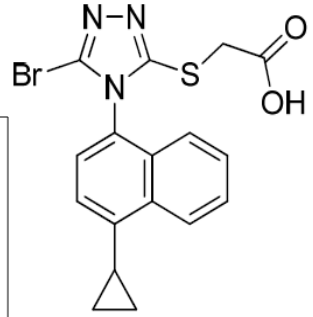
PL 04425/0322 - 0024

Approval - Page 1 of 1

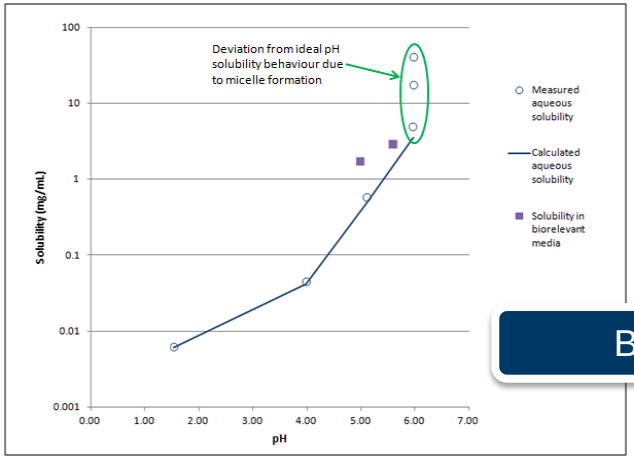
Zurampic®

Reply to FDA during review period
Support of dissolution specifications and drug substance particle size using PBPK and historical PK data on formulations with different release rates

Biopharmaceutical properties - Lesinurad



- Biopharm properties
  - pKa: 3.2 (25° C, acid)
  - Log P: 2.85
  - Solubility = 6 ug/mL at 37° C (@ pH 1.6)
  - Estimated human Peff = ~ 3 10^{-4} cm/sec
  - $f_{u,p}$ = 2%
  - B:P = 0.55
  - Limited impact of bile salts on solubility



BCS II

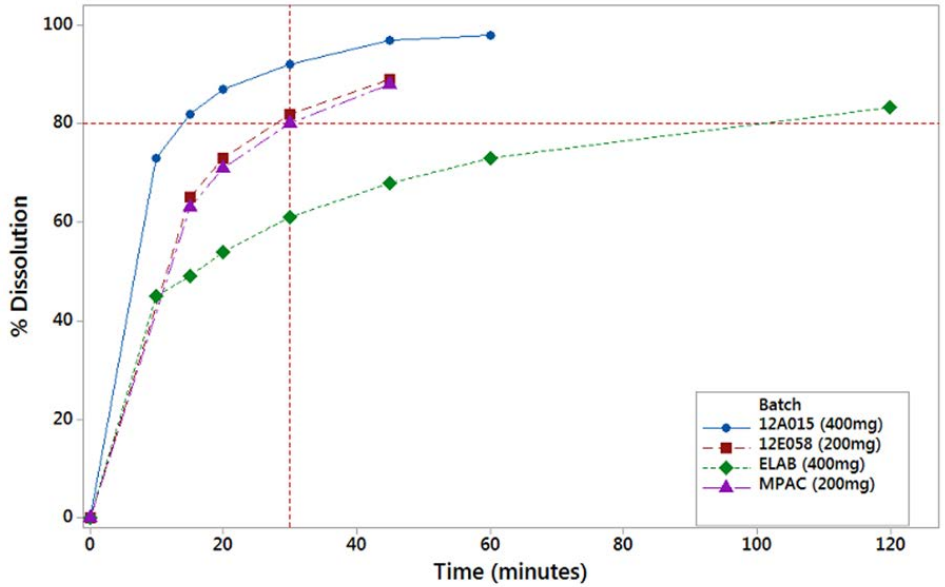
- API particle size

Drug product batch	Tablet strength	API Batch	D (v, 0.1)	D (v, 0.5)	D (v, 0.9)
12A015	400mg	HE00011	9.1	23.2	45.9
ELAB	400mg	HE00014	15.1	50.5	125.6
12E058	200mg	HE00012	19.6	49.3	102.6
MPAC	200mg	HE00015	23.2	54.0	111.3

