Totality of Evidence Including PBPK Modeling to Support BE Assessment and Approval of Mesalamine Delayed Release Tablets (Part II)

Advancing Generic Drug Development 2024:
Translating Science to Approval

Day (2), Session (5B):
(Spotlight Generic Drug Review Challenges and Solutions)

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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.

Learning Objectives

- Interpret how the totality of evidence was used to support BE assessment for locally acting products
- Explain how to develop PBPK model to predict local drug amount by incorporating dissolution data at different pH

BE: bioequivalence; PBPK: physiologically-based pharmacokinetic modeling

GI Locally Acting Products

- Assessing BE for locally acting GI drug products is challenging.
- Systemic exposure may not reflect drug concentrations at the site of action.
- BE recommendations of oral locally acting GI drug products are based on drug product properties and mechanism of action.
- PBPK models may be used to explore the correlation between dissolution in GI tract and plasma concentration profiles, predict local drug amount and support BE evaluation of such products.

PBPK Modeling to Support BE Evaluation of Mesalamine DR tablets

Background

- Mesalamine delayed release (DR) tablet is indicated for mildly to moderately active ulcerative colitis
- The product-specific guidance for this product recommends a fasting pharmacokinetic (PK) bioequivalence (BE) study, and a fed PK BE study and comparative dissolution studies at four different pH (6.5, 6.8, 7.2, and 7.5)
- f2 values for dissolution profile comparison between test product and reference standard were <50 at pH 6.8 and 6.9 buffer condition
- The test product and RLD were found to be bioequivalent for systemic PK under both fasting and fed conditions

Question: Whether the slower release of test product at certain pHs would significantly impact the local drug exposure compared to the reference listed drug (RLD).

PSG Recommendation

Active Ingredient: Mesalamine

Dosage Form; Route: Delayed release tablet; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, partially or fully replicated crossover design, in vivo
   Strength: 1200 mg
   Subjects: Healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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2. Type of study: Fed
   Design: Single-dose, partially or fully replicated crossover in vivo
   Strength: 1200 mg
   Subjects: Healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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3. Type of study: In vitro comparative dissolution study
   Strength: 1200 mg
   Apparatus: USP Apparatus 2 (paddle)
   Pretreatment Stage 1: 2 hours in 0.1 N HCl at 100 rpm (750 mL)
   Pretreatment Stage 2: 1 hour in pH 6.4 Phosphate buffer at 100 rpm (950 mL)
   Evaluation Stage: Each of
   (1) pH 6.5 Phosphate buffer at 100 rpm
   (2) pH 6.8 Phosphate buffer at 100 rpm
   (3) pH 7.2 Phosphate buffer at 100 rpm
   (4) pH 7.5 Phosphate buffer at 100 rpm
   Volume: 960 mL
   Temperature: 37°C
   Sampling times: 1, 2, 3, 4, 5, 6, and 8 hours or as needed for profile comparison
   Additional comments: The applicant should use at least 24 dosage units of the test product and at least 2 lots of the reference product (12 dosage units per lot) per test. The f2 metric will be used to compare dissolution profiles.

Draft Guidance on Mesalamine, revised June 2016,
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20tab%20DR_RLD%2022000_RC06-16.pdf

Dissolution data

- Three-stage dissolution data:
  - Stage 1: 0.1N HCl for 2 hours
  - Stage 2: pH 6.4 phosphate buffer for 1 hour
  - Stage 3: 6.5, 6.8, (6.9, 7.0), 7.2 and 7.5 phosphate buffer for 8 hours
- The in vitro dissolution testing over a range of pH serves as a surrogate of in vivo drug release in the GI tract.
- In this case the test product showed decreased release compared to RLD at pH < 7.

Stage 3 pH condition	F2 value
6.5	< 50
6.8	< 50
6.9	< 50
7.0	> 50
7.2	> 50
7.5	> 50

PBPK Modeling for BE Evaluation

Intravenous PK data obtained from the literature were used to estimate disposition parameters.

