How to obtain biowaivers for clinical trials using PBPK models, two case studies

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EUFEMED

Workshop 1: Modeling and simulations, including PBPK to improve the clinical development

May 15th 2019

Take home messages:

- FDA is open to proposals of using modeling approaches for bioequivalence (BE), or for new drugs, with the proper justification and model verification
- PBPK models can answer a variety of questions from regulatory agencies
- PBPK is a great tool to understand the interconnection between API properties, formulation attributes and human physiology

Outline:

- Case Study 1: Crossover trials to show BE after manufacturing changes
- Case Study 2: Long-acting injectables (LAI) generic products development

The Key points from U.S. FDA Workshop:

- *FDA is open to proposals using modeling approaches to establish bioequivalence for the "Test" products, as long as these proposals include information about the modeling approach, scientific justification of the proposed approach and in the end model verification.*

- *Discuss your proposed BE modeling approach through the pre-ANDA development meeting.*

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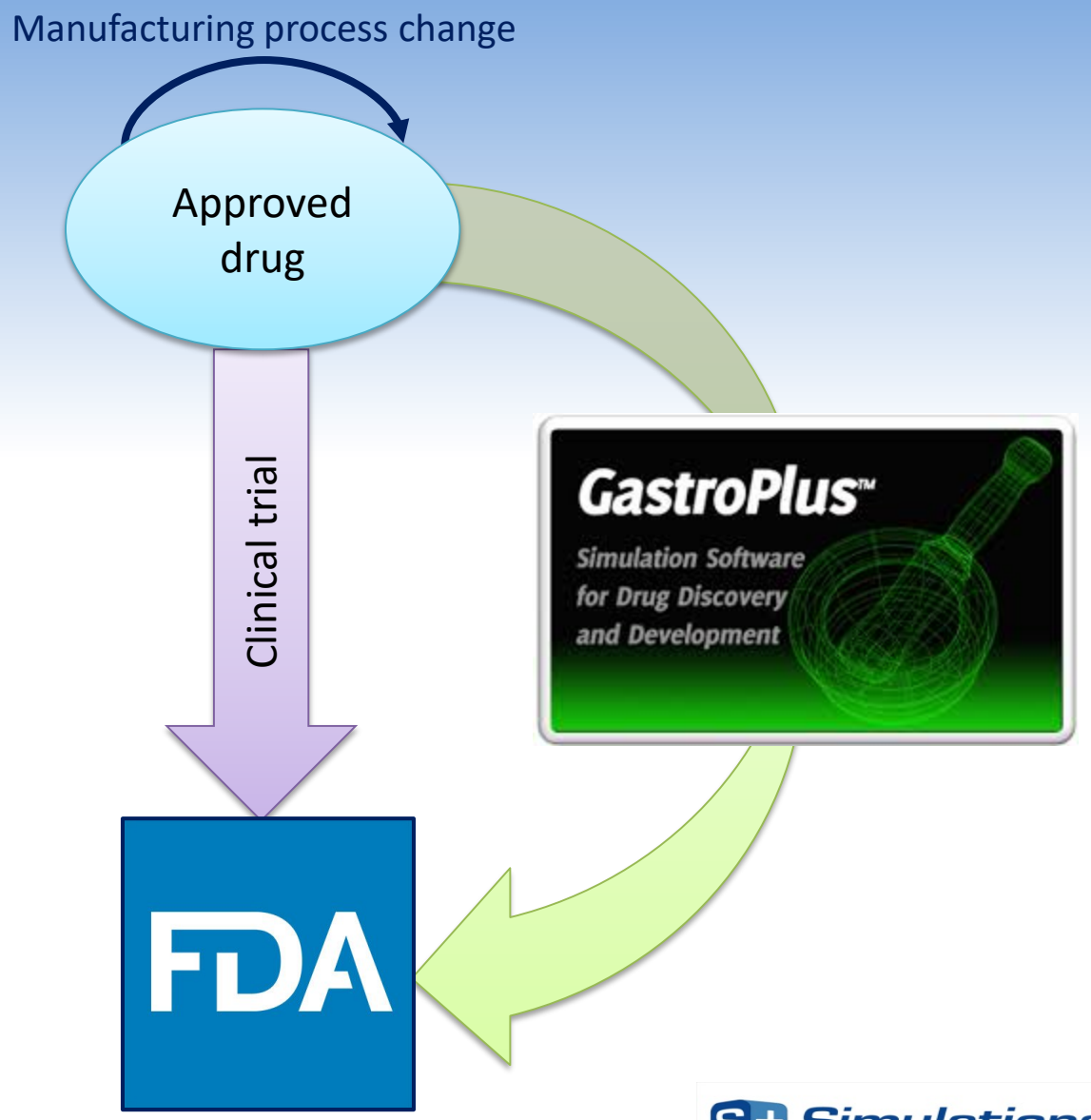
Case Study 1:
Crossover trials to show BE after manufacturing changes

Modeling & Simulations Objectives

- Post-approval, sponsor's manufacturing process changes resulted in different particle size distributions for new lots
  - Inline milling step added to crystallization process (PE)
- With GastroPlus®, they could apply for a **biowaiver** by:
  - assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability?
  - predicting the virtual bioequivalence between the "new" and "old" API lots?



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Proposed Modeling Tasks

- Part 1: Determine the most appropriate absorption/PBPK model for the API across several doses for the non-engineered lots
- Part 2: Assess the effect of particle size on API exposure for the immediate release (IR) formulation
- Part 3: Evaluate predicted bioequivalence of the tablets manufactured with particle-engineered (PE) API (narrower particle size distribution) versus the tablets manufactured with non particle-engineered (NPE) API (broader particle size distribution)

Part 1: Building the Baseline Model: Key Modeling Parameters

- BCS Class IV drug
- Neutral compound
- Aqueous solubility = 10 µg/mL
- Significant solubilization by bile salts
- Intermediate lipophilicity
- No food effect

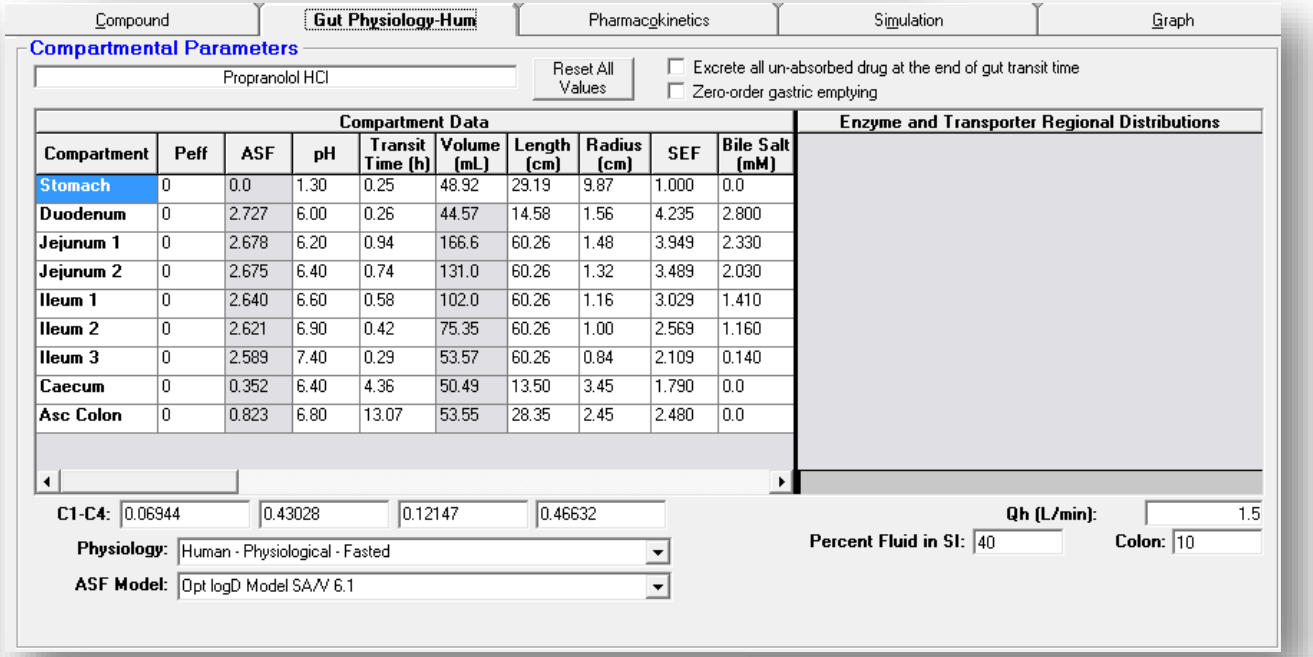
Parameter	Value
CL	0.115 L/h/kg
First pass extraction	17%
Vc	0.324 L/kg
K12	0.26 h^{-1}
K21	0.1 h^{-1}

Various Particle Size Used in Clinical Studies

NPE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
NPE Lot 1	20	63	173
NPE Lot 2	8	179	512
NPE Lot 3	15	49	142
NPE Lot 4	31	86	348
NPE Lot 5	26	78	276
NPE Lot 6	9	29	101
NPE Lot 7	11	35	114
NPE Lot 8	12	37	124
NPE Lot 9	10	36	119
NPE Lot 10	13	45	138
NPE Lot 11	11	35	99

PE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
PE Lot 1	16	40	88
PE Lot 2	20	49	102
PE Lot 3	22	53	108
PE Lot 4	19	39	71
PE Lot 5	17	35	67
PE Lot 6	23	48	93
PE Lot 7	21	44	87
PE Lot 8	21	45	90
PE Lot 9	24	50	94
PE Lot 10	21	45	89
PE Lot 11	19	42	88
PE Lot 12	22	47	95

API: active pharmaceutical ingredient; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value; NPE: non-particle-engineered; PE: particle-engineered



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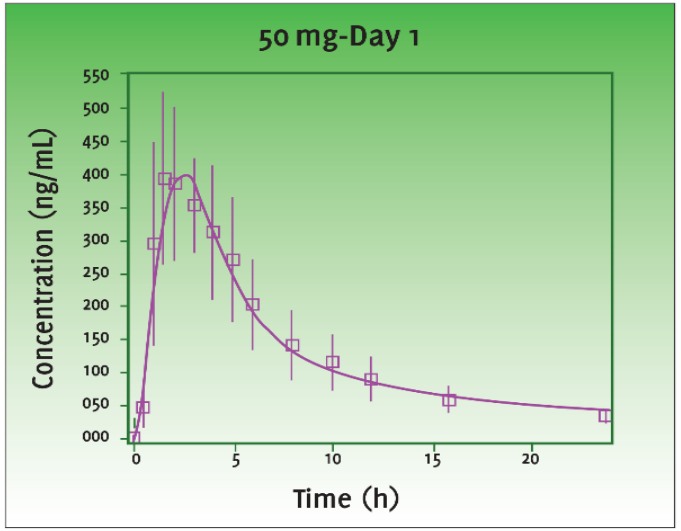
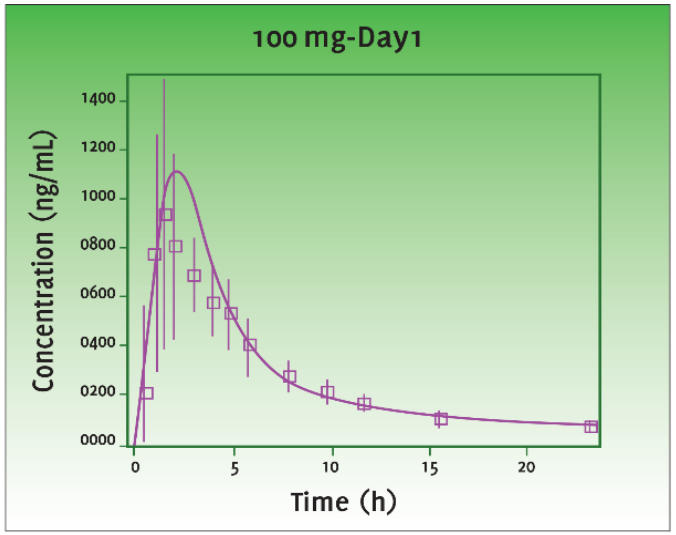
Part 1: Simulation Results for Baseline Models of Non-Engineered Lots



