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Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

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Session I: Oral PBPK as an Alternative BE Approach and a Tool for Supporting Risk Assessment and Biowaiver

Are We Ready to Apply Oral PBPK Modeling for BE Determination?

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Patients Need Affordable Medicines

- Apotex is a multinational generic company
- Generics significantly reduce cost of medicines but they need to be demonstrated to perform just as well as the brand products before being available to patients
- Regulators have to ensure proper testing of generic drugs be done
- Significant saving can only be passed on to customers if generics are not over-burdened with unnecessary studies or requirements
- It is important for regulators to foster this environment

Generics Need to be Bioequivalent to Brand Products

- Main in vivo study requirements are single-dose fasted and/or fed comparative bioavailability studies to demonstrate bioequivalence (BE)
- In general, current BE methodology works well
- BE studies are not cheap!
  - Could cost few thousands to over a million USD, depending on the sample size and the study duration
  - Typically take 3 or more months to complete, depending on the complexity of the study design
- Any waiver of BE studies would provide significant cost and time saving
  - Saving would be much greater if clinical endpoint studies are involved

Working Towards the Same Goal of Providing Affordable Medicines

We embrace the application of PBPK modeling for BE determination to reduce the burden of conducting BE studies!!

Application of PBPK Modeling for Generic Industry

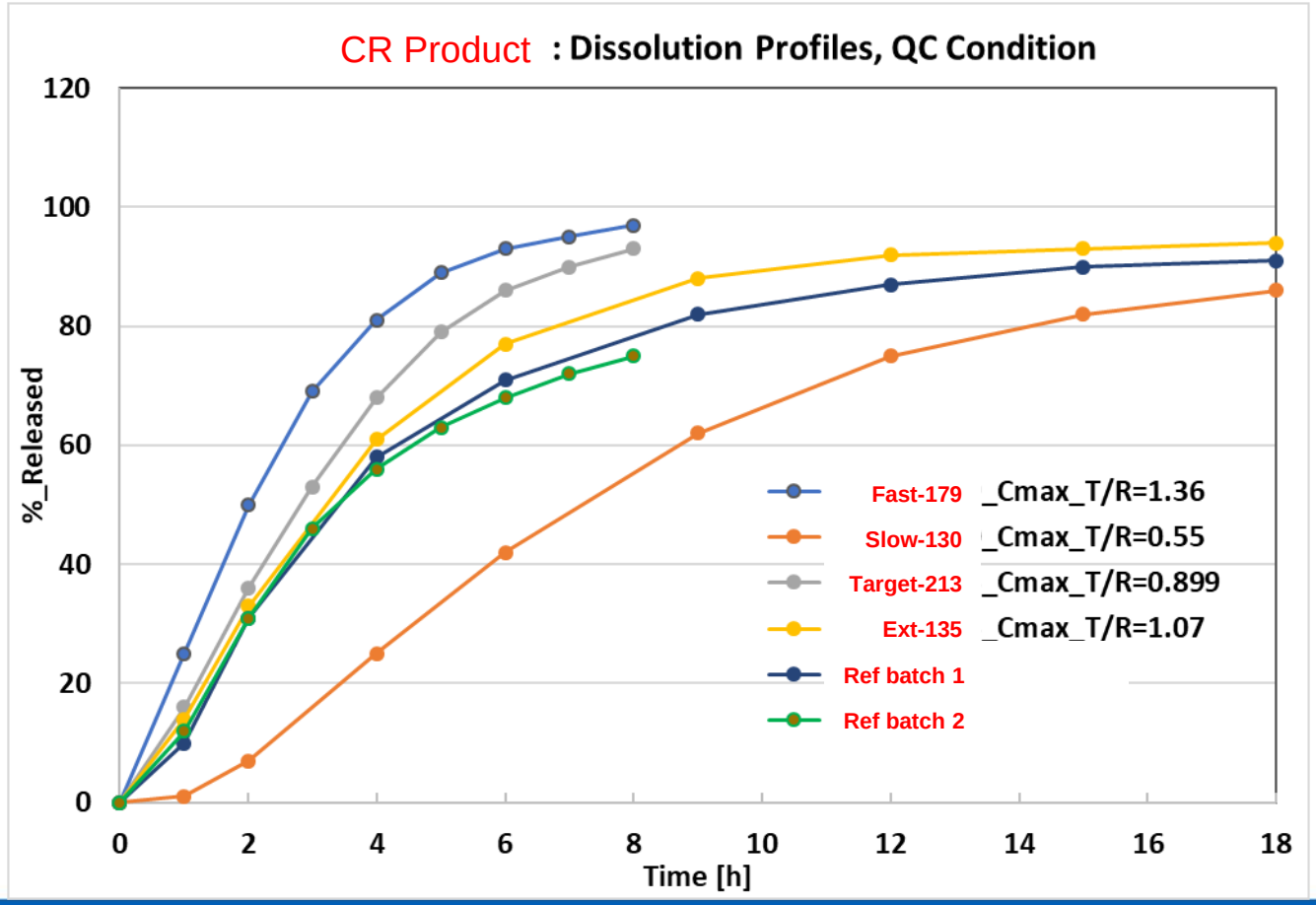
Develop clinically relevant dissolution specifications

