Physiologically Based Pharmacokinetic Modeling for BCS IV Drugs and Case Examples

2024 November FDA-CRCG Nitrosamine Workshop

Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products

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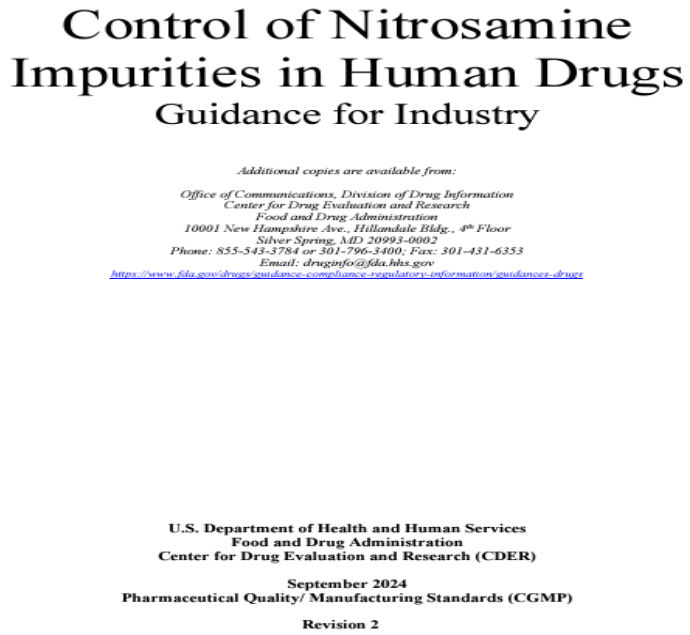
Disclaimer

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

Background



Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2024
Pharmaceutical Quality/ Manufacturing Standards (CGMP)

Revision 2

Reference: *Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs (September 2024). Link: https://www.fda.gov/media/141720/download*

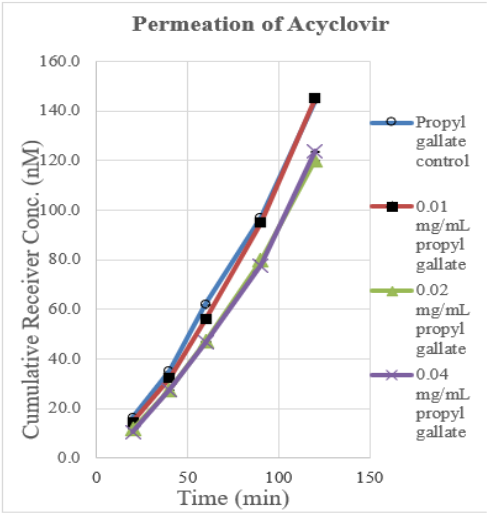
Approaches to inhibit Nitrosamine drug substance-related impurities (NDSRI) formation:

- The addition of small amounts of **antioxidants** to formulations may significantly inhibit the formation of NDSRIs in drug products
- Incorporating excipients that modify the microenvironment to neutral or basic pH (i.e., **pH modifiers**) could also inhibit NDSRI formation

Impact of Antioxidants on Permeability of BCS Class III Model Drugs

- Based on an FDA contract project with PHARMARON

Effects	Antioxidant	Model Drugs
No effect on permeation	Alpha-tocopherol	Acyclovir, atenolol, cimetidine, ranitidine
	Ascorbic acid	Acyclovir, atenolol, cimetidine, ranitidine
	Cysteine	Acyclovir, atenolol, cimetidine, ranitidine
	Propyl gallate	**Acyclovir**, atenolol, cimetidine, ranitidine



- **Notes**: The antioxidants tested, at the concentrations tested, had little or no effect on the permeation of the four Biopharmaceutics Classification System (BCS) Class III model drugs, which could suggest that reformulating drug products to include an antioxidant may be a feasible approach for reducing the formation of NDSRIs.

***Reference**: Chris Bode, Presentation in 2023 June CRCG Nitrosamine workshop*

Bioequivalence studies for reformulated products

Per Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, Section V.C.2.b.