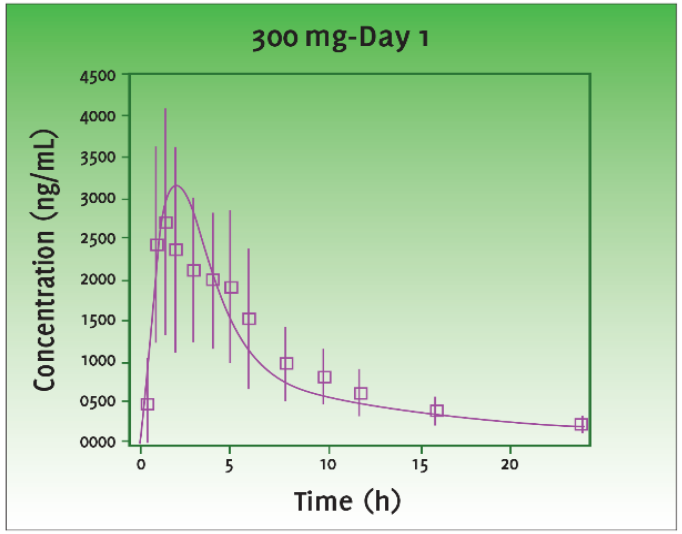
Total simulation time (h): 24

Result	Observ	Simul
Fa (%)	0	85.907
FD_p (%)	0	85.907
F (%)o	0	71.303
Cmax (ng/mL):	391.2	399.12
Tmax (h):	1.5	2.56
AUC o-inf (ng-h/mL)	3563.7	3739.6
AUC o-t (ng-h/mL):	3139.1	3702
Cmax Liver (ng/mL):		531.85



Total simulation time (h): 24

Result	Observ	Simul
Fa (%)	0	85.907
FD_p (%)	0	85.907
F (%)o	0	71.303
Cmax (ng/mL):	926.3	399.12
Tmax (h):	1.5	2.56
AUC o-inf (ng-h/mL)	7545.6	8462.2
AUC o-t (ng-h/mL):	6358.8	7117.3
Cmax Liver (ng/mL):		1385.9

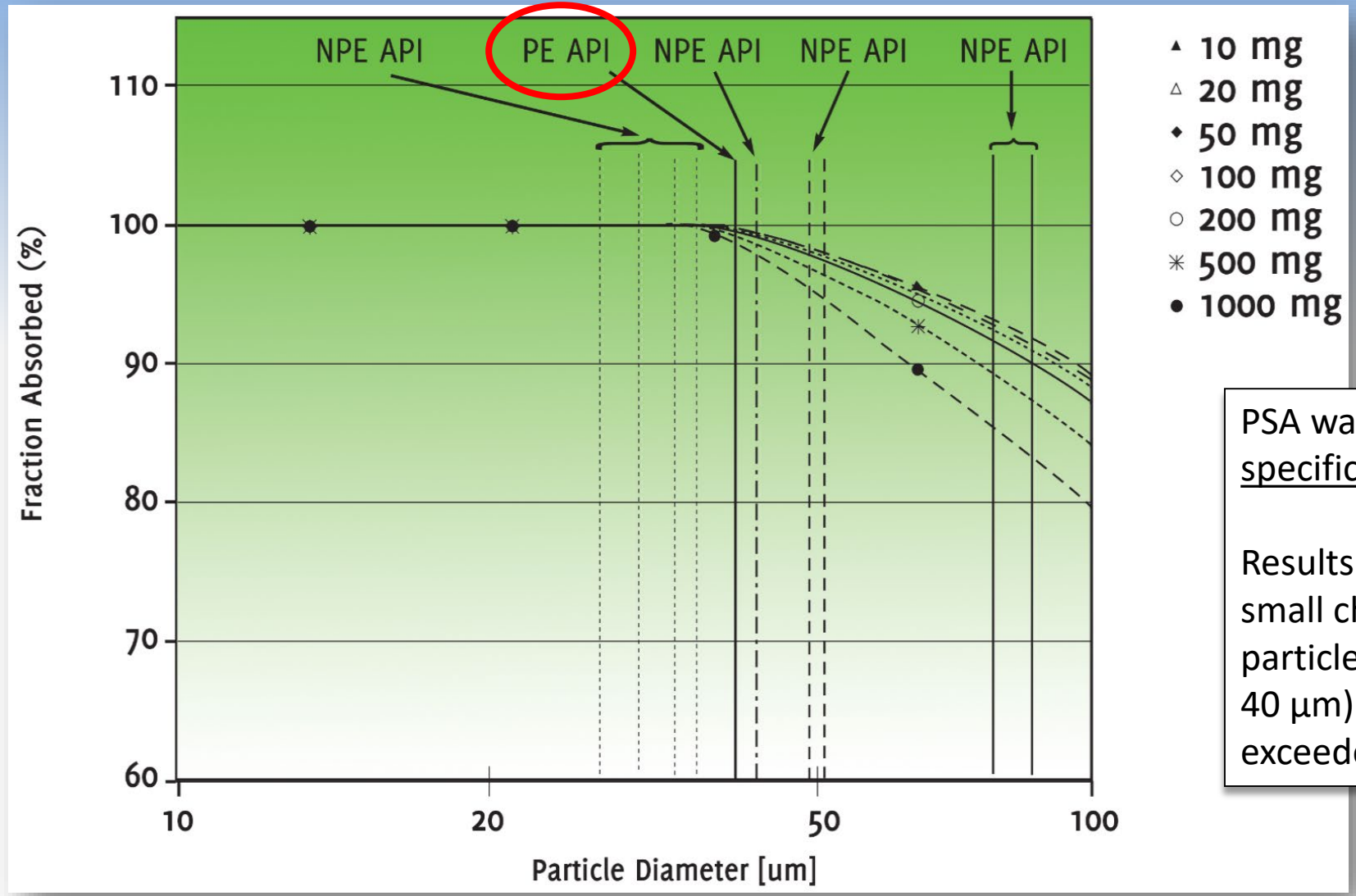


Total simulation time (h): 24

Result	Observ	Simul
Fa (%)	0	96.422
FD_p (%)	0	96.422
F (%)o	0	80.03
Cmax (ng/mL):	2768	3245.8
Tmax (h):	1.5	2.08
AUC o-inf (ng-h/mL)	26290	24970
AUC o-t (ng-h/mL):	22590	20990
Cmax Liver (ng/mL):		4079.7

Same baseline absorption model does a good job of predicting the observed plasma concentration-time data across the three different doses of the NPE (“old”) API lots.

Part 2: Parameter Sensitivity Analysis (PSA) Around Mean Particle Radius: Dose Range: 10 – 1000 mg



PSA was used to establish particle size specifications.

Results indicated that there would be small changes in Fa% until the largest particle sizes of the NPE API lots (> 30 - 40 µm) were reached *and* the dose exceeded 100 mg.

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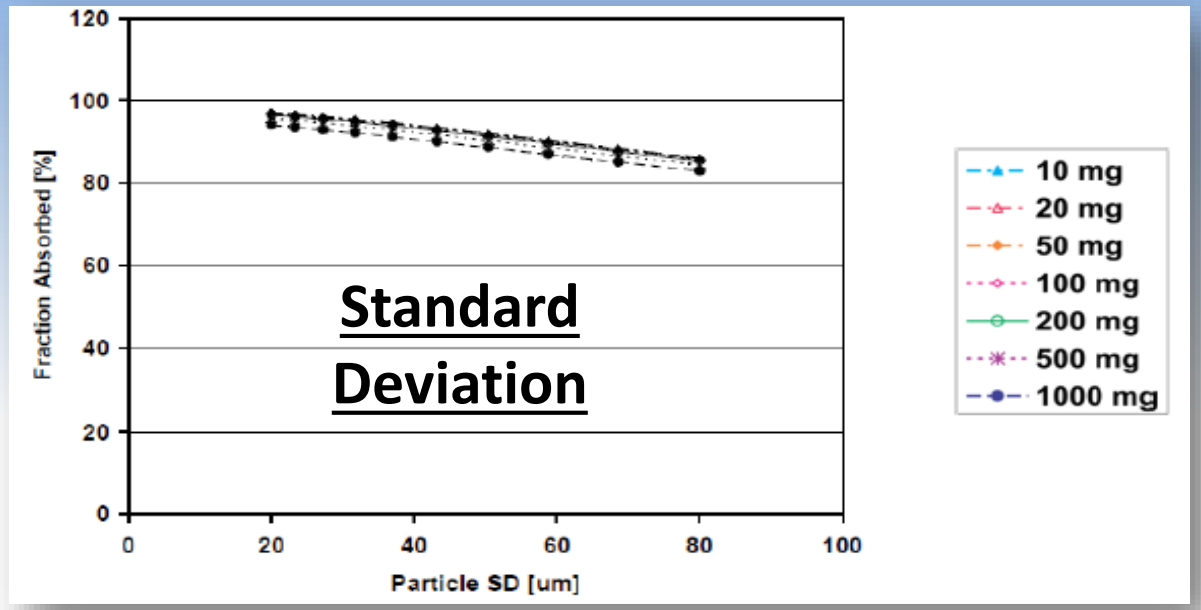
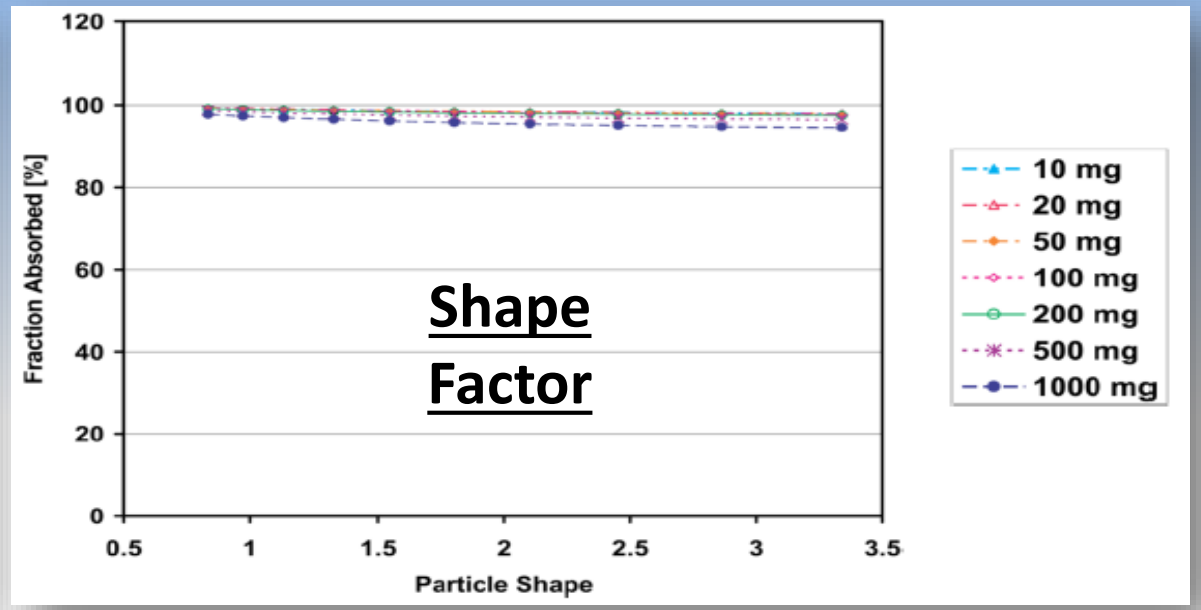
Part 2: Parameter Sensitivity Analysis (PSA) Around Standard Deviation & Shape Factor: Dose Range: 10 – 1000 mg





PSA was also run to evaluate changes in particle size standard deviation (assuming mean remained constant) and particle shape factor

Results indicated that there would be insignificant/moderate changes in Fa% across the range of values evaluated

Part 3: Virtual Bioequivalence Trials: Population Simulator

Incorporate measured variability for physicochemical, formulation and PK parameters into Population Simulator