- Following steps are typically involved:
  1. Assessment of clinical relevance of the dissolution test;
  2. Identification of physiologically relevant parameters contributing to consistent on-target AUC or Cmax Test/Ref ratios;
  3. Utilization of the established PBPK model to simulate the PK profiles for the pivotal bio-batches and hypothetical “lower-bound” and “upper-bound” batches;
  4. Bioequivalence assessment for “lower-bound” and “upper-bound” batches.
  5. Establishment of dissolution specifications

  ➢ Allows waiver of BE studies for post-approval changes in formulation of an approved drug product

Apotex Experience – A Controlled-Release (CR) Product with a Highly Soluble Drug

A strong rank-order correlation between the dissolution rate of the batches of the CR product used for model development and the T/R ratio of C_{max} observed in bio studies – support clinical relevance of the dissolution test



Note:

Fast-179, Slow-130 and Target-213 were batches with fast, slow and medium dissolution rate used for model development

Ext-135 was the batch served as the external batch for model validation

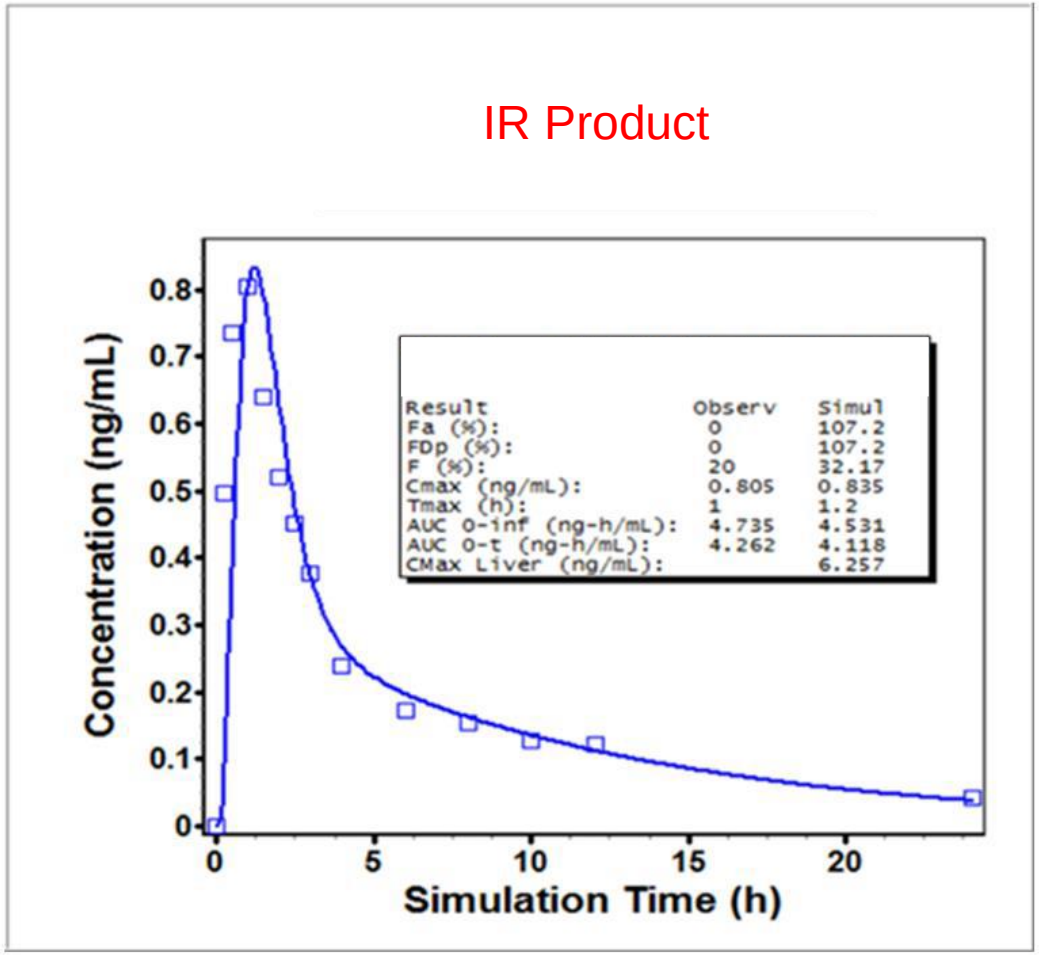
Next Step: Develop PBPK Model Using GastroPlus™ v 9.5