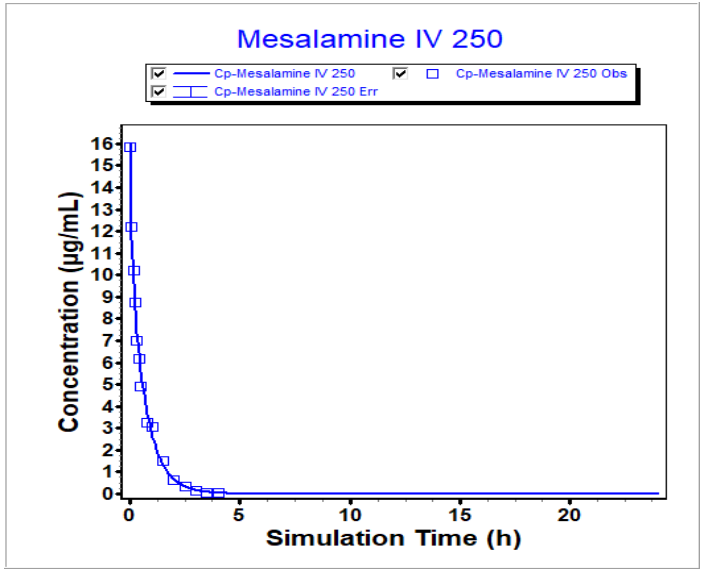
The PBPK model was developed for mesalamine DR tablet. The intestinal first pass effect was optimized. Three stage dissolution data (with pH 6.8, pH 6.9, pH 7.0 and pH 7.2 as stage 3) were incorporated into PBPK model.

PBPK model was validated using dissolution and PK data obtained from additional clinical BE studies.

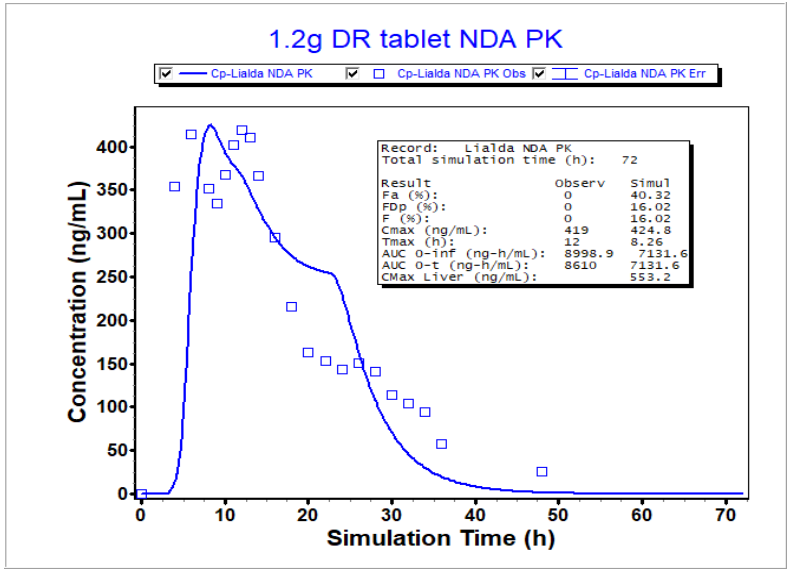
1) Evaluate whether the dissolution data at certain pH is biopredictive; 2) Predict local drug amount in the colon; 3) Population simulation to compare the predicted percentage of drug absorbed in the colon for T/R and support BE assessment