- The results from the **studies conducted on BCS III drugs** are appropriate to **extrapolate to BCS I and II drugs** that have high permeability.
- Immediate-release (IR) solid oral and oral suspension products incorporating an active pharmaceutical ingredients (API) that is BCS I, II, or III and reformulated to **include one of the antioxidants evaluated by FDA or a pH modifier would not be expected to change in quality or clinical performance**.
- For IR solid oral or IR oral suspension products containing **BCS IV APIs**, due to their poor solubility and permeability, and modified-release products for all BCS classes, due to the complexity of the release mechanism, FDA does not believe the alternative approach to establishing bioequivalence (BE) or bioavailability (BA) described above would be appropriate.
- A validated **in vitro-in vivo correlation**, **physiologically-based pharmacokinetic (PBPK) modeling**, or **in vivo BE** studies are appropriate to demonstrate BA or BE and support a formulation change.

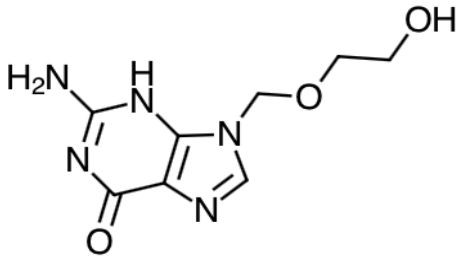
Reference: *Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs,* ***(September 2024).***
Link: ***https://www.fda.gov/media/141720/download***

Case Example 1: Using PBPK Modeling to Evaluate the Impact of Antioxidant on Bioequivalence of Acyclovir (RLD-Zovirax®)

Acyclovir is an antiviral drug

- ❑ Slightly soluble in water
- ❑ Ampholyte with both acidic and basic groups
- ❑ BCS III (at low dose) or BCS IV (at high dose)
- ❑ Available immediate release (IR) tablets are 200, 400, and 800 mg
- ❑ Absolute bioavailability (10 – 30%) in humans

This poor systemic BA is considered to be a result of the characteristics of the drug itself and not its delivery vehicle.



Acyclovir

***Reference**: Wu Fang, Presentation in 2023 June Nitrosamine Workshop*

RLD: Reference Listed Drug

PBPK Modeling for Risk Assessment

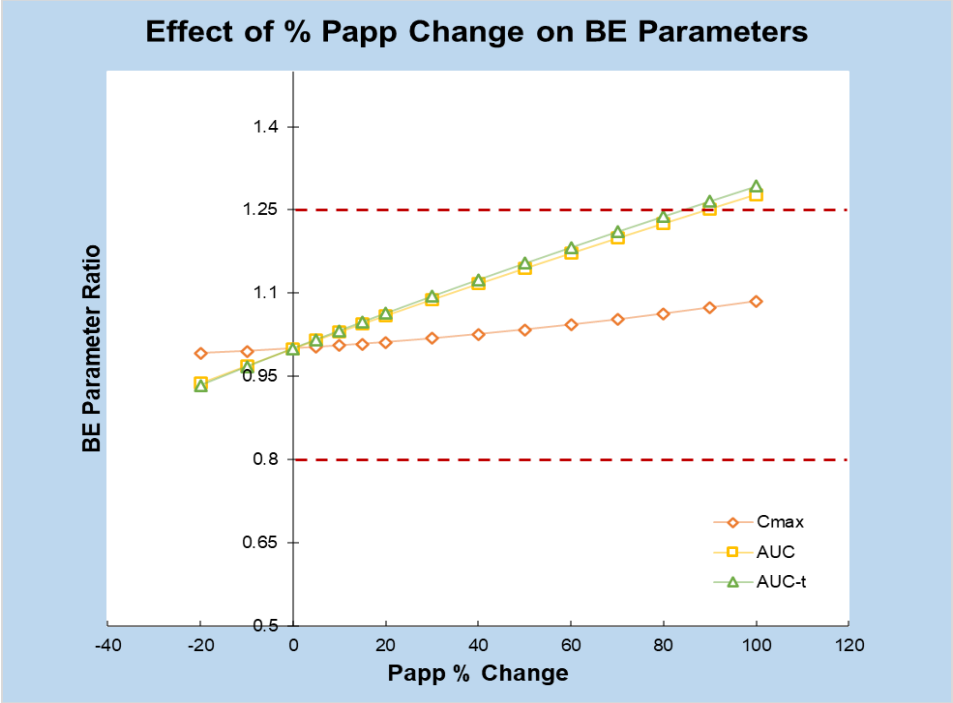
Intravenous PK data obtained from the literature were used to develop PBPK model for IV administration (2.5 mg/kg and 5 mg/kg IV infusion)

