U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Totality of Evidence Including Physiologically Based Pharmacokinetic Modeling to Support Bioequivalence Assessment and Approval of Mesalamine Delayed Release Tablets (Part I)

Advancing Generic Drug Development 2024:
Translating Science to Approval
Day (2), Session (5B):
(Spotlight Generic Drug Review Challenges and Solutions)

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Objectives

- Present a case study of an ANDA for Mesalamine Delayed Release (DR) Tablets with dissolution issues
- Understand OGD's BE evaluation based on the totality of evidence for the Mesalamine DR Tablets case study
- Understand the role of Physiologically Based Pharmacokinetic (PBPK) Modeling in regulatory decision making for the approval of Mesalamine DR Tablets

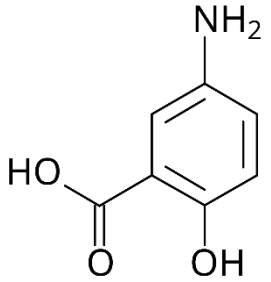
*ANDA: Abbreviated New Drug Application

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

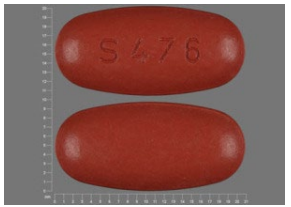
Reference Listed Drug and Product Specific Guidance

Reference Listed Drug (RLD)

- LIALDA® (mesalamine) Delayed-Release Tablets, 1.2 g
- NDA 022000, approved on 01/16/2007
- RLD holder: TAKEDA Pharmaceuticals USA Inc.
- Indication:
  - induction and maintenance of remission in adult patients with mildly to moderately active ulcerative colitis.
  - treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg.



Mesalamine



LIALDA®
(drugs.com)

Product Specific Guidance (PSG)

PSG Recommendations for Mesalamine DR Tablet (*Jun 2016*):

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.

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.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20tab%20DR_RLD%2022000_RC06-16.pdf

Evaluation of the Totality of Evidence in a Case Study for Mesalamine DR Tablet

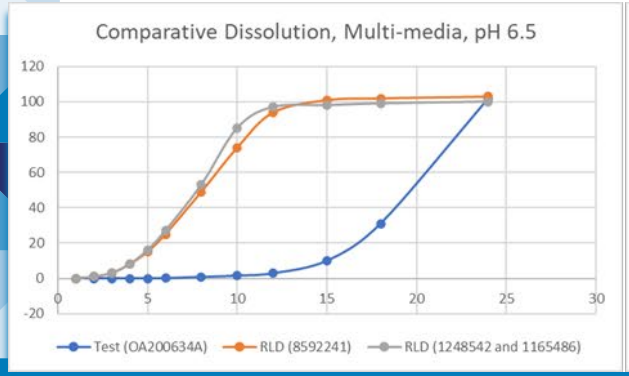
Case Study

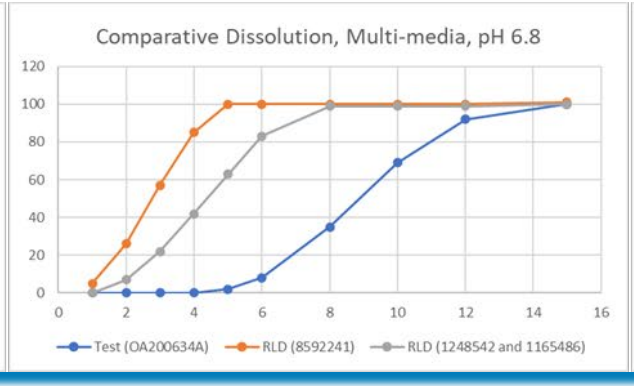
- The PK/statistical results for both fasting and fed studies met the BE acceptance criteria.

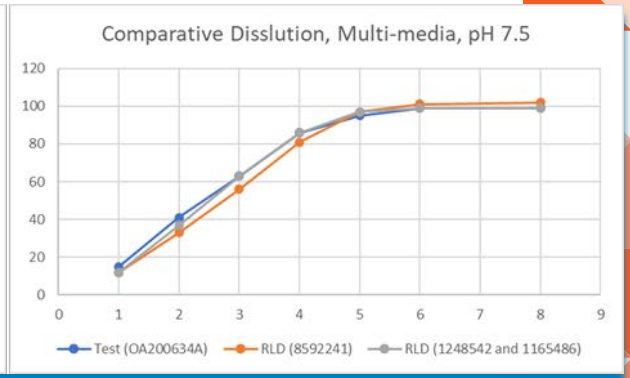
- Per the PSG, the following PK parameters were evaluated for BE determination between the Test product and Reference standard: C_{max}, $AUC_{0\text{-}t}$, ***$AUC_{8\text{-}48h}$*** *(Partial AUC)*

Case Study

- The Test formulation adopted similar mechanism of the drug release (e.g., same pH dependent release controlling excipients) as the RLD product.



