

A Review on Bioequivalence Studies Conducted with Soft Food

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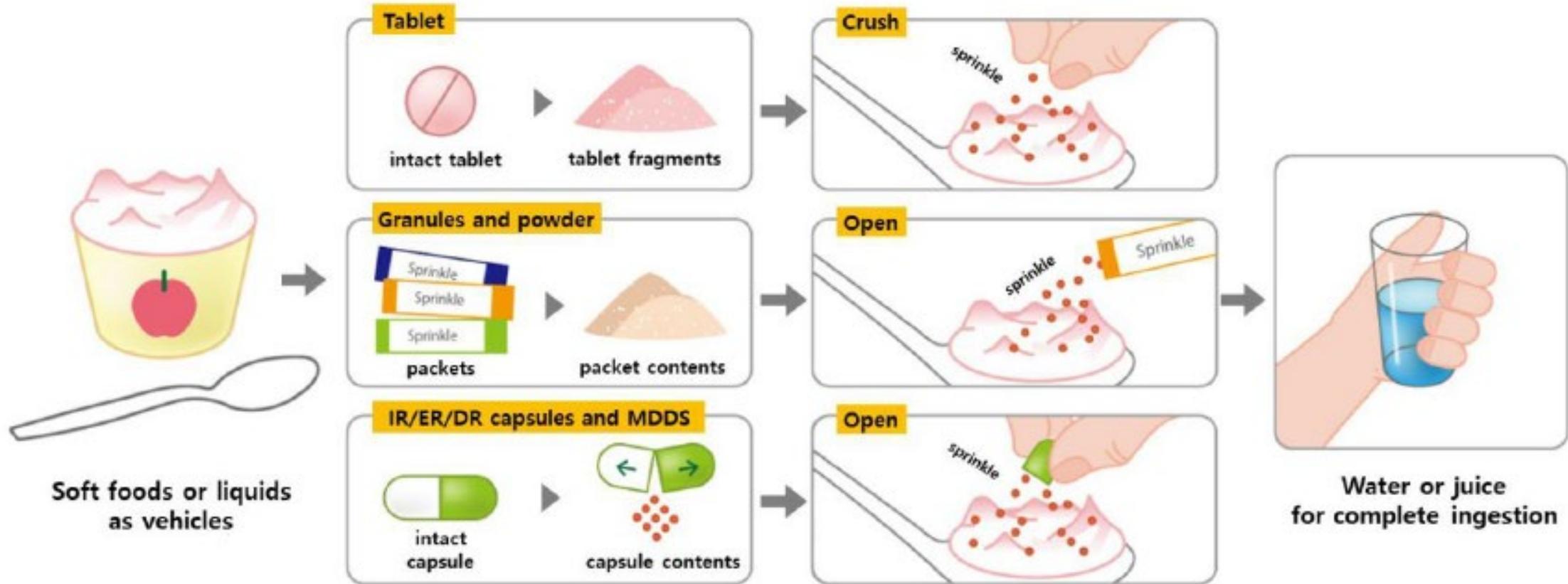
- ❑ Pediatric Research Equity Act (PREA) of 2003 - understanding the motivation behind sprinkle administration
- ❑ Regulatory considerations for fasting sprinkle administration
- ❑ Summary review of internal data review and analysis plan
- ❑ Summary conclusions on bioequivalence (BE) data of generic drug products administered under the fasting sprinkle condition
- ❑ Future regulatory considerations

Patient Centric Dosing for Pediatrics is an Essential Consideration in Drug Product Development



- PREA of 2003
 - PREA gives FDA the authority to require pediatric studies in certain drugs and biological products
 - Studies must use appropriate formulations for each age group
 - The goal of the studies is to obtain pediatric labeling for the product
- Mixing drug products with food or drinks improves pediatric dosing options:
 - Masks the unsatisfactory palatability of a formulation
 - Improves ease of swallowing of an otherwise already palatable product
 - Generally discouraged for medicines containing substances with a narrow therapeutic

Multiparticulate Dosage Forms Allow for Patient Centric Dosing



Data to Support Sprinkling Drug Product into Soft Food

- Sprinkling a drug product can potentially change the bioavailability, toxicity, and stability of the drug substance
- Sprinkling a drug product on soft food involves a multiple step procedure
- Data to support sprinkling should include:
 - Compatibility with the proposed vehicle(s) (e.g. in-use stability studies);
 - The volume or amount of soft food to be used

For product labeling to indicate a product can be sprinkled on soft food, a BA study comparing the sprinkled and not sprinkled product is recommended; in vitro studies for additional soft food may be included in the label if the BA study can extrapolate to those foods.