Oral PK data obtained from the literature were used to develop PBPK model for Acyclovir IR Tablet (200 mg and 400 mg dose)

PBPK model was validated using PK data and BE studies for Acyclovir IR Tablet (800 mg dose) and data from literature

1) Conduct sensitivity analysis to evaluate the effect of apparent permeability (Papp) on PK BE parameters (Cmax ratio, AUC ratio between Test and RLD); 2) Conduct virtual bioequivalence trials to assess the potential impact of excipient mediated permeability changes on BE of Acyclovir IR tablets and can support post-approval changes

Effect of Excipients on Virtual Bioequivalence (VBE) of Acyclovir IR Tablet-800 mg

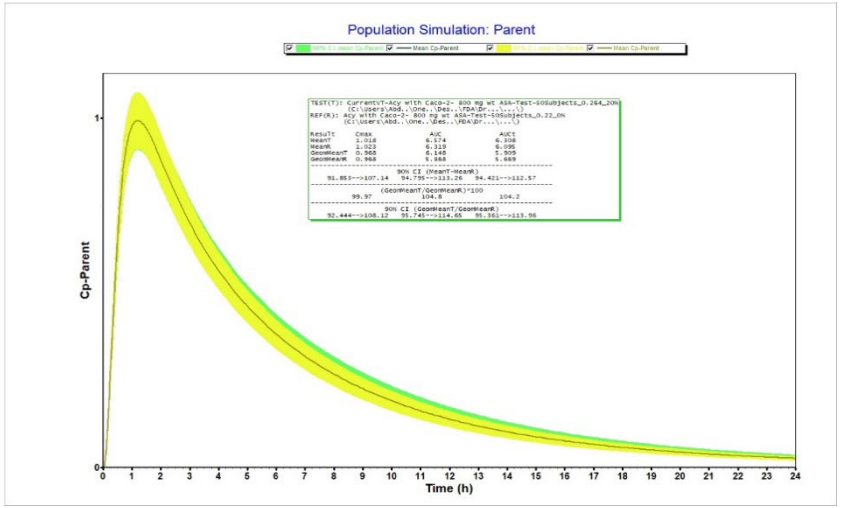


Fasted-Condition

***Reference**: Wu Fang, Presentation in 2023 June Nitrosamine Workshop*

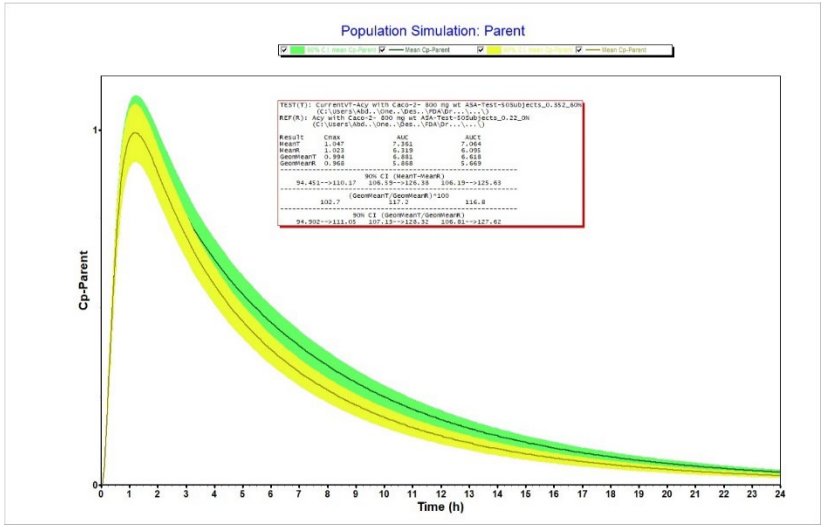
Effect of Excipient VBE of Acyclovir IR Tablet-800 mg