Proposed specs DS PSD
D(v, 0.5) NMT 70 µm
D(v, 0.9) NMT 159 µm

Dissolution of drug products

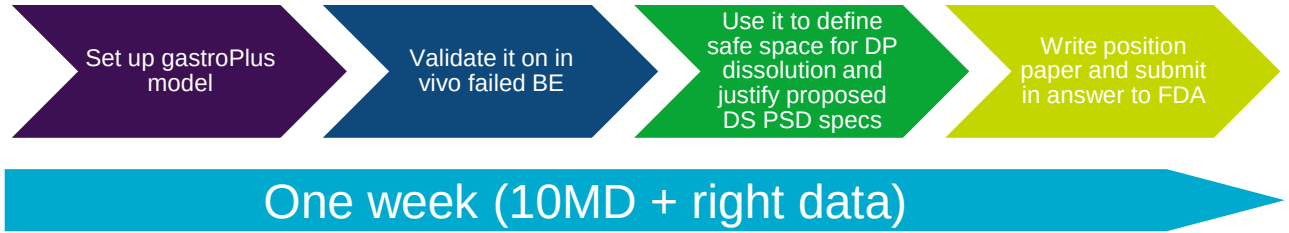
- QC dissolution method
  - 900 mL pH 4.5 acetate buffer plus 1% sodium lauryl sulfate (SLS) as the dissolution medium, in USP Apparatus 2 at 75 rpm
  - The solubility of lesinurad in this media is 1.77 mg/mL



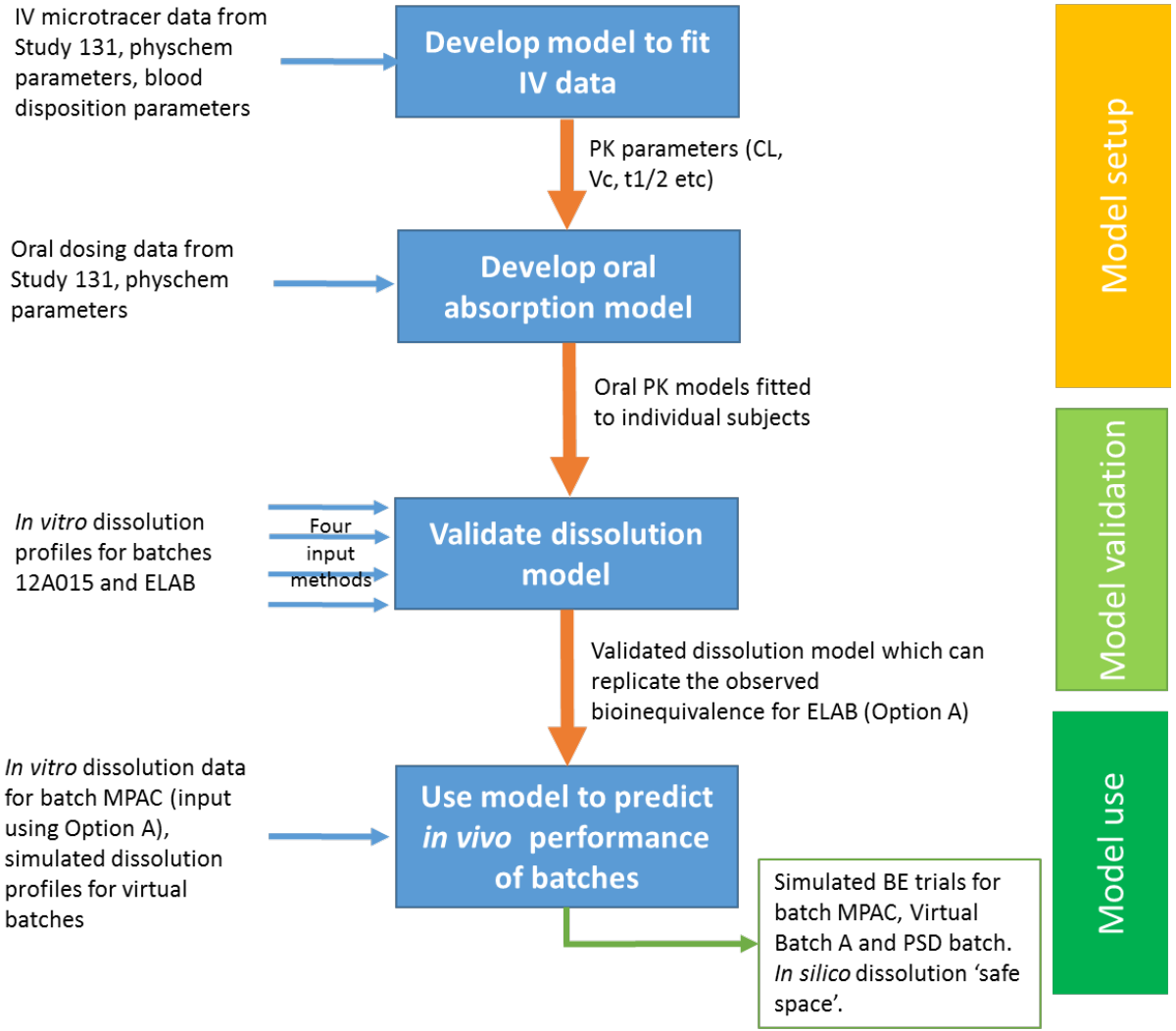
Proposed spec dissolution
Q = 80% at 30 minutes