A Sprinkle BA or BE Study is not the Same as a Food Effect Study

Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology at CDER_OCP_GPT.

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

February 2019
Clinical Pharmacology

02/21/19

Composition of fed state meals vs applesauce:

Fat meal	High-fat meal	Low-fat meal	Applesauce (1 Cup = 244 g)	Applesauce (15 g)
Total Calories	800-1000	400-500	102*	6
Calories from Protein	150	-	0.02	0.00125
Calories from Carbohydrates	250	-	12	0.75
Calories from Fat	500-600	100-125	2.2	0.1375

- The average volume of applesauce given in a fasting sprinkle BE study is between (5 g – 15 g)
- Applesauce pH: 3.1-3.6

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations>
 *<https://www.nutritionix.com/i/usda/unsweetened-applesauce-1-cup/513fceb475b8dbbc2100fac>
https://www.clemson.edu/extension/food/food2market/documents/ph_of_common_foods.pdf

Applesauce is Commonly Recommended on Approved U.S. Drug Product Labeling – A Consideration for Global Harmonization

Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments Guidance for Industry

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For questions regarding this draft document, contact (CDER) Mamta Gautam-Basak, 301-796-0712.

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

July 2018
Pharmaceutical Quality/CMC



APPENDIX A

Commonly Used Soft Foods and Liquids With Their Approximate pH Range

	pH range
Apples (puree)	3.34 – 3.90
Apple juice	3.35 – 4.00
Applesauce	3.10 – 3.60
Baby food, unstrained	5.95 – 6.05
Bananas (puree)	4.5 – 5.2
Buttermilk	4.41 – 4.83
Carrots (puree)	5.88 – 6.40
Chocolate pudding ^(a)	5.5 – 6.0
Coconut milk	6.1 – 7.0
Cranberry juice	2.30 – 2.52
Drinking water ^(b)	6.5 – 8.5
Fruit jellies	3.0 – 3.5
Fruit jam	3.5 – 4.5
Grapefruit juice ^(c)	2.90 – 3.25
Honey ^(d)	3.70 – 4.20
Infant formula	5.7 – 6.0
Maple syrup ^(e)	4.6 – 5.15
Milk	6.4 – 6.8
Orange juice	3.30 – 4.19
Orange marmalade	3.00 – 3.33
Peanut butter	6.28
Pineapple juice	3.30 – 3.60
Rice pudding ^(a)	4 – 5
Soybean milk	7
Strawberries	3.00 – 3.90
Strawberry jam	3.00 – 3.40
Yogurt	4.4 – 5.0

Sprinkle BE Studies are Recommended for Modified Release Products Only



Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

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*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

August 2021
Generics

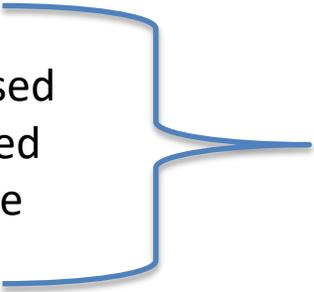
- Sprinkling modified-release drug products poses an additional risk of dose dumping due to the high level of active drug contents.
- Section III. Establishing Bioequivalence
 - Subsection A. Pharmacokinetic Studies
 - 11. Sprinkle Bioequivalence Studies
 - ✓ A modified release product reference listed drug (RLD) label states the product can be administered in soft food
 - ✓ ANDA applicants are recommended to conduct an additional fasting study with the product by sprinkling it on one of the soft foods mentioned in the RLD product label

The Regulatory Goal of the Sprinkle BE Study is to Assess Formulation Differences that can Impact Pharmacokinetic (PK) parameters



Capsule Shell Differences

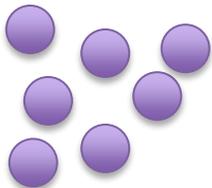
- Gelatin
- Cellulose based
- Enteric-Coated
- Hypromellose
- Pullulan



Does the capsule shell:

- Prolong gastric retention time?
- Delay dissolution and/or lower absorption?
- Provide protection in acidic media?
- Provide pH dependent or independent release properties?