Reference VS Test (10% Increased P_{app})



PK Parameter	Geometric Mean T/R (90% CI)
Cmax	99.97 (92.44-108.12)
AUC0-inf	104.8 (95.74-114.65)
AUC0-t	104.2 (95.36-113.96)

Reference VS Test (60% Increased P_{app})



PK Parameter	Geometric Mean T/R (90% CI)
Cmax	102.7 (92.99-111.05)
AUC0-inf	117.2 (107.13-128.32)
AUC0-t	116.8 (106.81-127.62)

BE Scenario **Fasted-Condition** **Non-BE Scenario**

***Reference**: Wu Fang, Presentation in 2023 June Nitrosamine Workshop*

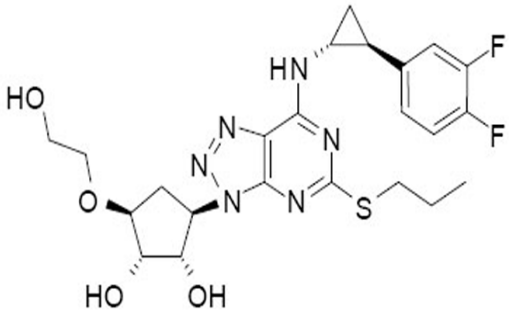
Summary

- Validated acyclovir PBPK was used to assess the impact of excipients on BE parameters.
- In vitro testing systems can be used to provide relevant information on in vivo permeability change by excipients.
- Sensitivity analysis was conducted to evaluate the impact of excipients on BE parameters of 800 mg Acyclovir IR Tablet.
- The VBE results suggested that more than 60% change of Papp value for test product due to presence of certain excipient may result in failed BE of acyclovir 800 mg IR tablet under fasted conditions.
- For other BCS IV drug products, use PBPK and VBE simulations to determine the boundary of acceptable permeability changes.

Case Example 2: PBPK Modeling to Evaluate the Impact of Solubility and Permeability on PK for IR Tablets of Ticagrelor (RLD-Brilinta®)

Ticagrelor is a $P2Y_{12}$ platelet inhibitor, indicated to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI.

- ❑ Aqueous solubility of approximately 10 µg/mL (0.01 mg/mL)
- ❑ Available immediate release (IR) tablets are 60 and 90 mg
- ❑ The mean absolute bioavailability of ticagrelor is about 36% (range 30%-42%).
- ❑ BCS IV drug



Ticagrelor

***Reference**: Label for BRILINTA® (ticagrelor) tablets*

Ticagrelor PBPK Modeling for Risk Assessment

Intravenous PK data obtained from the literature were used to estimate disposition parameters and develop Ticagrelor PBPK model for IV administration