Issue and strategy adopted

- FDA challenged the dissolution specification
- FDA proposed to perform BE study between batch ELAB and clinical reference 12A015 or run in silico GastroPlus modelling to compare batches
- FDA also challenged the DS PSD specifications which would have led to remanufacture of 3 DS validation batches

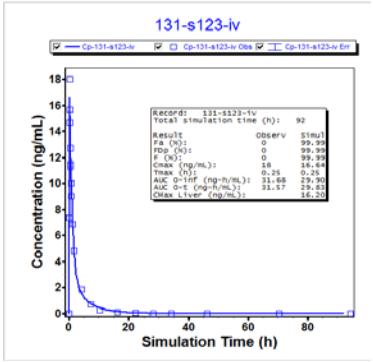


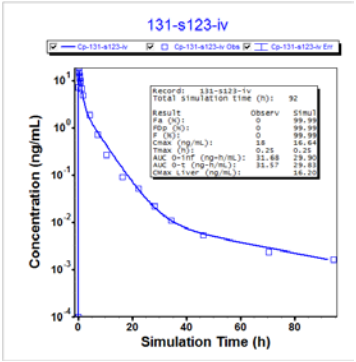
Modelling strategy



GastroPlus model setting – Disposition and elimination

- Use IV for each 10 subjects of RDEA594-131





Fit 10 x 3 compartment individual PK models and extract total clearance CL_T

- Extract renal from hepatic clearance on the basis of excretion balance studies

$$CL_H = CL_T \times 0.687 \qquad CL_R = CL_T \times 0.313$$

- Calculate fixed hepatic first pass effect

$$F_H = \left(1 - \frac{CL_H}{Q_H \times B2P}\right)$$

- Gut extraction estimated from Qgut model is negligible $F_g \approx 1$

GastroPlus model setting - Absorption

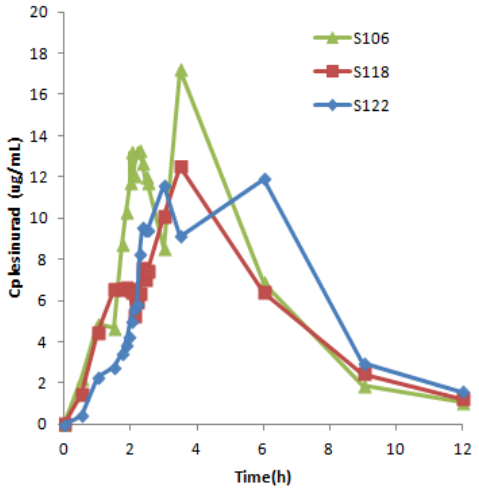
- Use oral PK data for the 10 subjects of of RDEA594-131 and dissolution performance of reference clinical batch to fit lag phases and gastric emptying patterns and adjust Peff individually

- Once model is set, use to test different inputs of dissolution or API particle sizes