- Identified physiologically relevant parameters from literature, in-house data or default values
- Some PK parameter values were estimated based on published data for the IR product of the drug

Parameter	Comment/Source
Log P	Pubchem database
pKa	Pubchem database
Solubility	In-house data
Human effective permeability	Derived from Caco-2 permeability from literature
Gut Physiology	Commonly recommended for IVIVC
Absorption scale factor	GastroPlus default
First-pass effect	Set to 70% for initial modeling based on the literature
Fraction unbound	Australian Prescriber
Vd	Estimated based on the IR product data
CL	Estimated based on the IR product data
Inter-compartmental constants	Estimated based on the IR product data

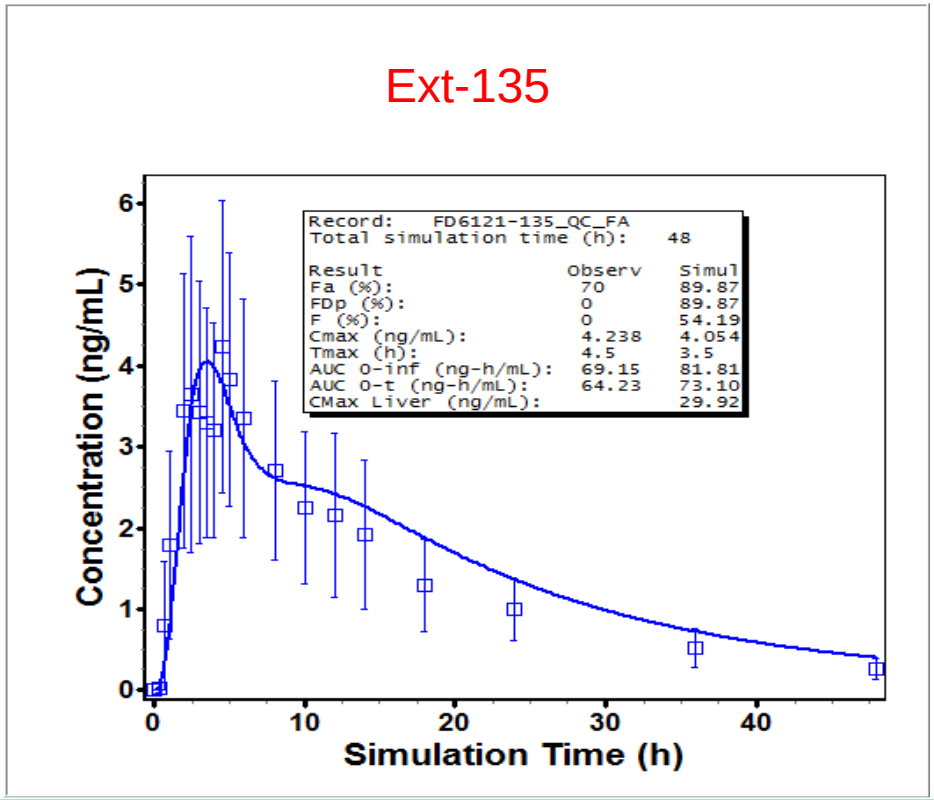
Initial Assessment of the PBPK Model

- Initial parameter values used fit the PK profile of IR product well



Appropriateness of the PBPK Model for the CR Product

- Using the in-vitro dissolution and in-vivo bio data of the fast, target and slow-batches, and after adjusting some PK parameter values, the PBPK model for the CR product was developed
  - Fits the PK profile of the external batch (Ext-135) reasonably well



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Internal and External Validation of the PBPK Model

- Accuracy of the simulation was calculated for all batches - summarized in the table below with the percent prediction error (%_PE) calculated for C_{max} and AUC_{0-t}

Percent Prediction Error for C_{max} and AUC_{0-t}						
	Fast-179	Slow-130	Target-213	Ext-135	Mean absolute %_PE	Mean absolute %_PE (including Ext-135)
C_{max}	13.9%	1.8%	-8.7%	4.4%	8.2%	7.4%
AUC_{0-t}	6.1%	-6.3%	-6.0%	-13.8%	6.1%	7.7%