Removal of the capsule shell in a fasting sprinkle BE study could expose these differences.



Internal Content Differences

- Layered beads with specialized coatings
- Lipophilic/waxy resin matrix
- Spheronized homogenous matrix
- Bead diameter size



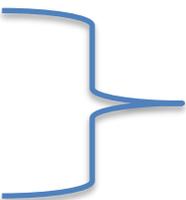
Do differences in the encapsulated pellets result in:

- Dissolution rate and absorption differences?
- Stability in acidic conditions?
- Drug bypassing or minimizing first-pass metabolism?



Soft Food Characteristics

- Amount (~5 – 15 g)
- Contact time of drug with soft food
- pH of soft food



Can soft food:

- Alter gastric emptying reducing PK variability?
- Improve drug absorption?
- Expose the drug to degradation?

We Reviewed Data Submitted in Approved ANDAs to Elucidate if the Fasting Sprinkle BE Study Accomplishes its Regulatory Goal



- 1) If a potential generic drug product is BE to the reference standard product with the capsule shell, can we assume BE without the capsule shell?
- 2) What type of effect does soft food have on the PK of a drug substance?
- 3) If differences in PK parameters are observed due to co-administration of soft-food:
 - a. What formulation factors, if any, may be responsible?
 - b. What drug substance properties, if any, may be responsible?

We Utilized an Estimated-Within Subject Variability (E-WSV) approach to answer our questions