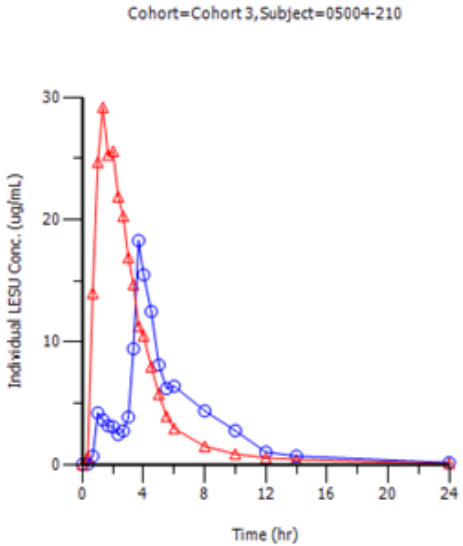
PK profiles – Gastric emptying phases

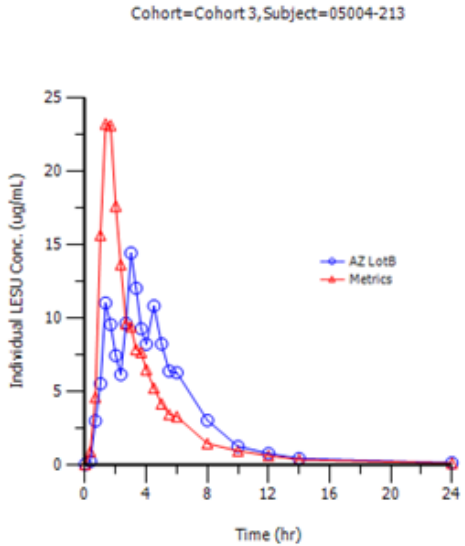
- Low solubility in stomach acid conditions → lag times and multiple peaks in fasted state. After stomach emptying solubility > 20mg/mL and larger permeability (BCS class I like)

RDEA594-131



RDEA594-129





Observed lag times and multiple peaks

Lag times from 0.06 to 3.17 hours

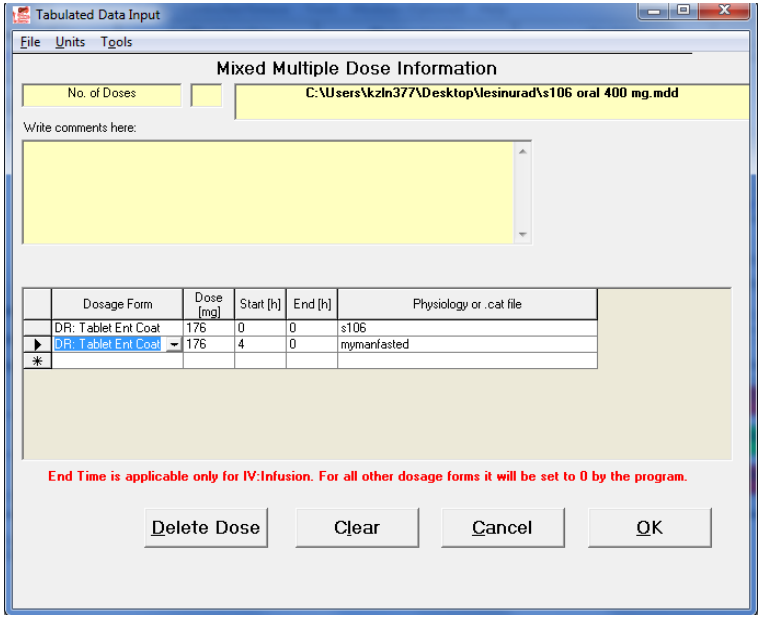
Table 1 **Gastric emptying patterns observed in Study RDEA594-131**