Model Development

- IV bolus 250mg



- Delayed release (DR) tablet 1.2 g



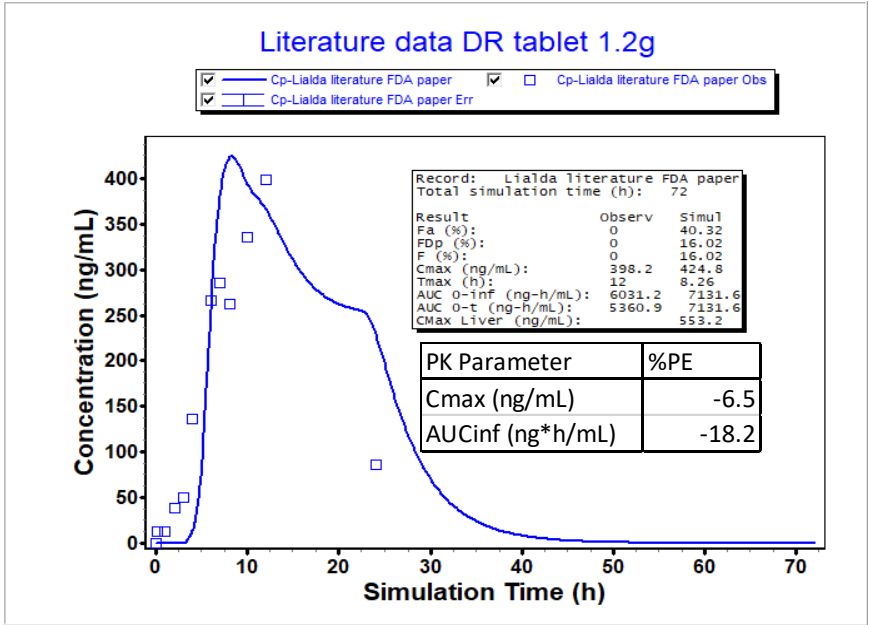
Reference: Vree TB, et al. Liver and gut mucosa acetylation of mesalazine in healthy volunteers. International Journal of Clinical Pharmacology and Therapeutics. 2000, 38(11): 514–22

- Three stage dissolution data with stage 3 at pH 7.2 was used as direct input
- Intestinal first pass effect (FPE) was optimized

Reference: NDA ClinPharm Review document available on drugs@FDA.

Model Validation

- Tablet DR 1.2g PK data from literature



PK Parameter	%PE
Cmax (ng/mL)	-6.5
AUCinf (ng*h/mL)	-18.2

- Additional internally available dissolution and PK data sets were used for model validation

PK Dataset - I	
PK Parameter	%PE
Cmax (ng/mL)	-7.2
AUCinf (ng*h/mL)	3.3
AUCt (ng*h/mL)	0.5
AUC4-48 (ng*h/mL)	-16.3

PK Dataset - II	
PK Parameter	%PE
Cmax (ng/mL)	12.7
AUCinf (ng*h/mL)	0.3
AUCt (ng*h/mL)	-1.5
AUC4-48 (ng*h/mL)	-14.5

Alex Yu et al. Measurement of in vivo Gastrointestinal Release and Dissolution of Three Locally Acting Mesalamine Formulations in Regions of the Human Gastrointestinal Tract. Mol. Pharmaceutics 2017, 14, 345−358.

Model Application

- Evaluate whether the dissolution data at certain pH is biopredictive
  - Dissolution profiles at both pH 7.0 and pH 7.2 (as stage 3) is biorelevant/biopredictive to the PK profiles with %PE < 22%.

Stage 3 pH 7.2			
PK Parameter	Obs	Pred	%PE
Cmax (ng/mL)	191.61	152.39	20.5
AUCinf (ng*h/mL)	2941	2608	11.3
AUCt (ng*h/mL)	2940	2608	11.3
AUC4-48 (ng*h/mL)	2280	2225	2.4
Stage 3 pH 7.0			
PK Parameter	Obs	Pred	%PE
Cmax (ng/mL)	191.61	153.55	19.9
AUCinf (ng*h/mL)	2941	2567	12.7
AUCt (ng*h/mL)	2940	2567	12.7
AUC4-48 (ng*h/mL)	2280	2238	1.8

Stage 3 pH 6.9			
PK Parameter	Obs	Pred	%PE
Cmax (ng/mL)	191.61	153.16	20.1
AUCinf (ng*h/mL)	2941	2422	17.6
AUCt (ng*h/mL)	2940	2422	17.6
AUC4-48 (ng*h/mL)	2280	2276	0.2
Stage 3 pH 6.8			
PK Parameter	Obs	Pred	%PE
Cmax (ng/mL)	191.61	125.55	**34.5**
AUCinf (ng*h/mL)	2941	2041	**30.6**
AUCt (ng*h/mL)	2940	2041	**30.6**
AUC4-48 (ng*h/mL)	2280	2036	10.7

Model Application

- Predict local drug amount in the colon and percentage of drug absorbed in the colon