Capture observed variability from existing clinical PK studies

Population Simulator

File

Parameters

Clear All | Add All | Add Select | Set Defaults

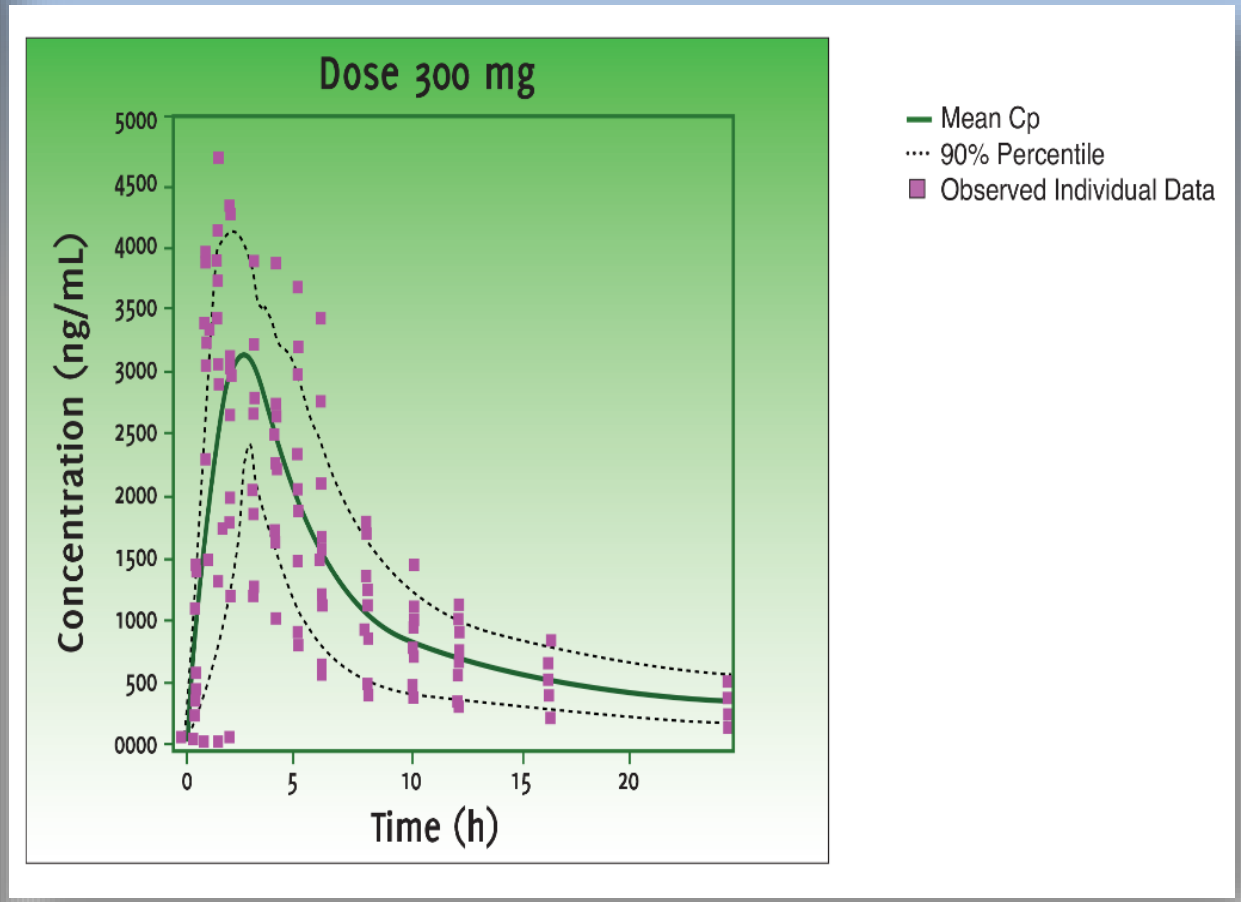
Population

Set PEAR | Load Previous | Create New

Parameter	Lower Limit	Mean Value	Upper Limit	CV%	Distribution
Dose of Valsartan (mg)	91.514	100	109.27	3	Log-Normal
Primary Permeability of Valsartan (c	0.2048	0.92	4.1328	65	Log-Normal
Particle Shape Factor of Valsartan	0.7513	1	1.331	10	Log-Normal
Mean Drug Particle Radius of Vals	18.783	25	33.275	10	Log-Normal
Precipitation Particle Radius of Val	0.7513	1	1.331	10	Log-Normal
Precipitation Time of Valsartan (sec	676.18	900	1197.9	10	Log-Normal
Reference Solubility of Valsartan (m	0.0738	0.0982	0.1307	10	Log-Normal
Fraction Unbound in Enterocytes o	0.7513	1	1.331	10	Log-Normal
Oral Transit Time of Valsartan (h)	0.1878	0.25	0.3328	10	Log-Normal
Oral Cavity ASF Valsartan	0.7513	1	1.331	10	Log-Normal
Duodenum ASF Valsartan	2.1011	2.7965	3.7221	10	Log-Normal
Jejunum 1 ASF Valsartan	2.0672	2.7514	3.6621	10	Log-Normal
Jejunum 2 ASF Valsartan	2.0506	2.7294	3.6328	10	Log-Normal
Ileum 1 ASF Valsartan	2.0273	2.6983	3.5914	10	Log-Normal
Ileum 2 ASF Valsartan	1.988	2.6461	3.522	10	Log-Normal
Ileum 3 ASF Valsartan	1.9416	2.5843	3.4396	10	Log-Normal
Caecum ASF Valsartan	0.0797	0.1061	0.1412	10	Log-Normal
Asc Colon ASF Valsartan	0.1551	0.2064	0.2747	10	Log-Normal
OralMucosaVolume (mL)	2.6296	3.5	4.6585	10	Log-Normal
SalivaProductionRate (mL/min)	0.7513	1	1.331	10	Log-Normal
Fraction of colon fluid volume in fas	7.5131	10	13.31	10	Log-Normal
Fraction of SI fluid volume in fasted	30.053	40	53.24	10	Log-Normal
Small Intestine Length (cm)	230.01	306.14	407.47	10	Log-Normal
Caecum Length (cm)	9.9118	13.193	17.559	10	Log-Normal
Colon Length (cm)	20.772	27.648	36.799	10	Log-Normal
Stomach Volume (mL)	34.981	46.56	61.972	10	Log-Normal
Small Intestine Radius (cm)	0.7513	1	1.331	10	Log-Normal
Caecum Radius (cm)	2.5433	3.3851	4.5056	10	Log-Normal
Colon Radius (cm)	1.8086	2.4073	3.2041	10	Log-Normal
Stomach Transit Time (h)	0.1447	0.25	0.432	20	Log-Normal
Small Intestine Transit Time (h)	1.857	3.2088	5.5448	20	Log-Normal

Number of Output Data Points: 300

OK | Cancel



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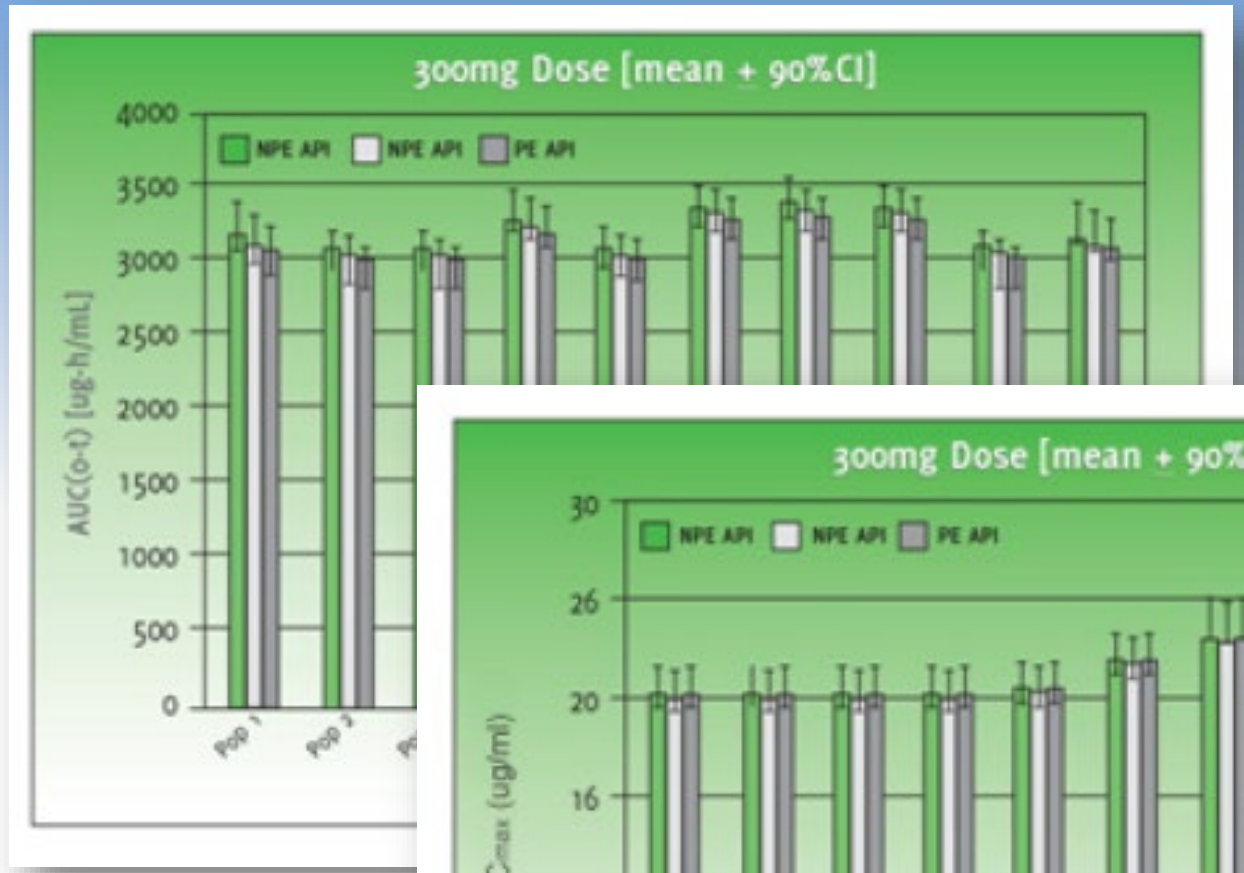
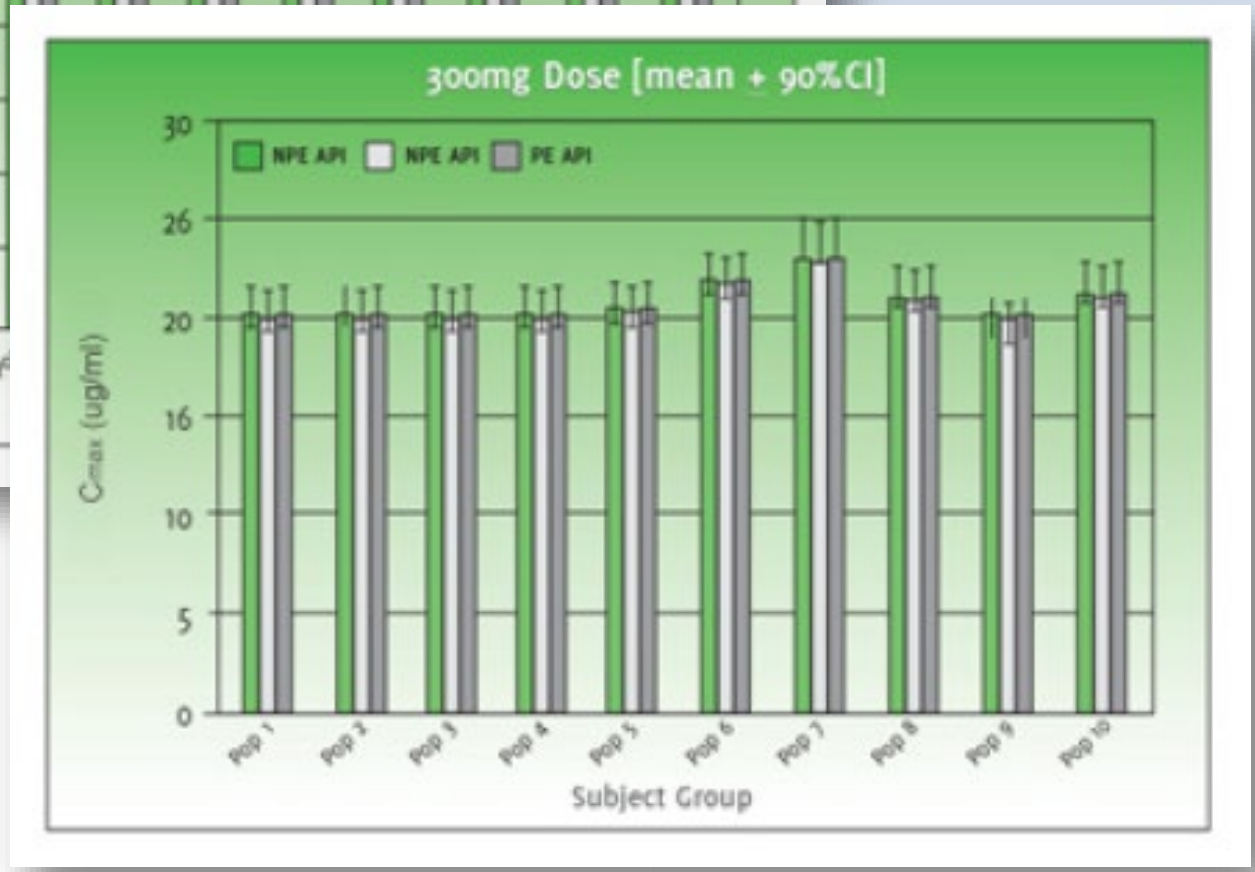
Part 3: Virtual Bioequivalence Trials: Population Simulator