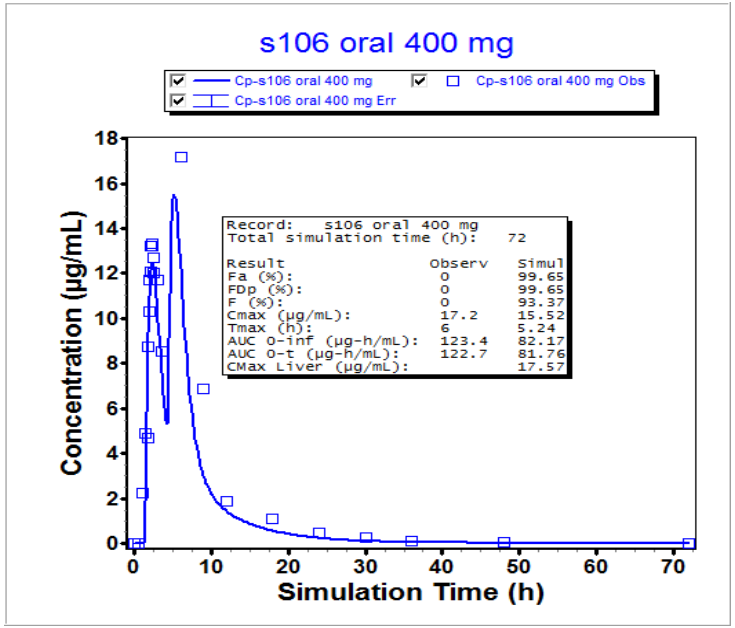
Subject	Gastric residence time (first peak)	Dose (first peak)	Gastric residence time (double peak)	Dose (double peak)
05003-101	3.17	400		
05003-102	0.81	400		
05003-103	1.73	400		
05003-106	1.32	200	4.25	200
05003-112	0.72			
05003-115	0.09			
05003-116	0.62			
05003-118	0.01	150	2.01	250
05003-122	1.37	200	5.37	200
05003-123	0.54			

30% multiple peaks consistent with other historical studies with larger number of subjects

PK profiles

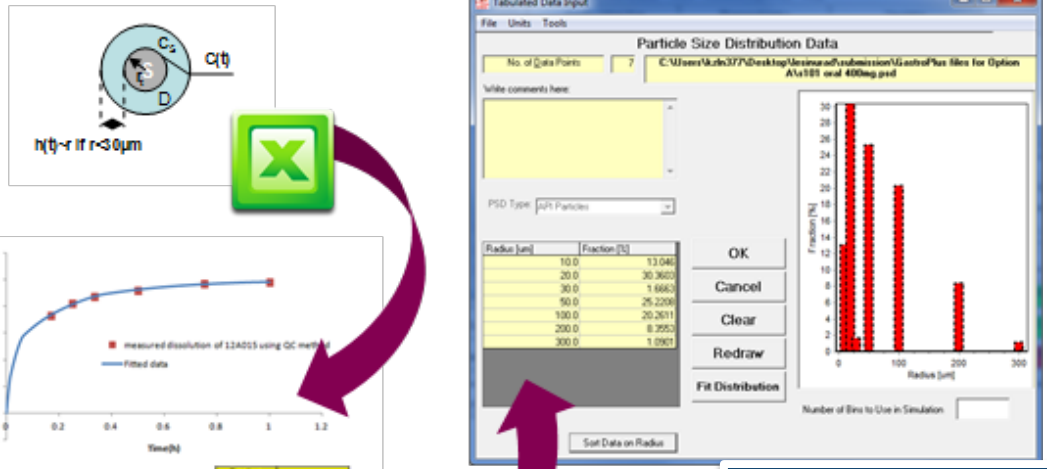
- Mixed Multiple Dose profile used to “fraction” the dose released from the stomach at different times





Integration of dissolution data

- Option A – Fit of particle size distribution and upload in G+ as an input for each batch of DP