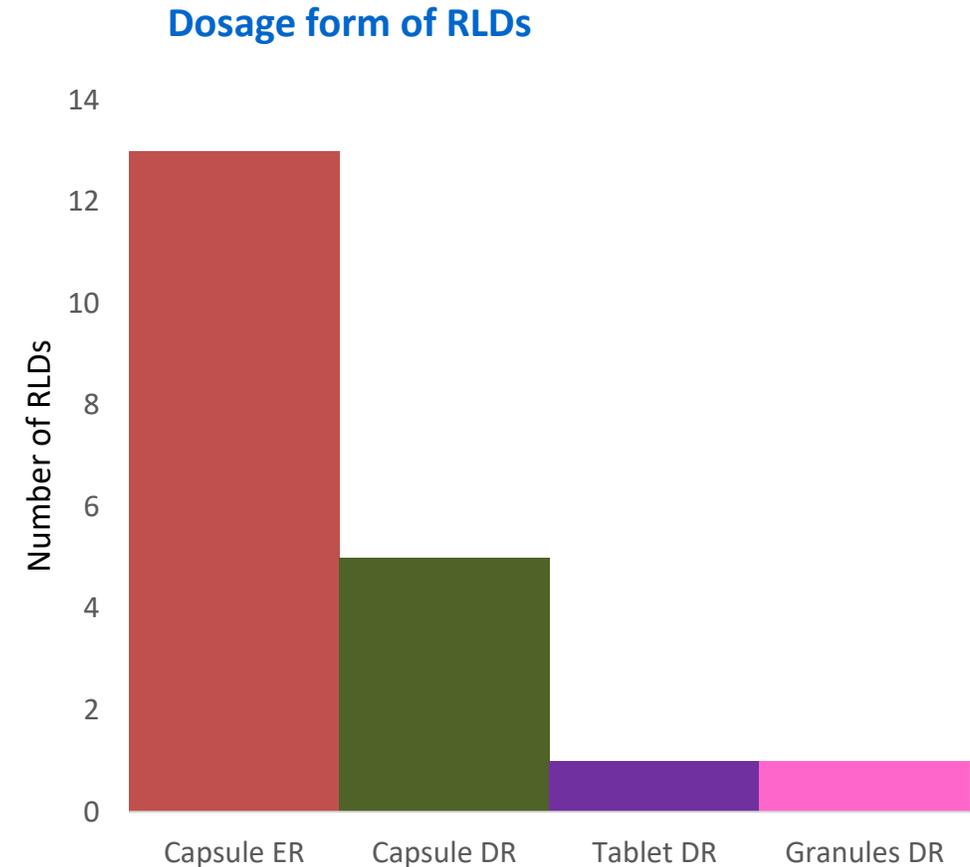
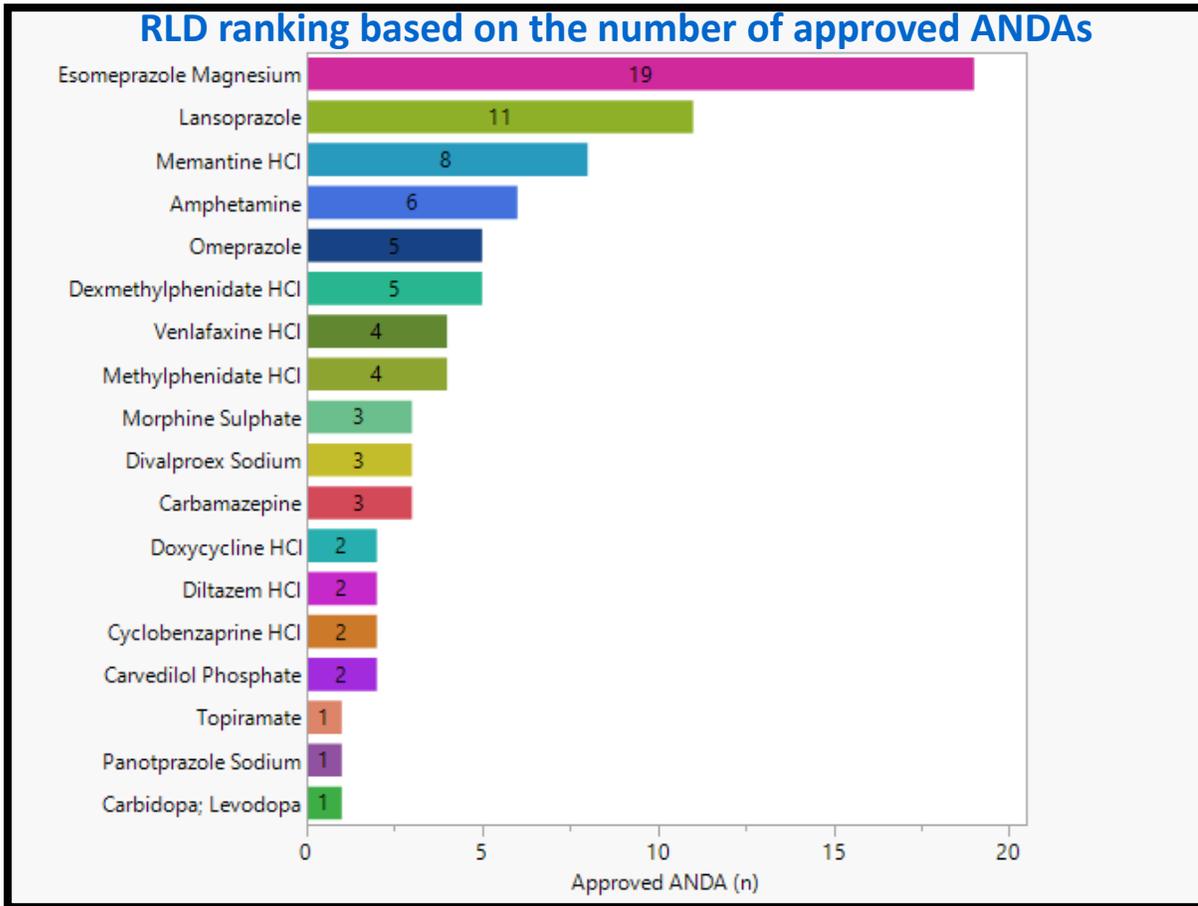
- Assessing absolute PK differences across studies does not tell us why differences exist, if any
- The two-way crossover is the most used study design for generic MR products with sprinkle administration in the label
- Lack of failed ANDAs that could provide valuable insight on the variabilities between fasting and fasting sprinkle BE studies
- E-WSV is used to tease out interactions between subjects, drug substance, and drug formulation interaction

Hypothesis

If E-WSV is different between fasting and fasting sprinkle conditions and the number of subjects is similar in each study, then the E-WSV difference must be driven by formulation-soft food interactions because we assume subject and drug substance differences should remain the same.