- The predictability of the PBPK model was considered adequate as %_PE for both PK parameters of all the batches did not exceed 15%, and the mean absolute %_PE was less than 10% for both parameters
- Next step: used the model to justify the dissolution test acceptance criteria for future batches

Hypothetical Dissolution Profiles Representing “Lower-bound” and “Upper-bound” Batches

- Based on the dissolution profile of the BE batch (Target-213), proposed the dissolution data of the “Lower-bound” and “Upper-bound” batches that are believed to still be bioequivalent to the reference product

Time [h]	% Released	
	"Lower"	"Upper"
0	0	0
0.5	3	12
1	10	25
2	30	48
3	42	65
4	55	78
5	63	90
6	70	100
7	73	100
8	77	100
9	82	100
10	85	100

Assess BE of the “Lower-bound” and “Upper-bound” Batches

- Used the established PBPK model to simulate the PK profile of the “Lower-bound” and “Upper-bound” batches for the same number of subjects (N=16) as in the pivotal BE study for Target-213
- To generate random variation of data, the GastroPlus default variability (e.g. 20%CV for the first pass effect, 40%CV for the systemic clearance, 20%CV for the Vd, 10%CV for body weight, etc.) was incorporated into the simulation
- For each simulated PK profile, determined the C_{max} and AUC_{0-t}
- For BE assessment, determined the ratio of the geometric means between the hypothetical batches and the reference product

Geometric mean of simulated data					Ratio of geometric means	
	Ref Batch 2 (Ref)	"Upper" (T1)	"Lower" (T2)		T1/Ref	T2/Ref
C_{max}	3.66	3.77	3.25		1.030	0.888
AUC_{0-t}	67.7	57.8	63.8		0.854	0.943

- The ratios are within 0.8-1.25 for both “Lower-bound” and “Upper-bound” batches, thereby supporting BE of these two hypothetical batches

Setting the Acceptance Criteria for Dissolution Profile of Future Batches

- Based on the dissolution profile of the “Lower-bound” and “Upper-bound” batches, the following specification times and limits were chosen

Time (Hr)	% Dissolved
1	NMT 25%
4	55-78%
6	NLT 70%
10	NLT 85%

- Meeting the dissolution specification limits allows a waiver of BE study for future batches of the CR product

More Application of Oral PBPK Modeling for BE Determination

Any opportunity to apply PBPK modeling for waiver of BE studies will be welcomed by generic companies – possible opportunities as shown below

1. Bio-waiver for post-approval changes beyond SUPAC Level 2 requirements
    - Could we extend the biowaiver from the example given before to post-approval manufacturing changes that exceed the SUPAC Level 2 requirements?
2. Bio-waiver for non-proportional formulations
    - BE studies are typically conducted on the highest strength
    - A waiver of bio studies can be obtained for lower strengths if they are similarly formulated and display similar dissolution as the highest strength
    - Could use PBPK modeling for demonstrating BE of non-proportionally formulated lower strengths or proportional formulations with dissimilar dissolution profile?
3. Waiver of fed BE study
    - BE study under fasting conditions instead of fed conditions is typically required by regulatory agencies because it has been demonstrated to be more discriminatory in detecting differences in bioavailability between formulations or products
    - Some agencies like FDA still require fed BE study
    - Could use PBPK modeling for simulating fed conditions to assess BE?
4. Bio-waiver of BCS Class III drugs
    - For BCS Class III drugs, all of the excipients should be qualitatively (Q1) the same and quantitatively (Q2) similar to obtain a waiver of BE studies
    - Could use PBPK modeling to justify biowaiver for Q1/Q2 noncompliant formulation?

Challenges Faced by Application of PBPK Modeling for BE Determination

- Many people, including regulatory authorities and clinicians, do not trust modeling
  - Too complicated to understand – presence of black boxes
  - Estimation by simulation
    - Unlike computer fitting, simulation results may be performer-dependent as different performers can stop the simulation at different points
    - Results could be “manipulated” to produce favorable outcome!
  - Different softwares used may result in different outcome for the same set of data
    - Assumption of certain physiological parameters may be different between softwares
- Simulation of GI conditions like the fed state with high fat, high calorie food is difficult
  - Difficult to simulate the interaction between food and the drug particles
  - Impact of food on GI motility of drug could be highly variable
- Model validation process could be demanding
  - Extensive validation could require a large amount of in-vivo data that may negate the cost and time saving

Thank you!

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