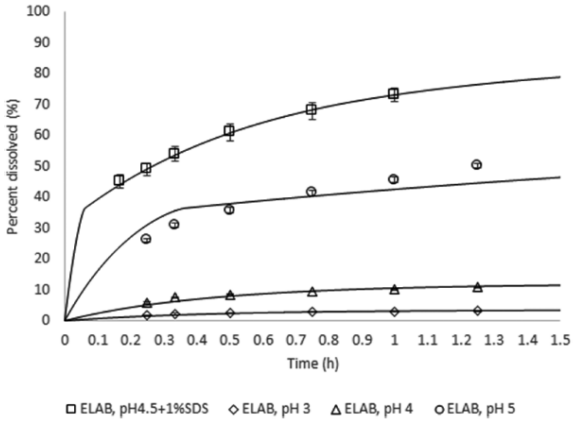


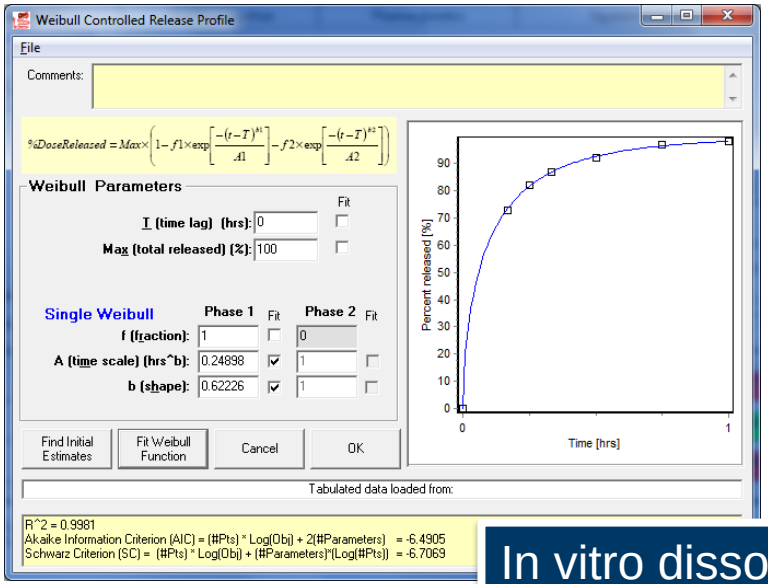
Figure 5. Simulation of ELAB dissolution in pH 3, pH 4, and pH 5 using particle size distribution derived from QC dissolution method profile (pH 4.5 + 1% SLS) vs observed data ±1 SD.

In vivo dissolution is calculated on the basis of local pH and volumes using “DP particle size”

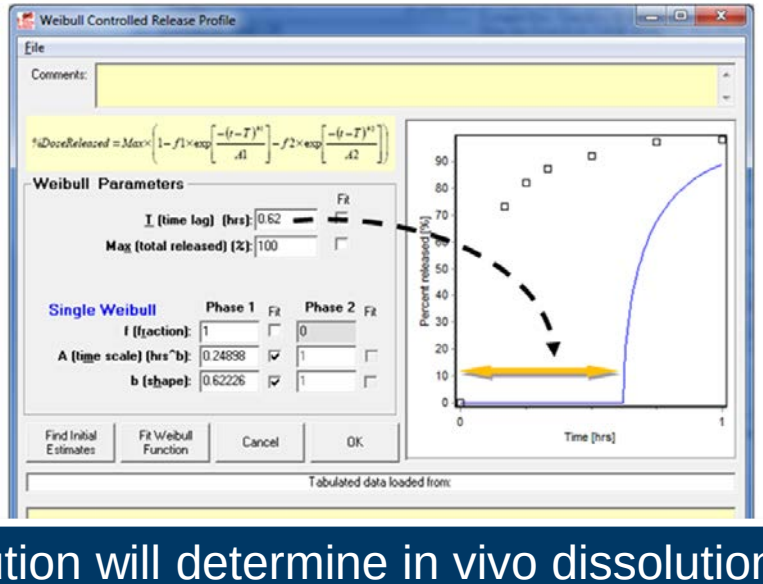
Integration of dissolution data

- Option B – Use the Weibull function to upload dissolution data for each batch – Set dosage form to CR Dissolved (in vitro)

1- Fit in vitro (Weibull)