- Crossover studies simulations for **10 different populations**, **each with 25 virtual subjects**, were run to predict bioequivalence

- 100% passing ratios for C_{max} and AUC were predicted (within the 80-125% limits) between the “new” and “old” API lots (up to 40 µm)





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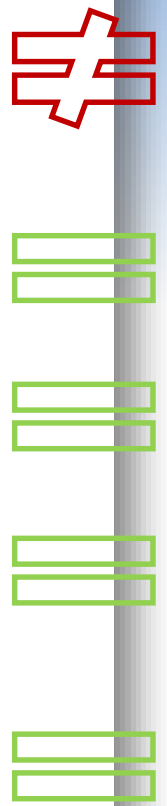
Virtual Bioequivalence Study Simulations

API Lot	PE/NPE	Dose (mg)	AUC_{∞} (ng.h/mL) (N=250)		C_{max} (ng/mL) (N=250)	
			GM	GMR (90% CI)	GM	GMR (90% CI)
Lot 5	PE	50	4180	113.3 (110.7, 116.1)	551	139.3 (136.0, 142.7)
Lot 1	NPE	50	3688		395	
Lot 5	PE	100	8242	103.0 (100.9, 105.1)	551	106.4 (104.3, 108.6)
Lot 3	NPE	100	8001		395	
Lot 5	PE	300	24998	102.2 (99.8, 104.6)	3118	100.0 (97.7, 102.4)
Lot 2	NPE	300	24460		3117	
Lot 5	PE	100	8242	98.2 (96.2, 100.2)	1068	95.1 (93.2, 97.0)
Lot 4	NPE	100	8395		1123	
Lot 5	PE	300	24998	101.9 (99.8, 104.1)	3118	98.3 (96.3, 100.4)
Lot 4	NPE	300	24525		3171	



API: active pharmaceutical ingredient; AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered

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Summary

- A mechanistic, physiologically-based absorption/PK model was constructed in GastroPlus and validated across three dose levels (50, 100, and 300 mg) using *in vivo* data collected from tablets manufactured with non-particle engineered API.

- Parameter sensitivity analysis showed that mean particle size would be the main property that determines whether formulations are likely to be bioequivalent, regardless of dose.

- Virtual bioequivalence trial simulations showed, that for a sufficiently powered study the population-derived C_{max} and AUC values would be bioequivalent between the tablets manufactured with non-particle engineered (NPE) vs. new particle engineered (PE) API, up to 40 µm particle size, regardless of the dose.

- **Regulatory agencies approved the sponsor's biowaiver application**

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Case Study 2:
Long-acting injectables generic product development

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Goal of the project

- Long-acting injectable (LAI) formulations include biodegradable injectable microspheres and in-situ gelling implants. Compendial in *vitro* release methods for these complex formulations are not well developed, and demonstration of BE for these products can be challenging.

https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-long-acting-injectable-formulations

Contains Nonbinding Recommendations

Draft Guidance on Naltrexone

Active Ingredient: Naltrexone

Dosage Form; Route: Extended-release suspension; intramuscular

Recommended Studies: One study

1. Type of study: In vivo single-dose fasting
   Design: Parallel
   Strength: 380 mg/vial (dose: 380 mg)
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{1-10}, AUC_{10-28}, and $AUC_{0-\infty}$) should fall within the limits of 80-125%

The FDA consider these LAI as "complex products"

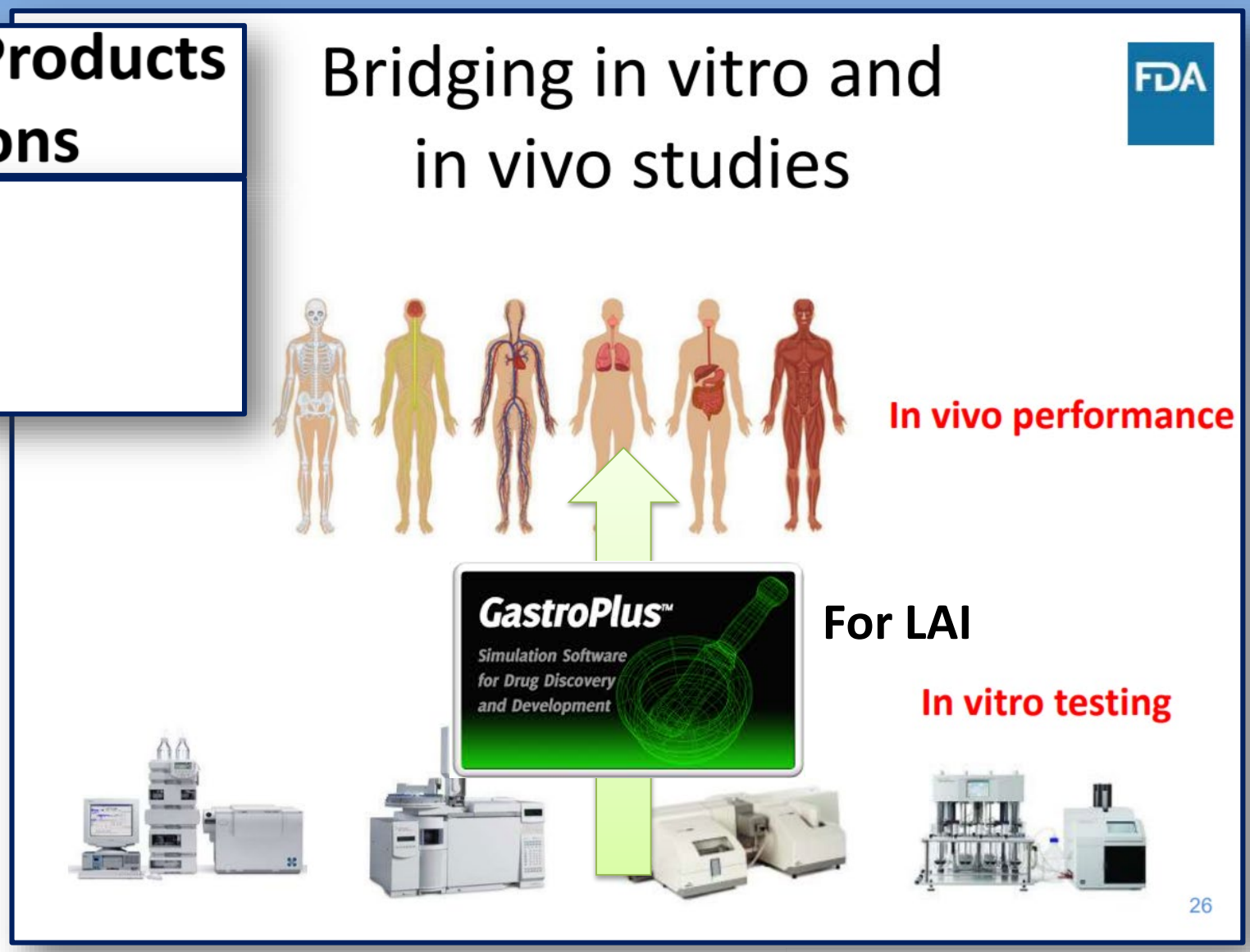
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Naltrexone_ER%20intramuscular%20inj.%20suspension_021897_RV09-15.pdf

Aims of the project

Introduction to Complex Products and FDA Considerations

Xiaohui (Jeff) Jiang, PhD
Deputy Director
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

In 2015, Simulations Plus and a major pharmaceutical company received a grant from the FDA to improve the pre-existing model for in *vitro in vivo* correlation (IVIVC) within GastroPlus®.



https://www.fda.gov/media/108937/download

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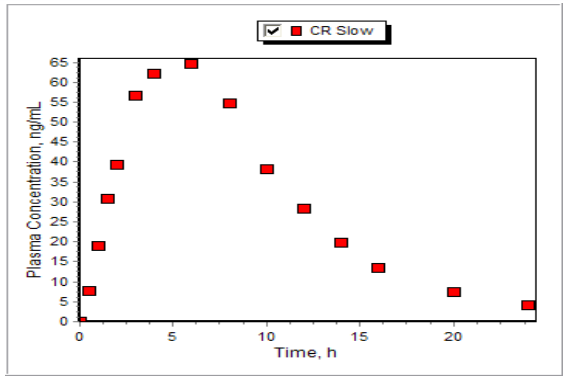
In *vitro-In vivo* correlation: Mechanistic absorption model

- Working definition:

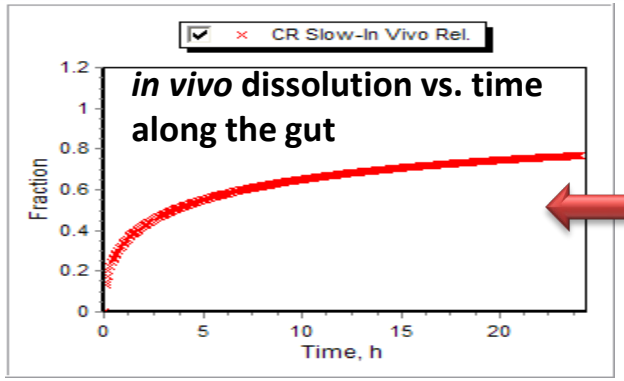
  "A predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form (e.g., the rate or extent of drug release) and a relevant *in vivo* response (e.g., plasma concentration-time data)"

  FDA Guidance for Industry Extended Release Solid Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro*/*In Vivo* Correlations (1997)

- Method:



Deconvolution



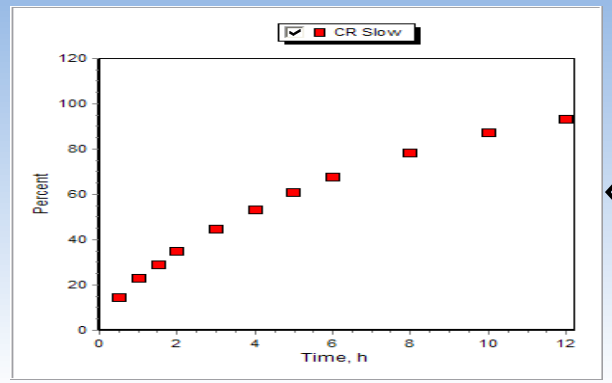
Weibull Function

  - *Inputs*:
    - Physiological parameters
    - Drug properties (solubility, Peff, logP, pKa, etc.)
    - PK data
    - In vitro dissolution profile
  - *Outputs*:

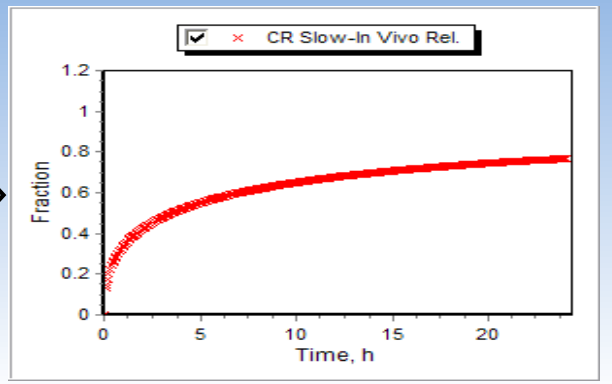
    A model that combines all available *in silico*, *in vitro* and *in vivo* information and provides:
    - *in vivo* dissolution, absorption and bioavailability vs. time profiles
    - Description of site dependent absorption
    - Description of tissue contributions to first pass extraction

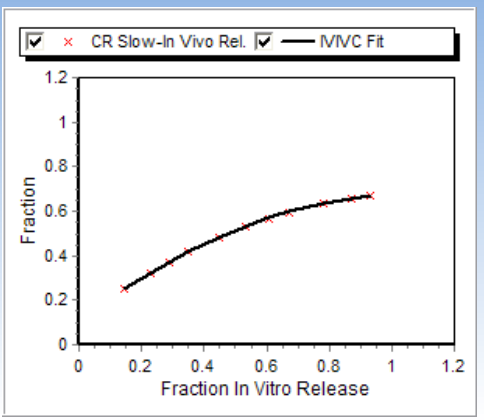
In *vitro-In vivo* correlation (IVIVC): Mechanistic absorption model