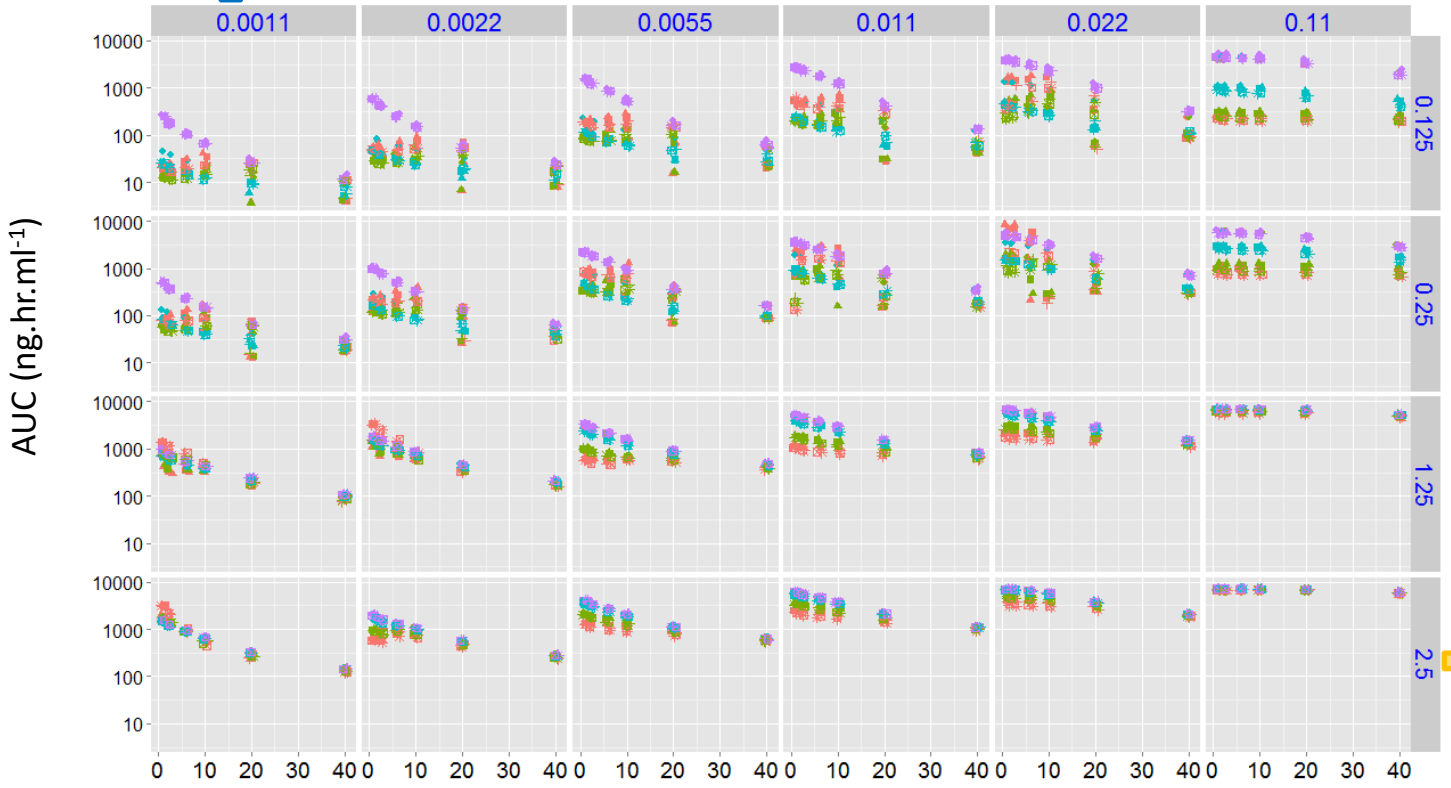
Particle size of drug substance and oral PK data obtained from Ticagrelor IR tablets were used to develop PBPK model (with Johnson dissolution model) for Ticagrelor IR Tablets

PBPK model was validated using PK data from in vivo clinical studies with different formulations: (1) solution; (2) generic IR tablets with different API particle size.

1) Conduct sensitivity analysis to evaluate the impact of solubility and permeability on PK parameters; 2) Conduct VBE trials to assess the risk of non-BE by using the upper limit of particle size specification (boundary) proposed by the generic firm