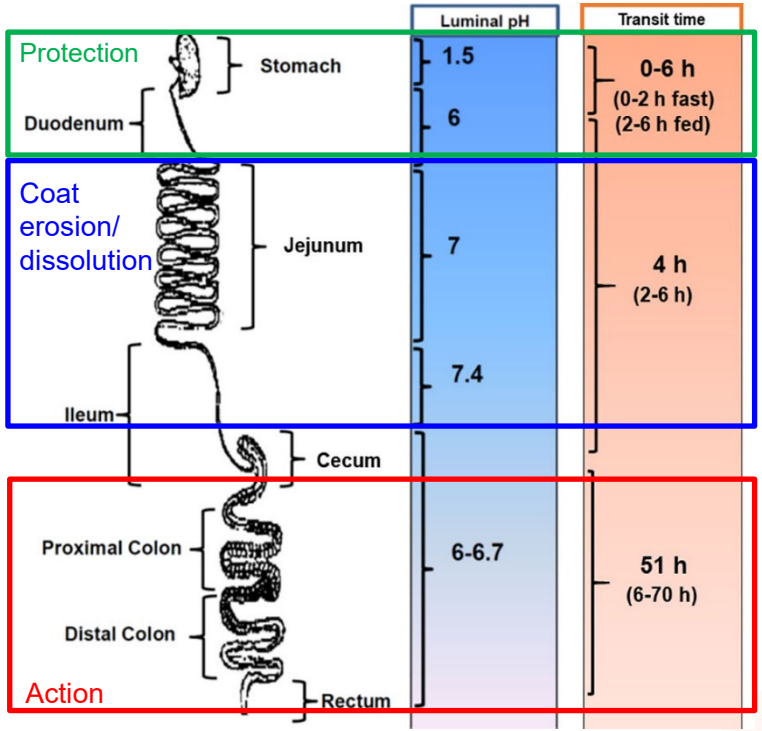




Delayed Drug Release Mechanism for the RLD

Why is LIALDA coated?

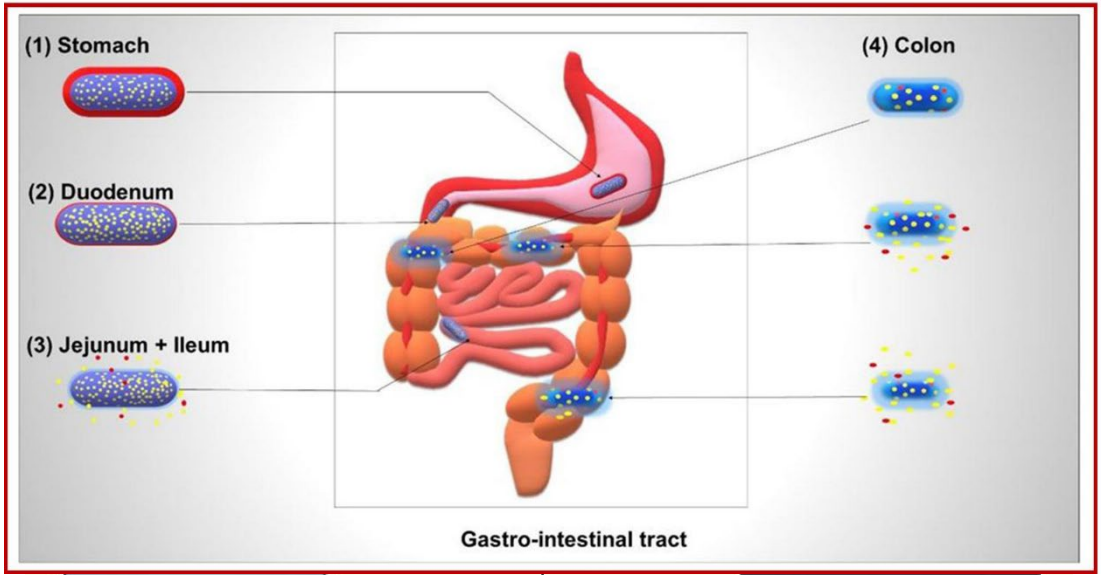
- The majority (~80%) of mesalamine is absorbed, if not protected by film coating, before leaving the proximal small intestine (e.g., duodenum, pH ~6)
- The majority of mesalamine can't reach the colon to exert its pharmaceutical function



Hua, S. *et al. Nanomedicine 2015,* 11 (5)

Delayed Drug Release Mechanism for the RLD

Per the RLD label: "*The tablet is coated with a pH-dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core*".