- Method:

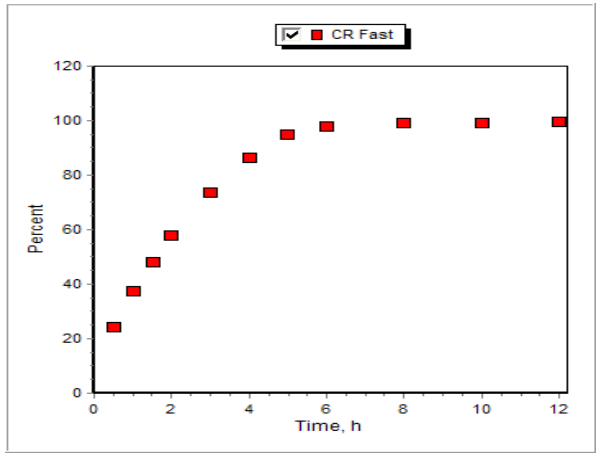


Correlation



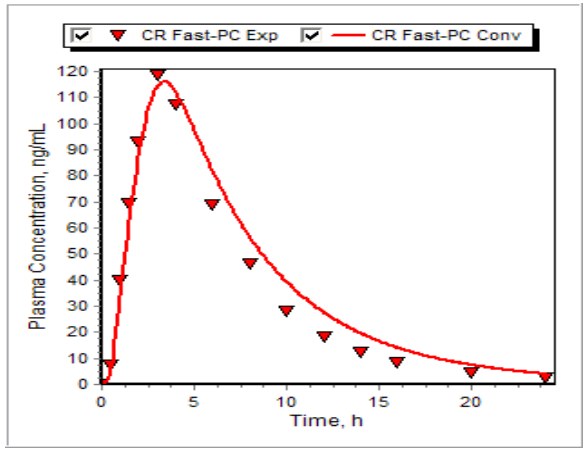


Find the correlation between the deconvoluted *in vivo* release and *in vitro* dissolution profiles



IVIVC

Convolute



Predict the plasma concentration-time profile using the IVIVC and *in vitro* dissolution curve

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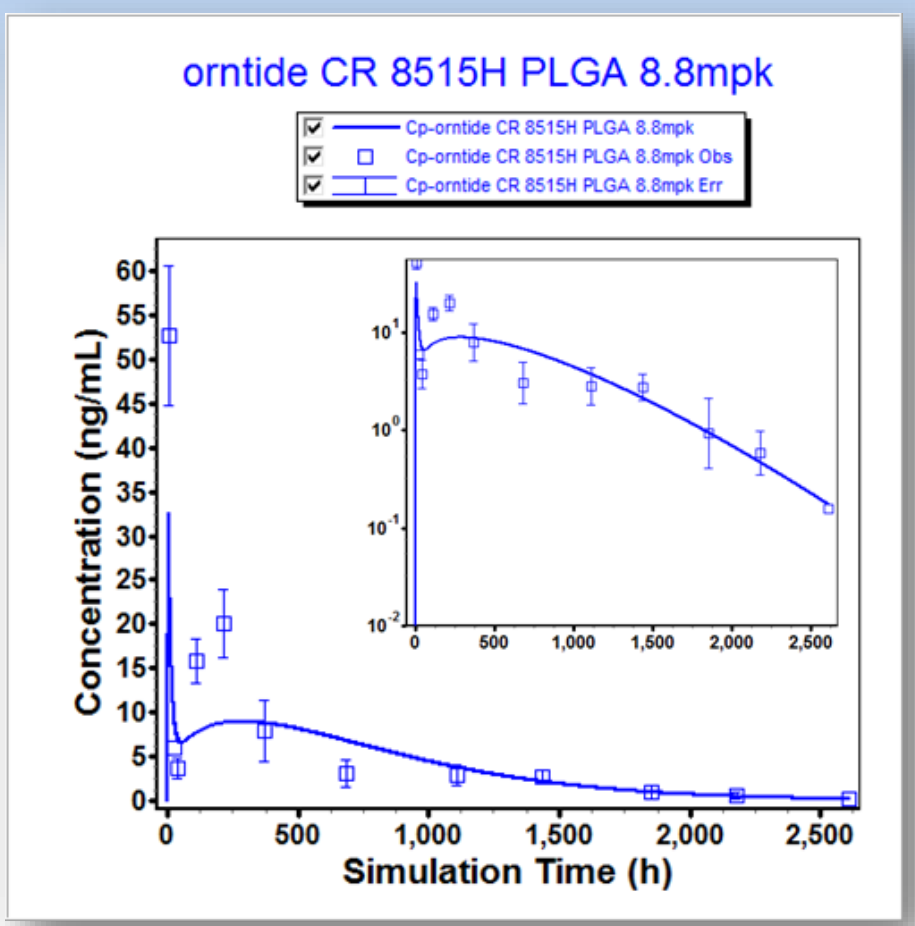
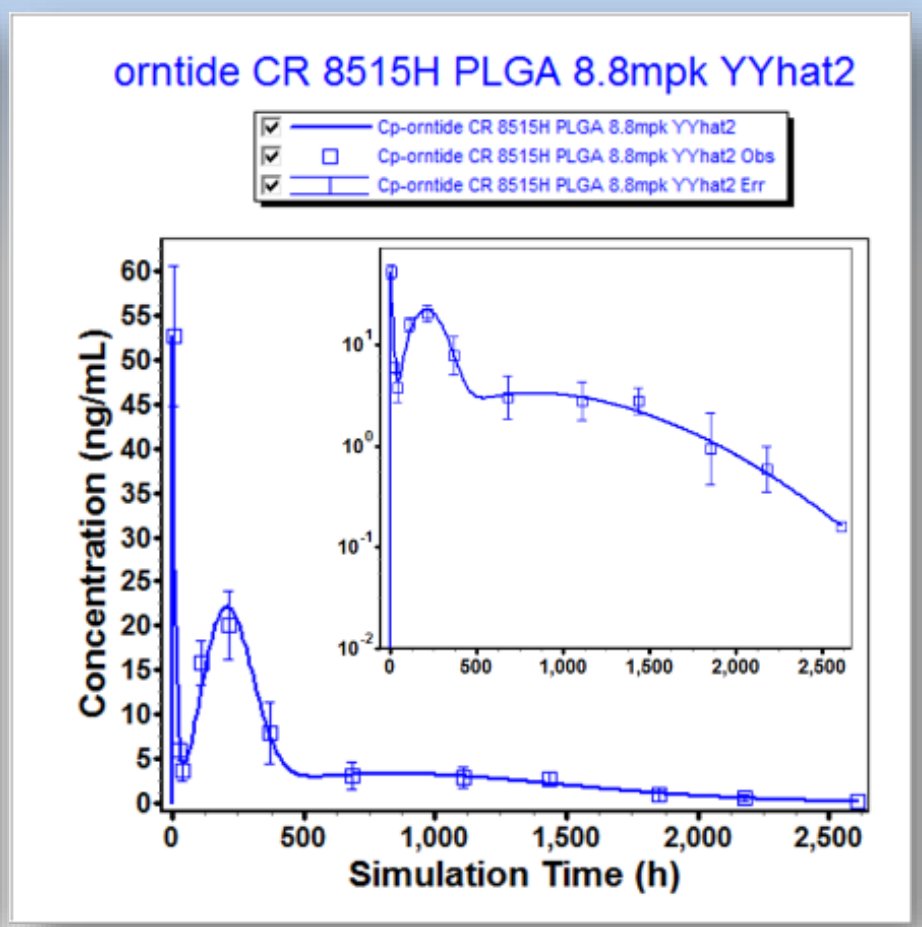
Complex *in vivo* Profile

The *in vivo* release profiles for LAIs are often complex and cannot be described well with a single or double-Weibull function (typically sufficient for deconvolution of *in vivo* release profiles for standard oral formulations). **This issue was addressed by adding triple-Weibull function**.

Simulated Cp-time profiles after SC injection of one LAI formulation in rat. The *in vivo* release profile was fitted as double-Weibull (top) and triple-Weibull (bottom) function with 3 objective function weighting schemes





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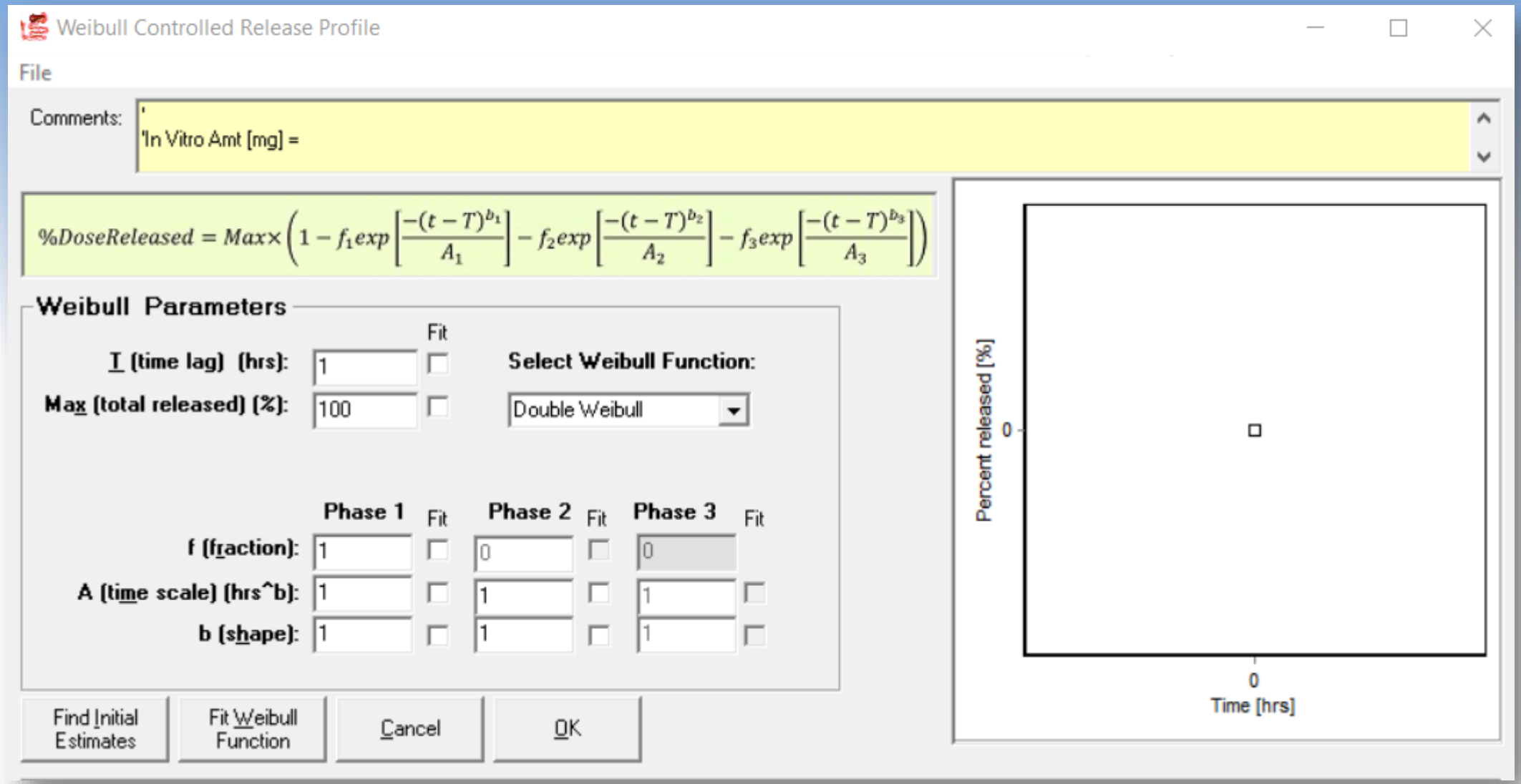
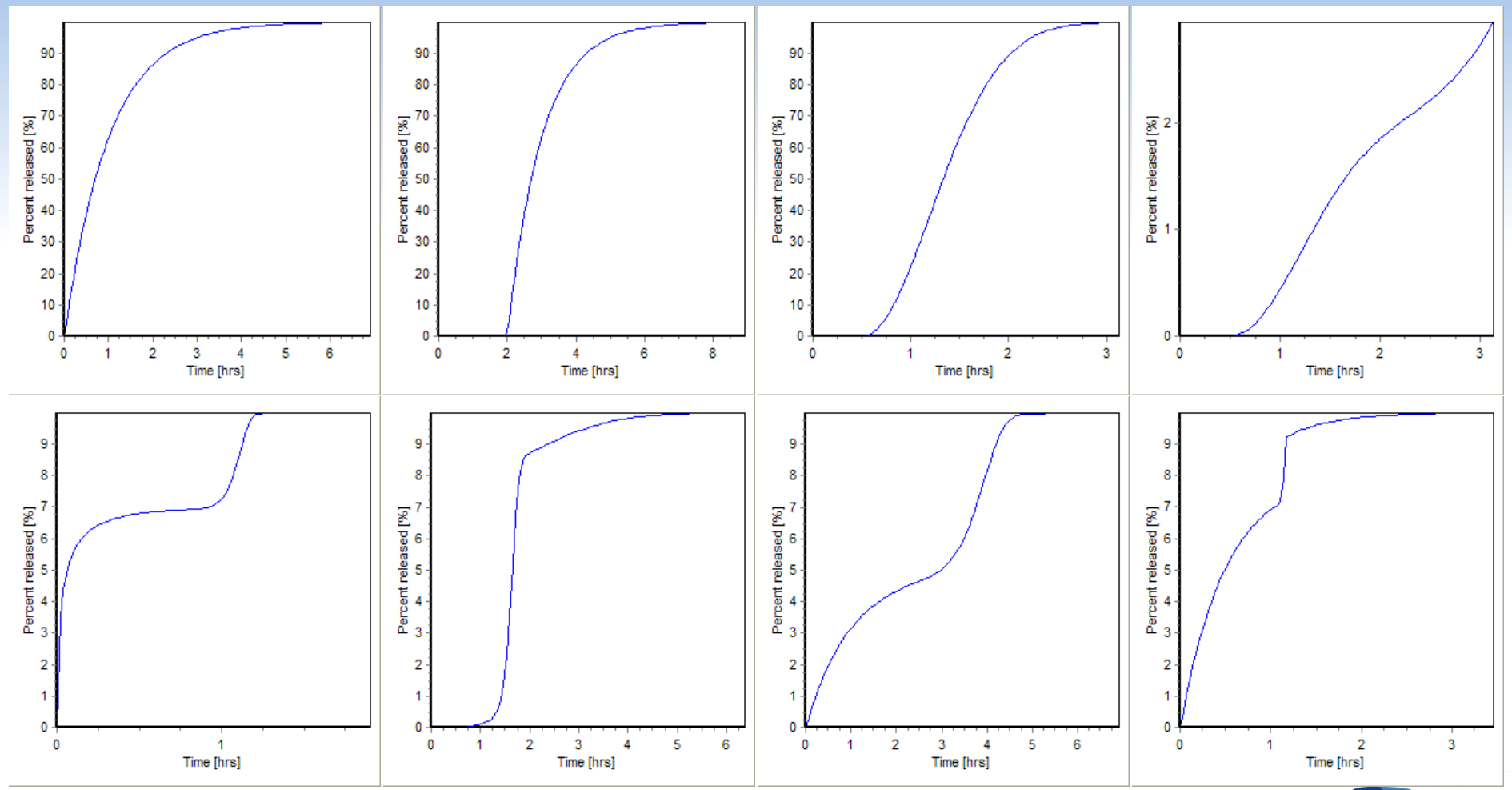