2- Apply human lag time



In vitro dissolution will determine in vivo dissolution

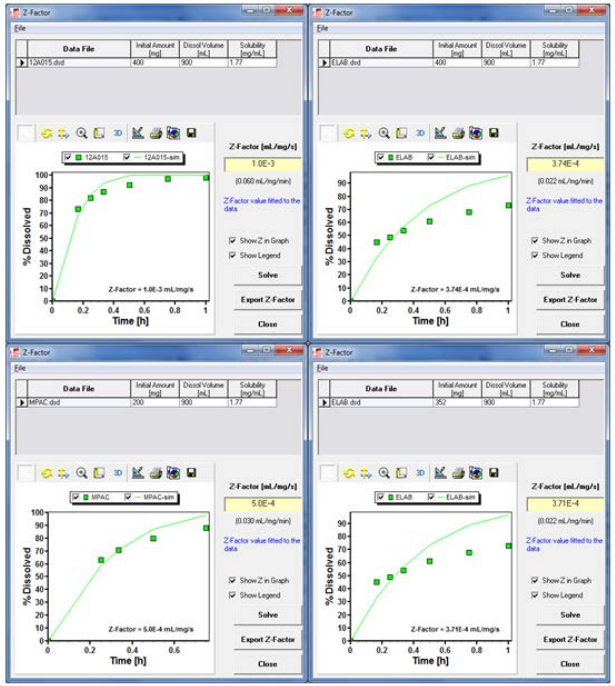
Integration of dissolution data

- Option C – Use the Weibull function to upload dissolution data for each batch – Dosage form set to CR undissolved and integrate particle size distribution of the DS to allow in vivo dissolution calculation by the software

In vitro release will determine in vivo disintegration
DS particle size will determine in vivo dissolution

Integration of dissolution data

- Option D – Fit Z factor [1] to multiple pH data for each formulation and use Z factor vs pH profile as an input to the model



$$\frac{dX_{d,vitro}(t)}{dt} = \frac{3D}{\rho h r_0} \times X_{o,vitro}\left(\frac{X_{s,vitro}(t)}{X_{o,vitro}}\right)^{2/3}\left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)$$

$$= z X_{o,vitro}\left(\frac{X_{s,vitro}(t)}{X_{o,vitro}}\right)^{2/3}\left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)$$

In vivo dissolution is calculated on the basis of local pH and volumes z vs pH profiles

1 : R. Takano et al., Oral Absorption of Poorly Water-Soluble Drugs: Computer Simulation of Fraction Absorbed in Humans from a Miniscale Dissolution Test, Pharm Res 23(6), 2006, 1144-1156

Choices of options

Only Option A allowed to reproduce the non bioequivalence observed with ELAB vs 12A015

- **A :** Use of *in vitro* dissolution data to fit a particle size distribution. set formulation to DR to delayed release enteric coated tablet

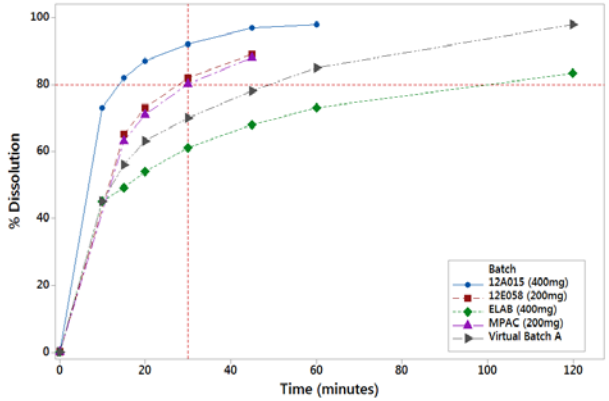
- **B :** Use of *in vitro* dissolution data to fit one Weibull function per batch, where the dosage form is switched to CR dissolved
- **C :** Use of *in vitro* dissolution data to fit a Weibull function per batch, where the dosage form is switched to CR Undissolved with drug substance particle size distribution
- **D:** Use of *in vitro* dissolution data to fit a Z-factor which accounts for the dose volume and solubility and set formulation to DR to delayed release enteric coated tablet.

For all options, stomach residence and gastric emptying patterns are fitted to the observed PK profiles.

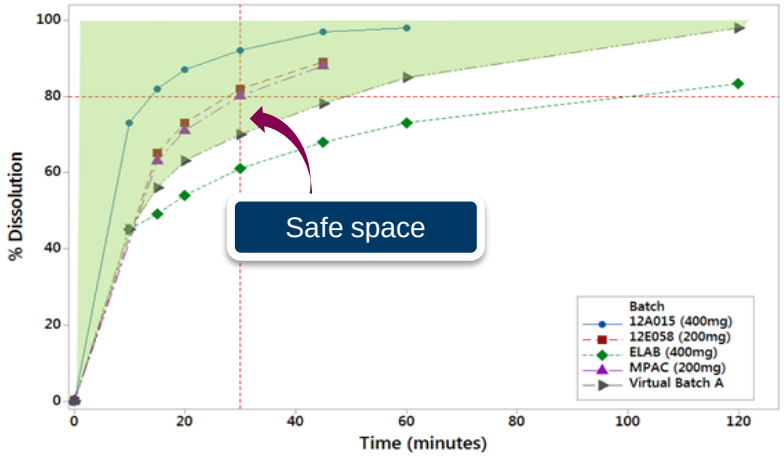
Model use – Design space for dissolution of Lesinurad tablets