  - The simulation results using biopredictive dissolution data suggest that the local amount in colon is similar between RLD and test product.

pH at Stage 3 Dissolution	PK Parameter	Predicted for Colon for RLD	Predicted for Colon for Test
7.2	Cmax (mg)	157.7	152.4
	AUCt (mg*h)	2592	2609
7	Cmax (mg)	156.6	153.6
	AUCt (mg*h)	2580	2567
6.9	Cmax (mg)	157	153.2
	AUCt (mg*h)	2521	2422

  - Population simulations (n=25) showed that the percentage of drug absorbed in the colon is similar between the RLD and test product with the 90% CI of the T/R ratio falling within 80-125%.

Stage 3 pH	T/R Ratio	90% CI lower	90% CI upper
pH 7.2	99.71	99.21	100.20
pH 7.0	101.58	98.06	105.10

Release Mechanism Evidence

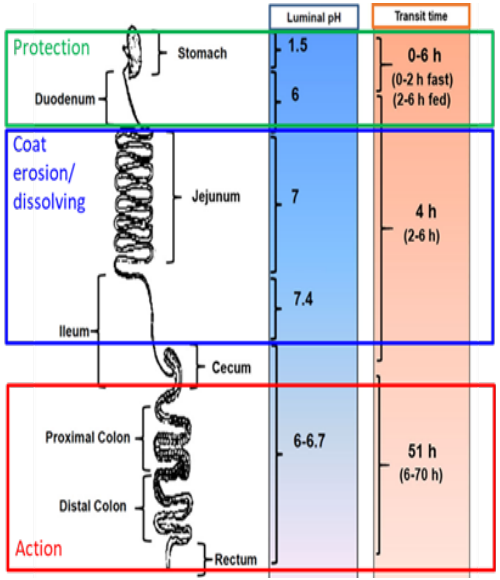


Figure. pH of GI tract and release mechanism of mesalamine DR tablets (Hua et al. Nanomedicine: Nanotechnology, Biology, and Medicine. 2015;11:1117–32.)

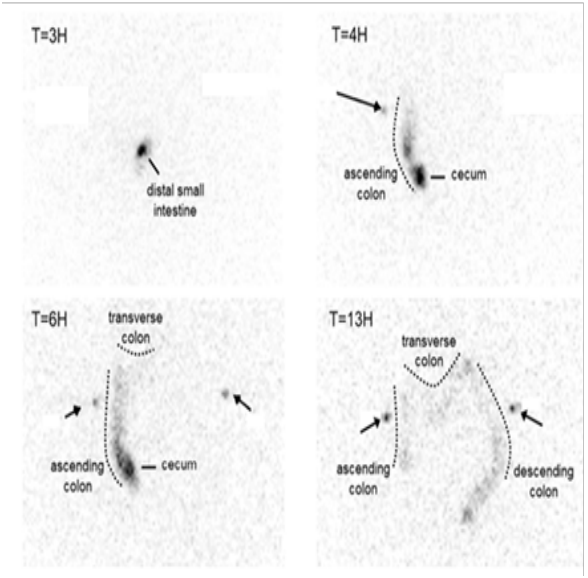


Figure. Gamma scintigraphy imaging of mesalamine DR tablet disintegration in GI tract (Varum F et al. Int J Pharm. 2022; 625:122055.)

Summary

- PBPK model developed by the reviewers to predict local drug amount in the colon by incorporating dissolution data at different pH conditions supported that:
  - The three-stage dissolution profiles at both pH 7.0 and pH 7.2 (as stage 3) may be biopredictive/biorelevant to the local and systemic exposure.
  - The predicted amount of mesalamine in colon is similar between RLD and test product.
  - The percentage of drug absorbed in the colon is similar between the RLD and test product.
- Totality of evidence based on dissolution data, formulation differences, gut physiology considerations along with PBPK modeling results was used to conclude that the test product was low risk for bioinequivalence at site of action. This work supports the approval of mesalamine generic drug product.

Challenge Question

To evaluate the BE for locally acting products, the evidence could include the following:

A. Formulation and Dissolution Comparison

B. Gut Physiology Considerations and Release Mechanism

C. PBPK Modeling and Simulations

D. All of the above

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