Flexibility of the Weibull Function?

GastroPlus offers single-, double-, and triple-Weibull function for optimization of *in vivo* release profile, which cover a wide variety of release profile shapes.



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Optimization Target Criteria

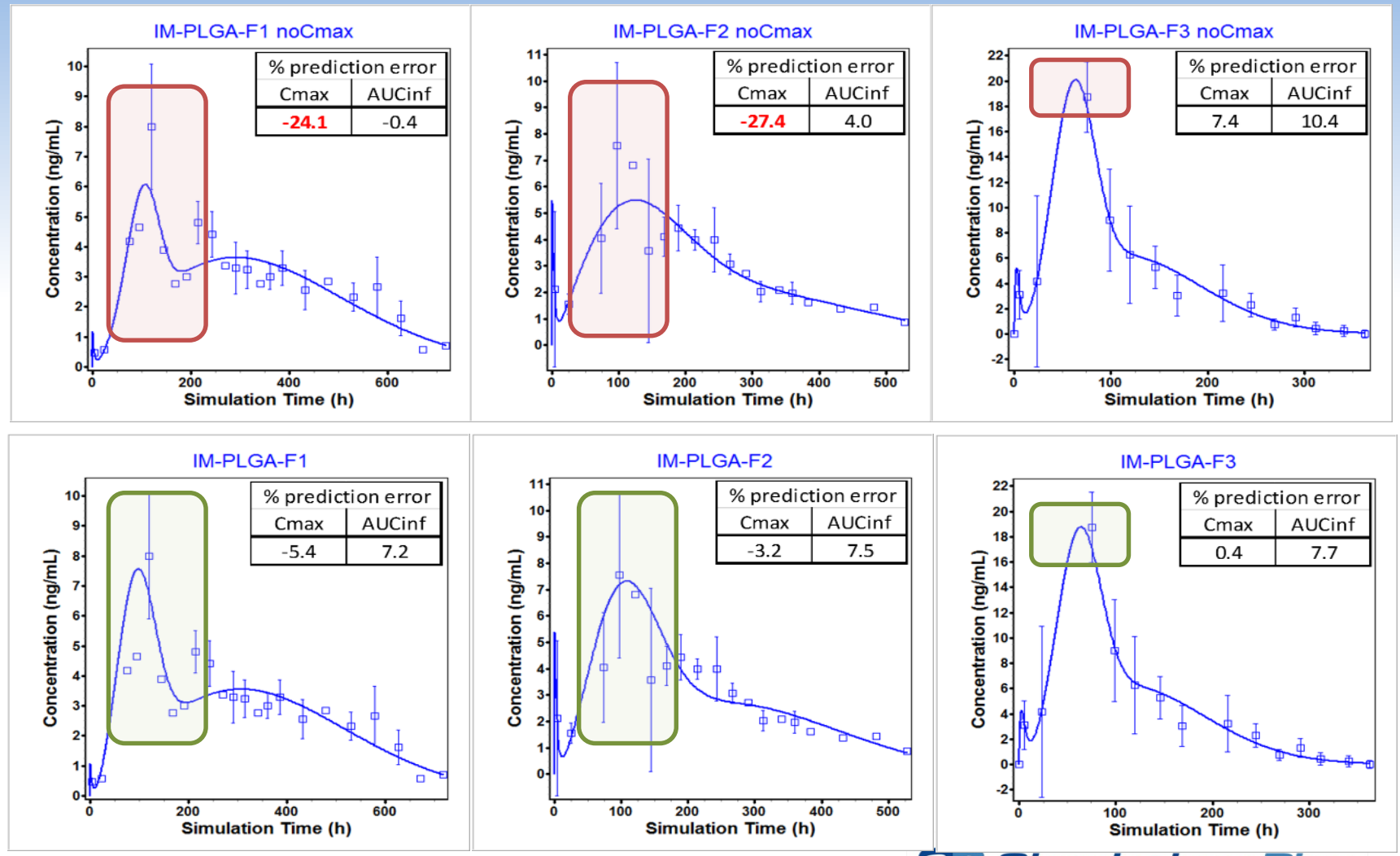
When fitting the *in vivo* release profile against the entire observed Cp-time profile, the error on Cmax is often higher than allowed by the IVIVC criteria due number of other concentration points outweighing the contribution of the single Cmax value.

This issue will be addressed by adding option to include additional weight on Cmax during deconvolution in IVIVCPlus™ module.

Simulated Cp-time profiles for 3 naltrexone LAI microsphere formulations.

Top row shows deconvolution results with target observed Cp-time profile,

Bottom row shows deconvolution results with additional weight added to Cmax value.



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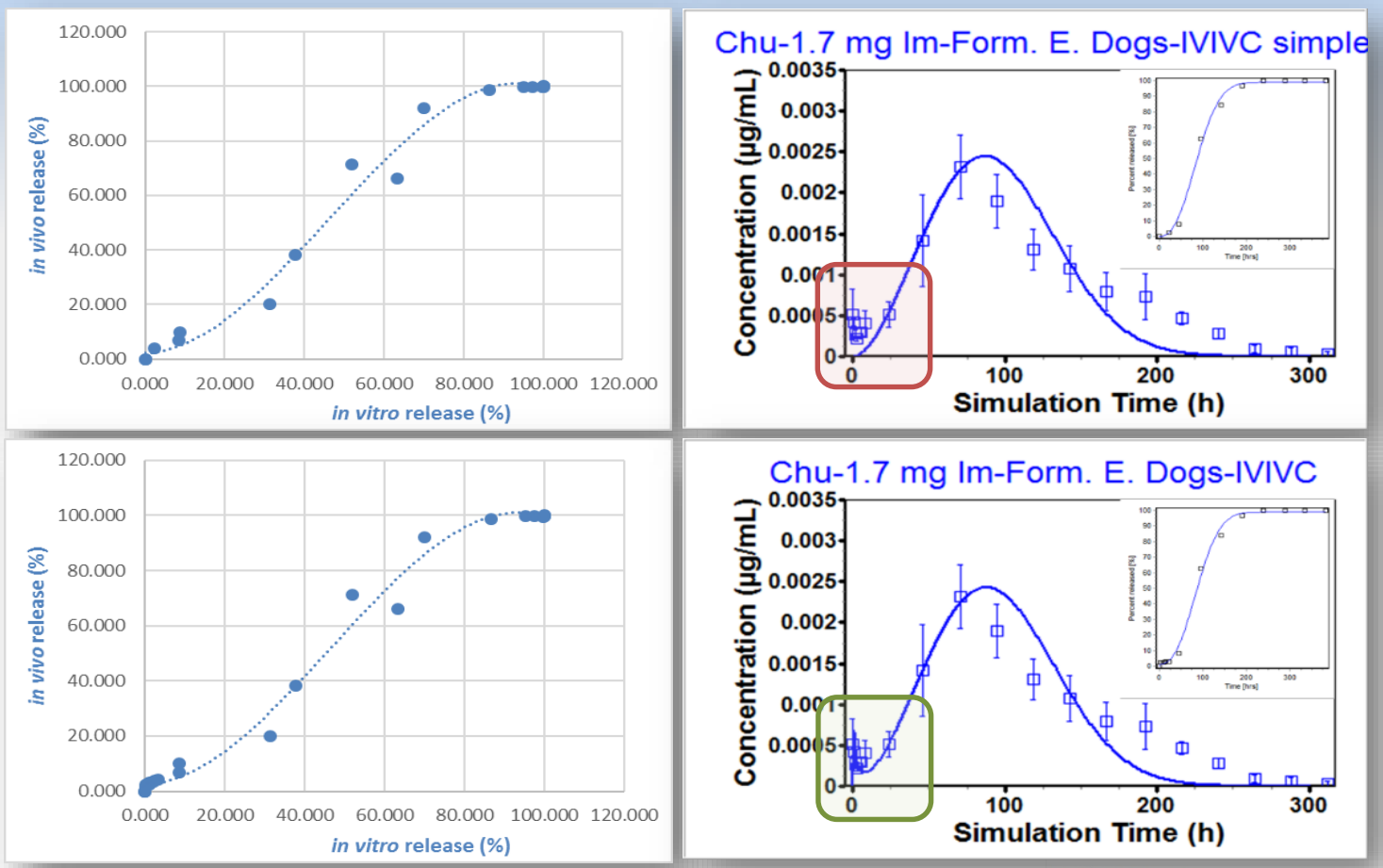
Insufficient *in vitro* Sampling

Insufficient *in vitro* sampling may cause difficulties matching the shape of the predicted Cp-time profile even with an otherwise valid IVIVC (correct prediction of Cmax and AUC).

This issue will be addressed by adding an option to use interpolated *in vitro* profile in IVIVCPlus module.

IVIVC for huperzine A LAI microspheres. Plots on the left are showing IVIVC created from 2 LAI formulations using only the measured *in vitro* points (top) and interpolated *in vitro* points at the early timepoints (bottom). Plots on the right are showing corresponding predicted and observed Cp-time profiles for third LAI formulation.