- Add a virtual batch A with dissolution outside of spec

Virtual cross over trial n=25 with within subject variability of stomach residence and pH



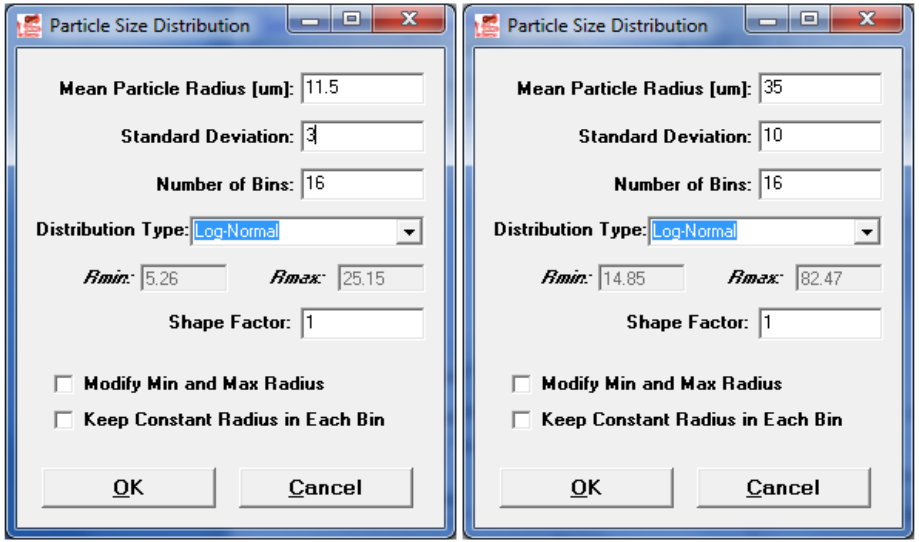
	Predicted C_{max}		Predicted AUC (0-96)	
	Geomean Ratio	90% CI	Geomean Ratio	90% CI
Virtual Batch A vs. 12A015	0.992	(0.990, 0.993)	0.989	(0.988, 0.990)



Our dissolution spec is well justified (MPAC was also anticipated bioequivalent using virtual trial)

Model use – Justification for DS Particle size specs

- Reference and virtual DS lot at specs limits as inputs



Cmax and AUC ratios of 1 on n=10 subjects of Study RDEA594-131

DS particle size specs are justified

Lesinurad 2015 in silico based biowaiver lessons learnt

- Work carried out in a week

supportive oral + micro-dose IV data

- Open communication with FDA
  - Submission of comprehensive report
  - Submission of GastroPlus database and all support files
  - Follow-up TC with 3 modellers from FDA to explain where the data was and how the model was set up

- Independent validation of GastroPlus with batch showing “different” behaviour
- Need to have microdose data to inform model building
- Elaboration of strategy

Development of IVIVe and biowaiver strategy

PoC or first read on efficacy = +

IR product with rapid dissolution is rapid >80% in 15 min

BCS I or III

MR product envisaged

Waive BE requirements using BCS based biowaiver guidance

Develop formulation variants n=3 with different release profiles

Prototype dissolution using Preclinical method 1

Run IVIVe human study
in vivo human evaluation with IV microdosing, markers of gastric emptying, pH probe in stomach.

Extract in vivo absorption profiles from PBPK modelling

Use PBPK model for QbD, safe space, specs justification (dissolution and DS PSD), support changes within safe space during R&D and PAC

Clinical relevant dissolution method development

Use refined PK-PD or PK-Tox to maximize therapeutic index, define best commercial formulation or LCM opportunities through PBPK

Mol. Pharmaceutics
2016, 13 (9)
pp 3256–3269

Thanks

Sanofi
Sylvie Fabre-Decourt
Victor Ariel
Anne Lanotte

Ardea Biosciences
Colin Rowlings
Anna Eidelman
Don Treacy

AstraZeneca
Talia Flanagan
David Holt
Simon Hartas

Questions ?

Confidentiality Notice