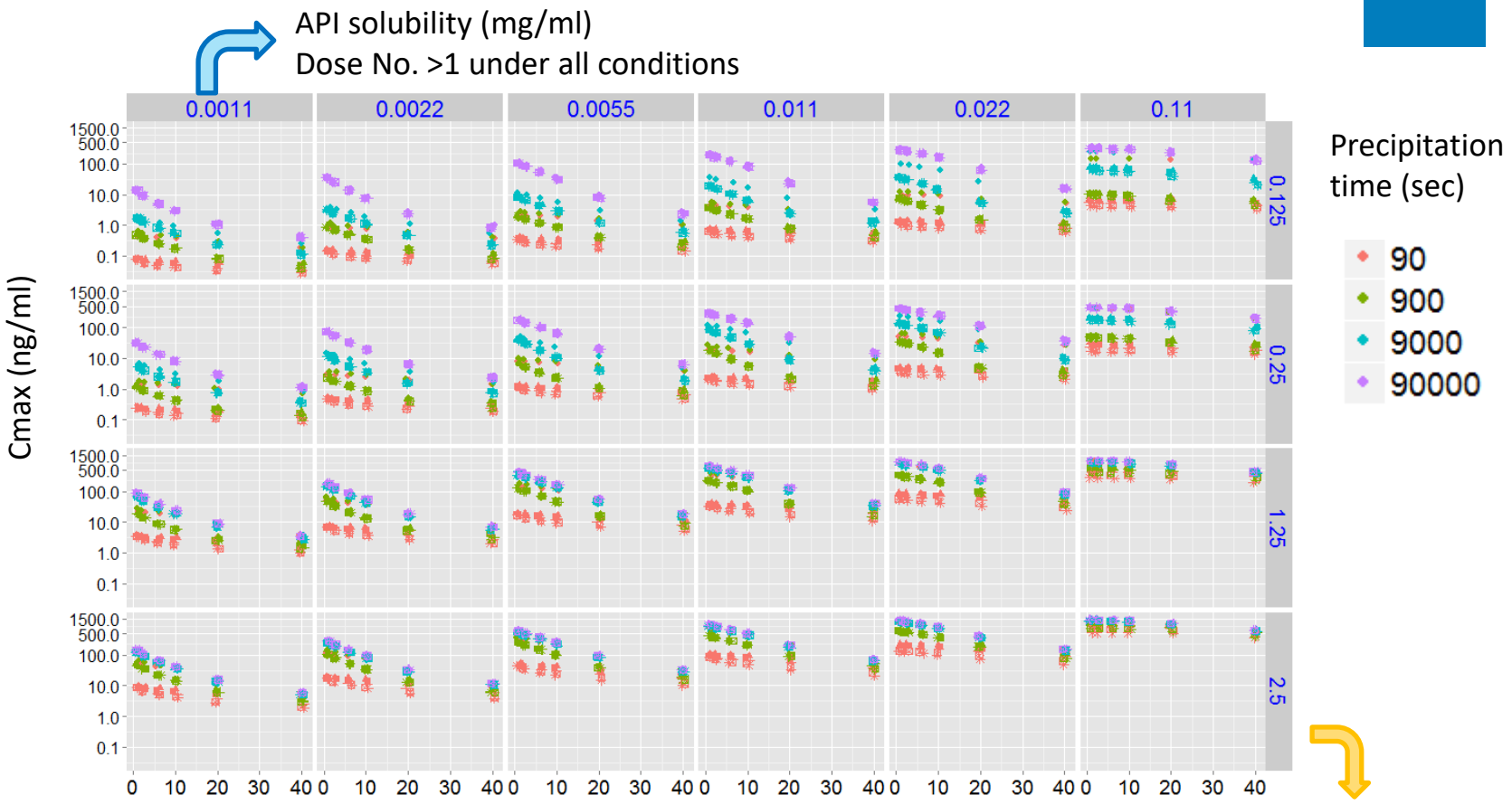
Sensitivity Analysis of Impact of Parameters on Cmax

API solubility (mg/ml)
Dose No. >1 under all conditions



***Reference**: Lin H, Poster Presentation in 2016 AAPS conference*

Sensitivity Analysis of Impact of Parameters on Cmax



***Reference**: Lin H, Poster Presentation in 2016 AAPS conference*

Summary

- Multi-dimensional sensitivity analysis using PBPK was performed. The outcomes on PK parameters (Cmax and AUC) from the combination of a range of values of these uncertain/optimized parameters were tested.
- Sensitivity analysis results suggested that various parameters, including solubility, permeability, and API precipitation time can influence the sensitivity of oral absorption toward API particle size distribution.
- For Ticagrelor case (BCS class IV drug), solubility and permeability interplay with each other.
- Lower permeability results in more sensitivity of PK parameters towards solubility or particle size changes. Also, lower solubility results in more sensitivity towards permeability or particle size changes.

Practical Advice

- FDA is open to alternative approaches, e.g., PBPK modeling to support demonstration of BE for reformulated BCS IV drug products.
- Conduct sensitivity analysis using PBPK modeling to determine the boundary of acceptable permeability changes (also with the incorporation of dissolution information) and support risk assessment.
- Model-Integrated Evidence (MIE) Industry Meeting Pilot program can be used to get FDA feedback on these model based alternative approaches.

Reference: MIE Industry Meeting Pilot Program https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/model-integrated-evidence-mie-industry-meeting-pilot-between-fda-and-generic-drug-applicants

Acknowledgement

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