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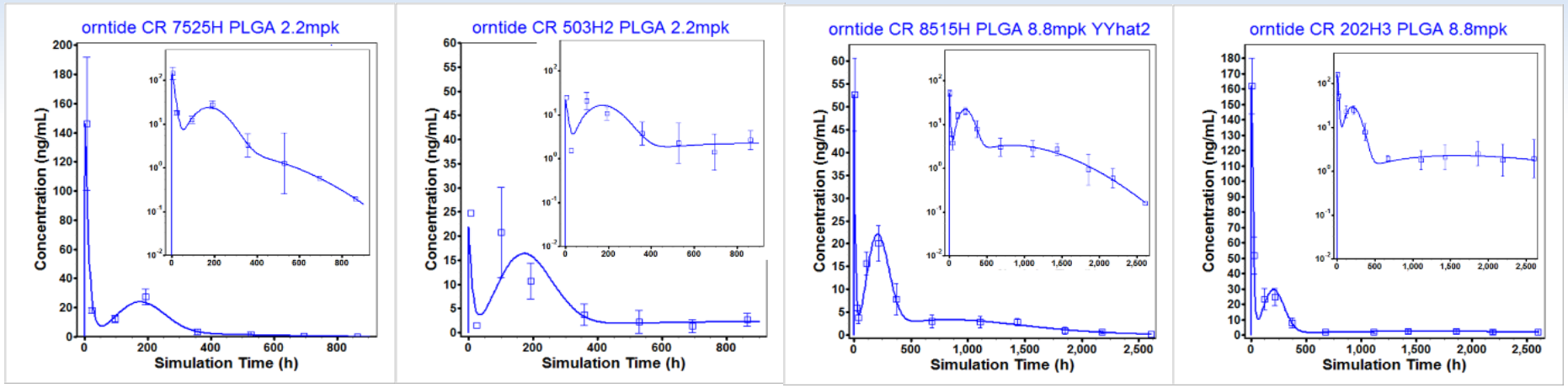
Variability in IVIVC Across Formulations

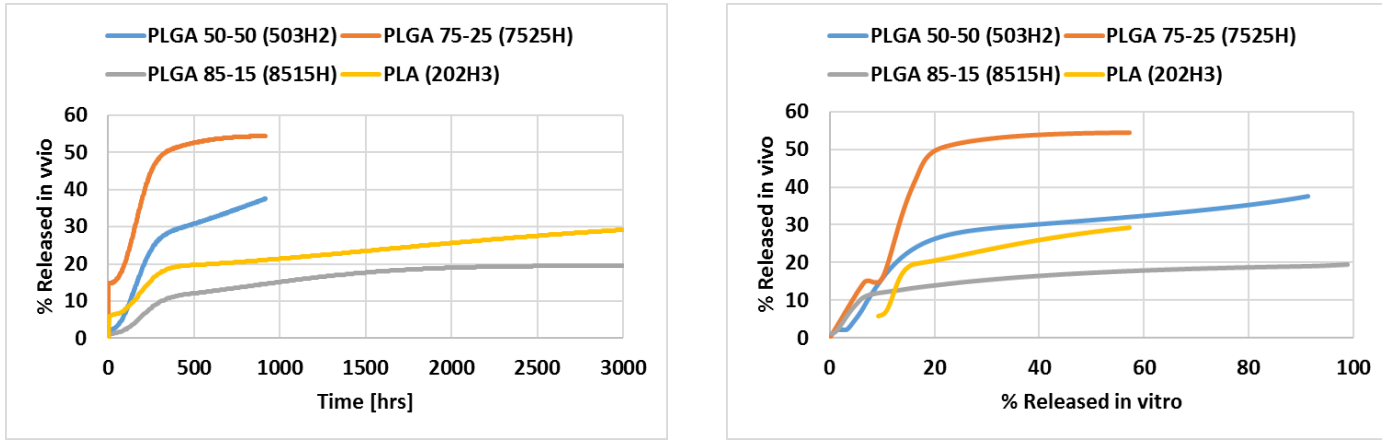
The *in vivo* release profiles were successfully deconvoluted using a triple-Weibull function for all formulations; however, the differences in the deconvoluted *in vivo* release profiles are not accurately captured by the differences in the measured *in vitro* release profiles.

Literature search was performed to identify possible mechanisms responsible for differences between *in vitro* and *in vivo* release for LAI formulations.

Top: Simulated Cp-time profiles for 4 orntide LAI microsphere formulations after successful deconvolution of *in vivo* release profiles.



Bottom: Deconvoluted *in vivo* release profiles (left) and IVIVC plot (right) for 4 orntide LAI microsphere formulations.



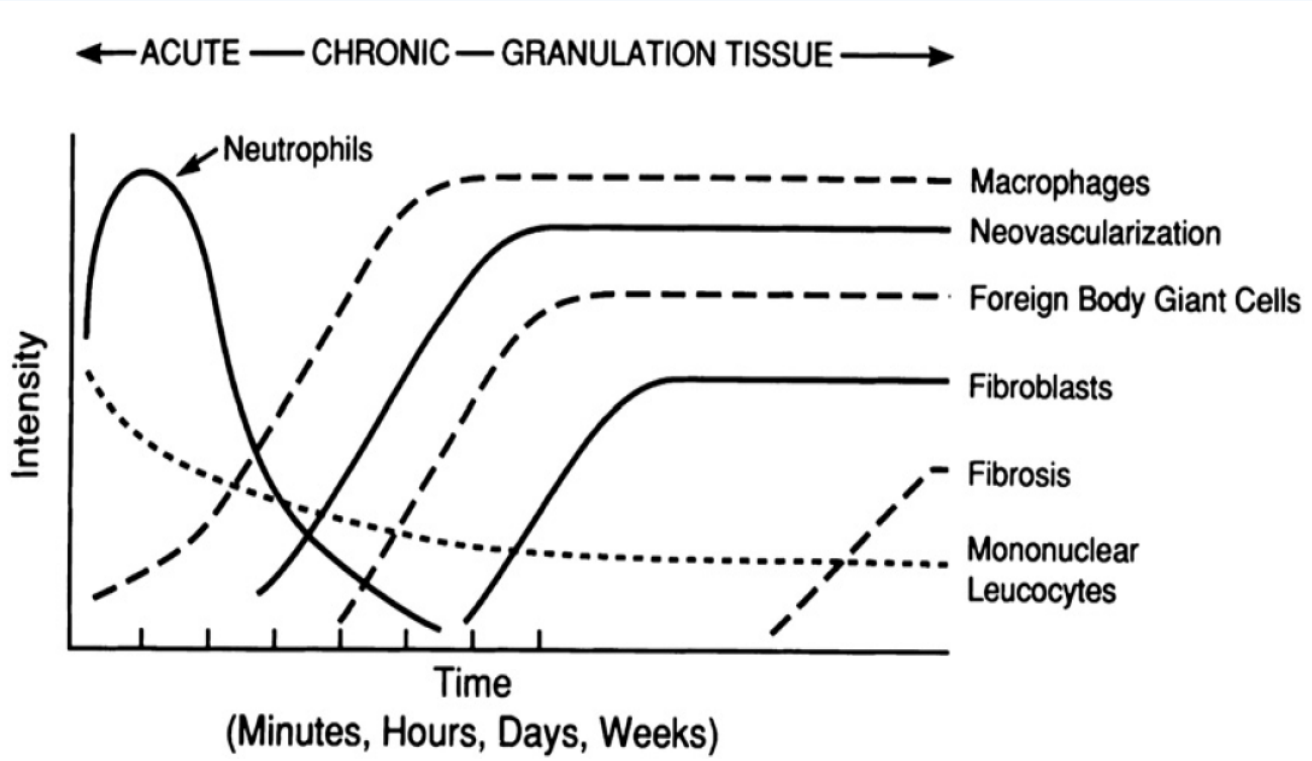
The Tissue Response to PLGA Microsphere Administration

- The tissue response to PLGA microsphere administration can be divided into three phases:

I. Acute phase of the inflammatory response

II. Onset of the chronic phase of inflammation

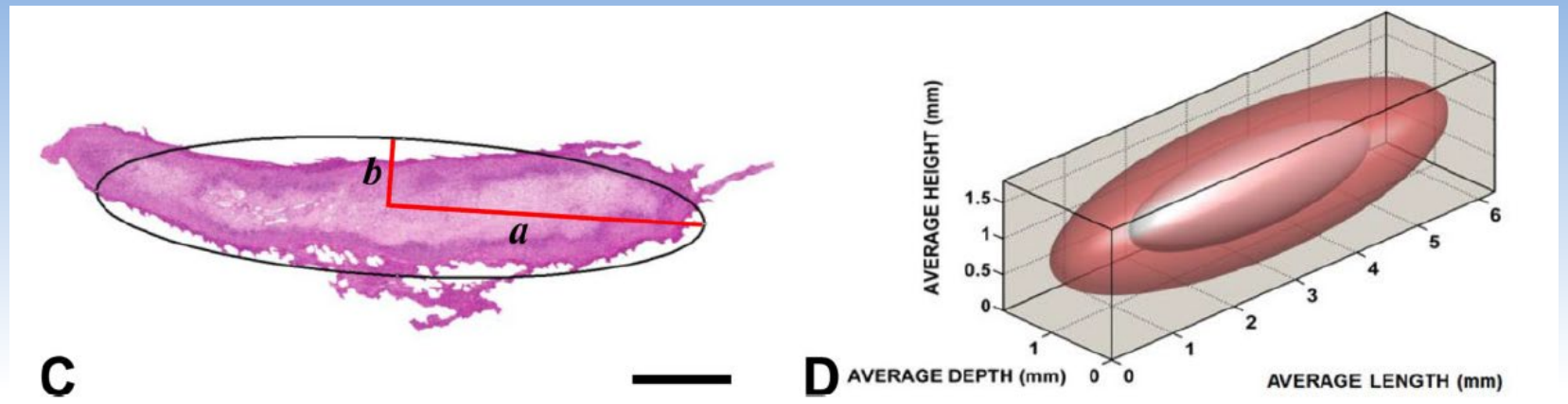
III. Fibroblasts infiltration and collagen deposition



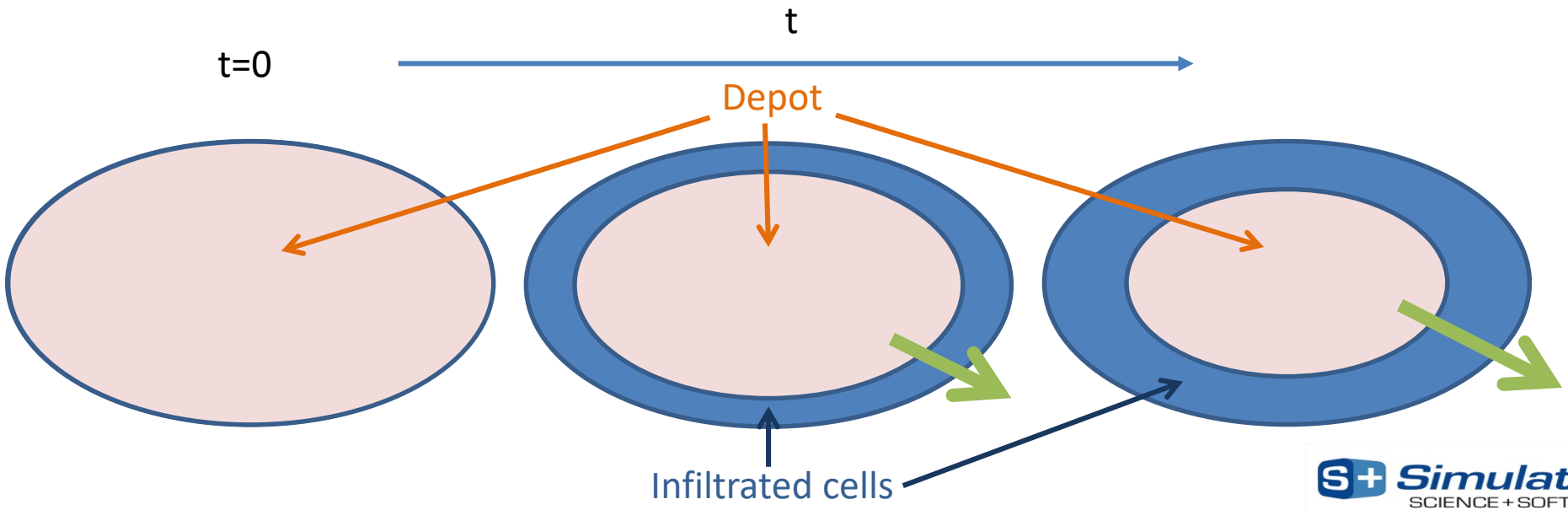
The temporal variation in the three phases of inflammatory response resulting from administration of biodegradable microspheres