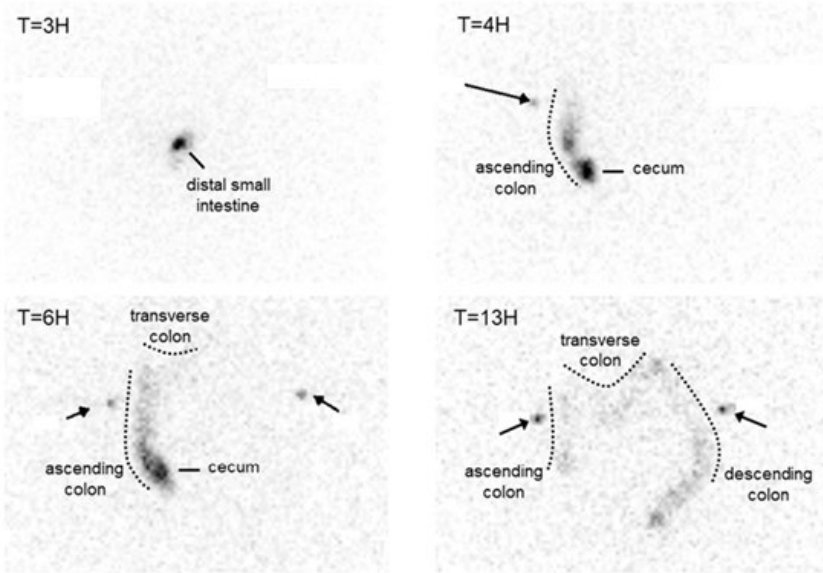


Anitha Sriram, et al. AAPS PharmSciTech, Volume 22, 264 (2021)

Baker, D., Reviews in Gastroenterological Disorders, Feb 2004, 4(1), 25-8

Delayed Drug Release Mechanism for the RLD

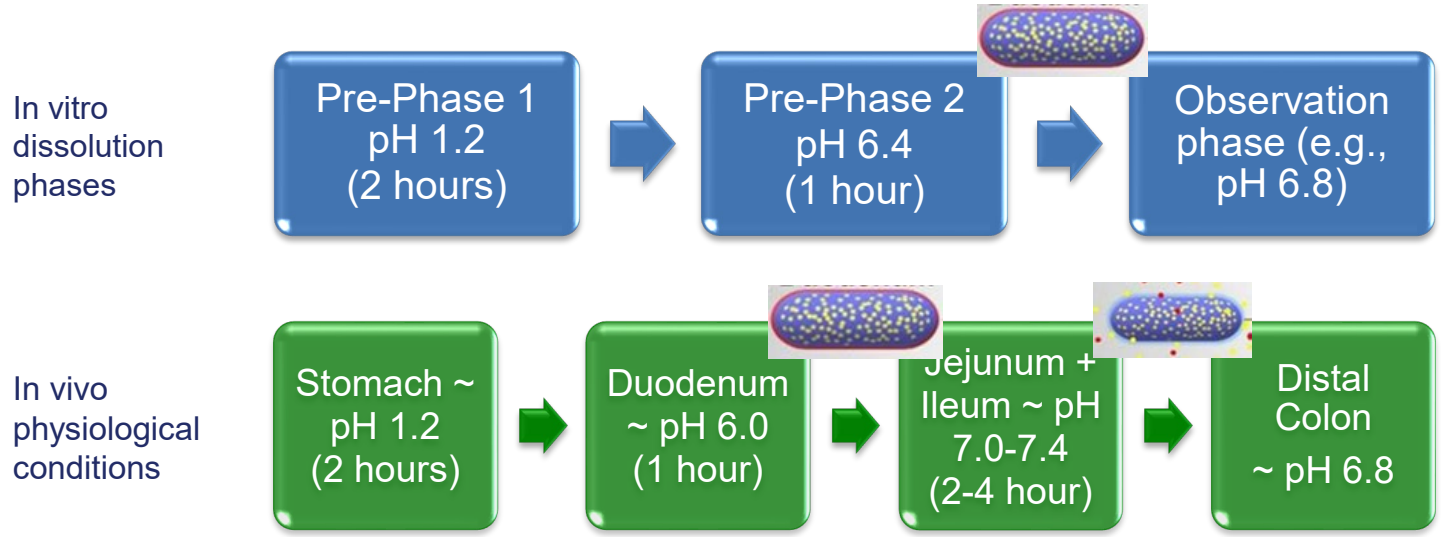
Per the RLD label, "*Gamma-scintigraphy studies have shown that a single dose of LIALDA 1.2 g passed intact through the upper gastrointestinal tract of fasted healthy subjects. Scintigraphic images showed a trail of radio-labeled tracer in th colon, suggesting that mesalamine had distributed through this region of the gastrointestinal tract*".



Varum, F. et al. International Journal of Pharmaceutics, 625 (2022)

Delayed Drug Release Mechanism for the RLD

The coating of LIADA DR Tablet is unlikely to stay intact as it transits through the small intestine and arrives the colon.



Correlation of the physiological, pharmacokinetic and dissolution data as a totality of evidence?

In vitro – in vivo correlation: PKPB modeling

- In vitro dissolution at pH ≤ 6.9 conditions are non-comparable between the test and the RLD product.
- In vivo drug dissolution and release through the GI tract may vary due to physiological conditions
- The applicant was recommended to perform in vitro – in vivo correlation (IVIVC) to further demonstrate the bio performance of the test product (e.g., using a validated PBPK model)
- The applicant's PBPK model and IVIVC data was reviewed as a part of the totality of evidence supporting the final 'approval' regulatory decision making.

Challenge Question

After oral administration, evidence showed that the coating of LIALDA® Delayed-Release Tablet would stay intact and prevent early drug release until the tablet reaches its site of action (the colon).

- True
- False

Acknowledgement

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Thank You!