Anderson et. al., Advanced Drug Delivery Reviews 64 (2012), 2012

Quantitative Evaluation and Modeling of the Depot Infiltration: Immune Cell Layer



Darville et al, Toxicologic Pathology, 2016, Vol. 44(2) 189-210



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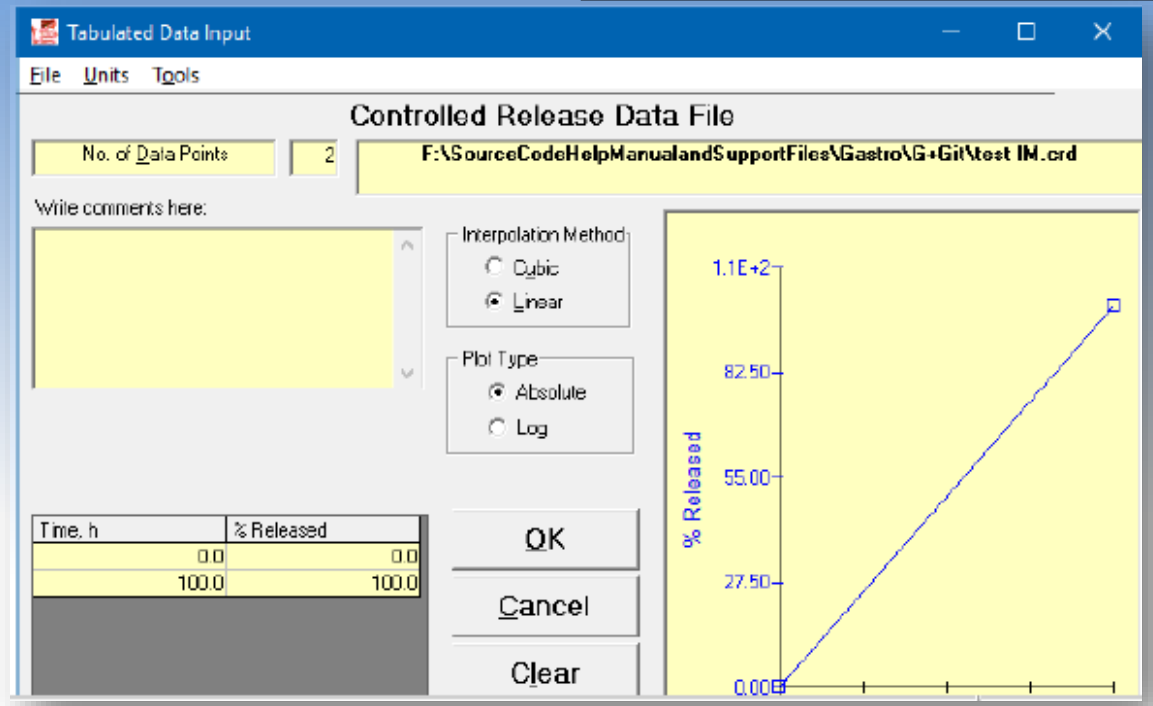
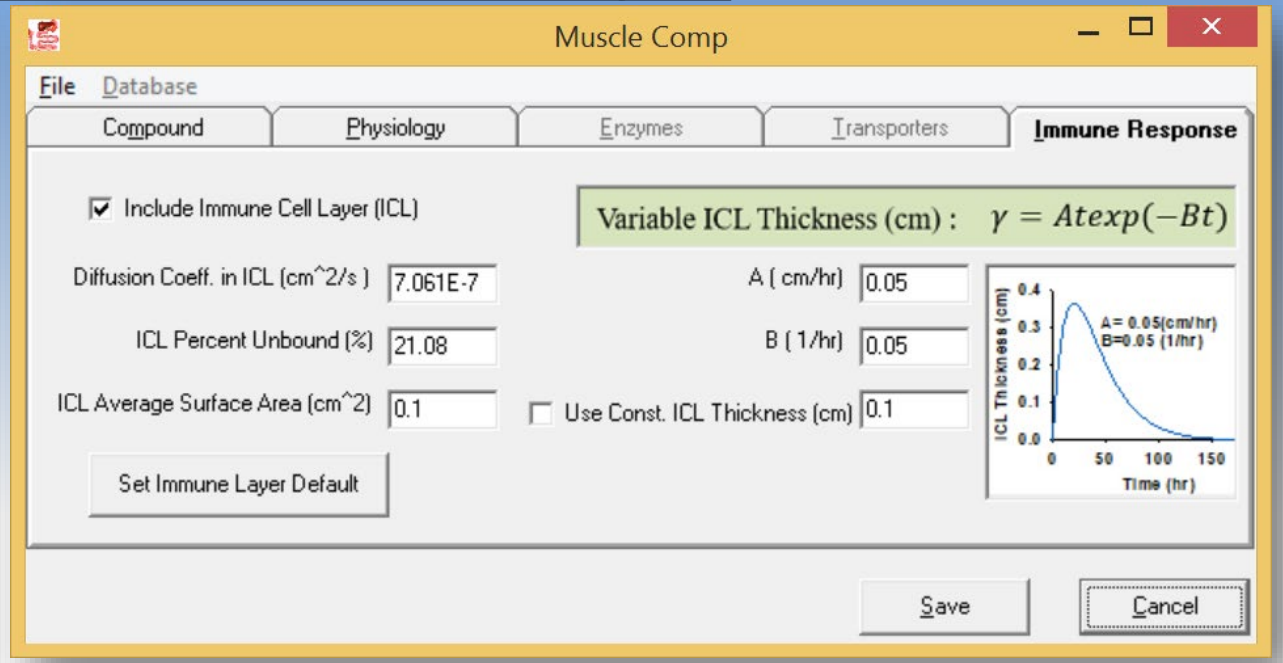
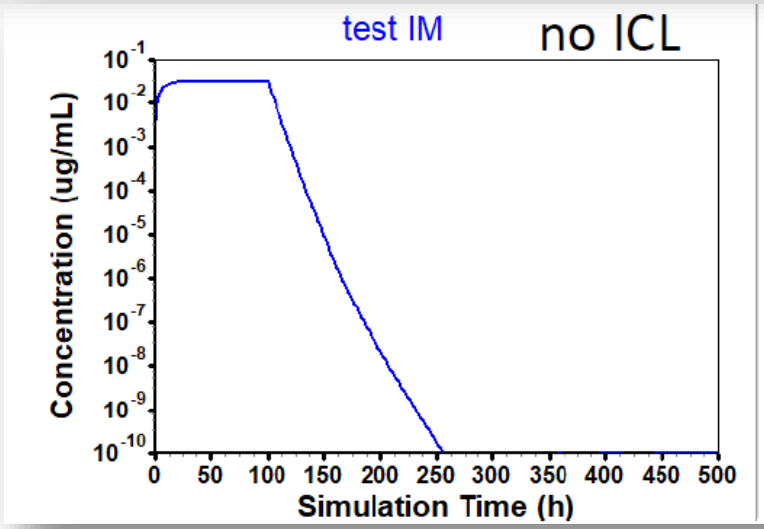
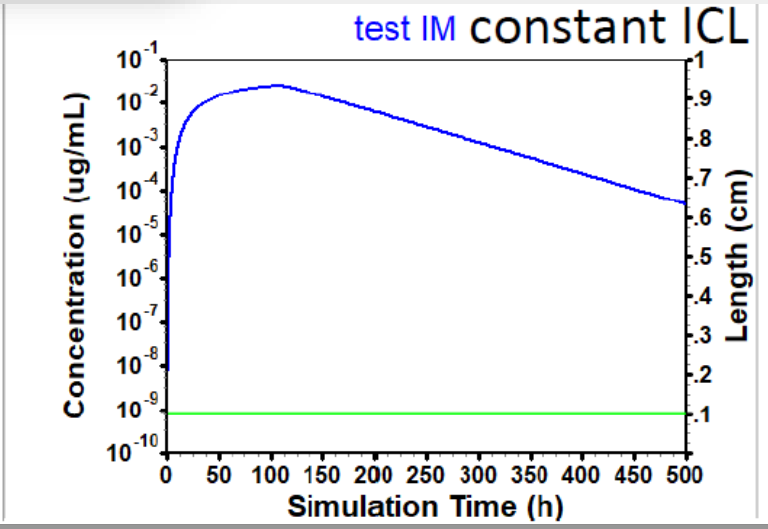
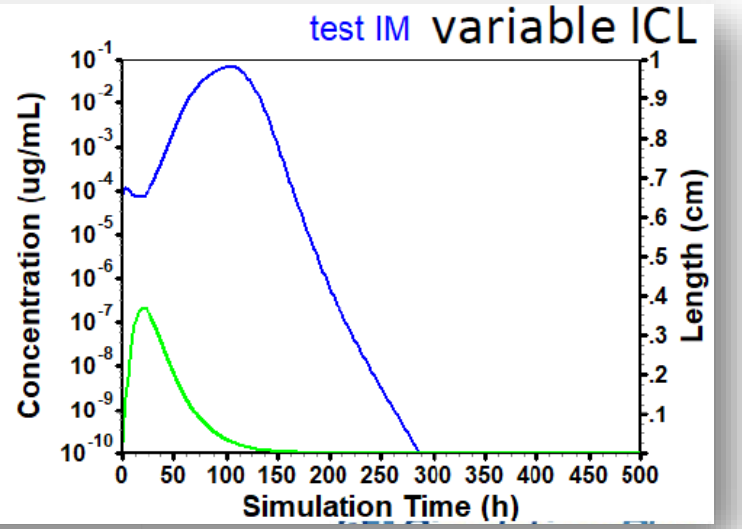
Intramuscular: Immune Cell Layer











Outcomes

- Implementing *in vitro* drug release from PLGA microspheres in DDDPlus.

- Additional functionalities added to the IVIVC module in GastroPlus
  - ***Triple Weibull*** *function for deconvolution*
  - *The capability of perfuming IVIVC using* ***interpolated data***
  - *Adding* ***Shifting and Scaling*** *function to the list of correlation functions*
  - *Adding users the capability of choosing different optimization function as part of deconvolution*
  - *Adding the option for* ***Setting the intercept to zero*** *to Deconvolute then Correlate.*
  - *Adding Intramuscular and Subcutaneous route of administration to the IVIVC module in GastroPlus.*

- Immune Cell Layer (ICL) Model

Summary

- The mechanistic absorption model-based IVIVC was improved to be able to successfully deconvolute the *in vivo* dissolution profile for LAI based on clinical PK data.
- Correlation process was improved to better linked in *vitro* and *in vivo* release profiles
- Other mechanism seem to be important *in vivo*: inflammation and immune cell infiltration

- **Regulatory agencies have access to these models and will use them for BE guidance development and reviews**

Publications/Presentations

- Jul 16, 2017-CRS

Simulation of in vitro Dissolution and Degradation of Orntide-loaded PLGA Microspheres

Mullin J, van Osdol W, Lukacova V, Woltosz WS, Bolger MB

- Nov 2016-AAPS

Development of an In Vitro Mechanistic Model that Describes Drug Release from Risperidone Long Acting Injectable Microspheres

James Mullin; Viera Lukacova; Walter Woltosz; Michael B. Bolger

- Nov 14, 2017-AAPS

Development of In Vitro-In Vivo Correlation for Long Acting Injectable Microsphere Formulations

Shahraz A, Mullin J, Spires J, Lukacova V, Bolger MB, Woltosz WS

- Poster accepted for ACoP10

Modeling and Simulation of the Local Tissue Response to Long-acting Injectable Formulations

Azar Shahraz, James Mullin, Viera Lukacova

GastroPlus® PBPK Consulting: Regulatory Submissions

- Since 2016, our consulting team has built PBPK models for over 110 applications, some of which were used to support submissions to various regulatory agencies:
  - Preclinical development and First-in-Human predictions
  - Formulation optimization
  - DDI predictions
  - Virtual bioequivalence trial simulations
  - Pediatric population simulations and dose projections
  - Food effect modeling
  - Parent-metabolite and prodrug PBPK modeling
  - Pulmonary/dermal/oral cavity product assessment
  - Mechanistic IVIVCs to define product specifications

Key Points to be Addressed to Regulators

- Objective and intended regulatory purpose of the PBPK modeling
- Sufficient background information to place the PBPK modeling in its context in the clinical development of the drug
- Model validation and explicit/systematic discussion of the assumptions made in the submitted drug model and analysis, i.e. supportive data and biological plausibility and impact of the assumptions on the model and the outcome
- Sensitivity analysis, especially on the parameters that were fitted in the model

Questions?