38* Modified Release Products are Labeled for Sprinkle Administration

- Twenty RLD have approved ANDAs and represent 18 active pharmaceutical ingredients
- Eighty approved ANDAs reference the 20 RLDs



14 of the Approved Products are Indicated for Pediatric Populations

	RLD	Dosage Form	Pediatric Indications
Approved for Pediatric Indications	Divalproex Sodium**	Capsule, DR	<ul style="list-style-type: none"> Complex partial seizures that occur either in isolation or in association with other types of seizures.
	Esomeprazole Magnesium	Capsule, DR	<ul style="list-style-type: none"> Erosive Esophagitis (EE) Heartburn and Treatment of symptomatic gastroesophageal reflux disease (GERD)
	Omeprazole ^a	Capsule, DR	<ul style="list-style-type: none"> GERD EE due to acid-mediated GERD Maintenance of healing of EE due to acid-mediated GERD
	Lansoprazole ^a	Capsule, DR	<ul style="list-style-type: none"> GERD EE
	Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate ^a	Capsule, ER	<ul style="list-style-type: none"> Attention Deficit Hyperactivity Disorder (ADHD) Narcolepsy
	Omeprazole ^a	Capsule, DR	<ul style="list-style-type: none"> GERD EE due to acid-mediated GERD Maintenance of healing of EE due to acid-mediated GERD
	Dexmethylphenidate HCl ^a	Capsule, ER	<ul style="list-style-type: none"> Patients new to methylphenidate
	Carbamazepine **	Capsule, ER	<ul style="list-style-type: none"> Anticonvulsant drug
	Doxycycline Hyclate ^a	Tablet, DR	<ul style="list-style-type: none"> Severe or life-threatening infections
	Methylphenidate HCl ^a	Capsule, ER	<ul style="list-style-type: none"> ADHD
	Methylphenidate HCl ^a	Capsule, ER	<ul style="list-style-type: none"> ADHD
	Methylphenidate HCl ^a	Capsule, ER	<ul style="list-style-type: none"> CCR5-tropic HIV-1 infection
	Topiramate ^a	Capsule, ER	<ul style="list-style-type: none"> Epilepsy Partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut Syndrome
Pantoprazole Sodium ^a	Powder, DR	<ul style="list-style-type: none"> Short-Term EE associated With GERD 	
Geriatric Related	Carbidopa; Levodopa ^a	Capsule, ER	<ul style="list-style-type: none"> Parkinson's disease Post-encephalitic parkinsonism Parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
	Memantine HCl	Capsule, ER	<ul style="list-style-type: none"> Moderate to severe dementia of the Alzheimer's type
Not Indicated for Pediatric Patients	Venlafaxine HCl	Capsule, ER	<ul style="list-style-type: none"> Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), Panic Disorder (PD) Effexor XR is not approved for use in pediatric patients
	Morphine Sulfate ^a	Capsule, ER	<ul style="list-style-type: none"> Chronic Pain The safety and efficacy of KADIAN in patients less than 18 years have not been established.
	Diltiazem HCl ^a	Capsule, ER	<ul style="list-style-type: none"> Hypertension Safety and effectiveness in children have not been established.
	Cyclobenzaprine HCl ^a	Capsule, ER	<ul style="list-style-type: none"> Muscle relaxant for relief of muscle spasm associated with acute, painful musculoskeletal conditions Safety and effectiveness of AMRIX have not been studied in pediatric patients.
	Carvedilol Phosphate ^a	Capsule, ER	<ul style="list-style-type: none"> Mild to severe chronic heart failure Left ventricular dysfunction following myocardial infarction in clinically stable patients Hypertension Effectiveness of carvedilol in patients younger than 18 years has not been established.

There were No Apparent Tmax Differences Observed between Drug Products Administered with and without Soft Food



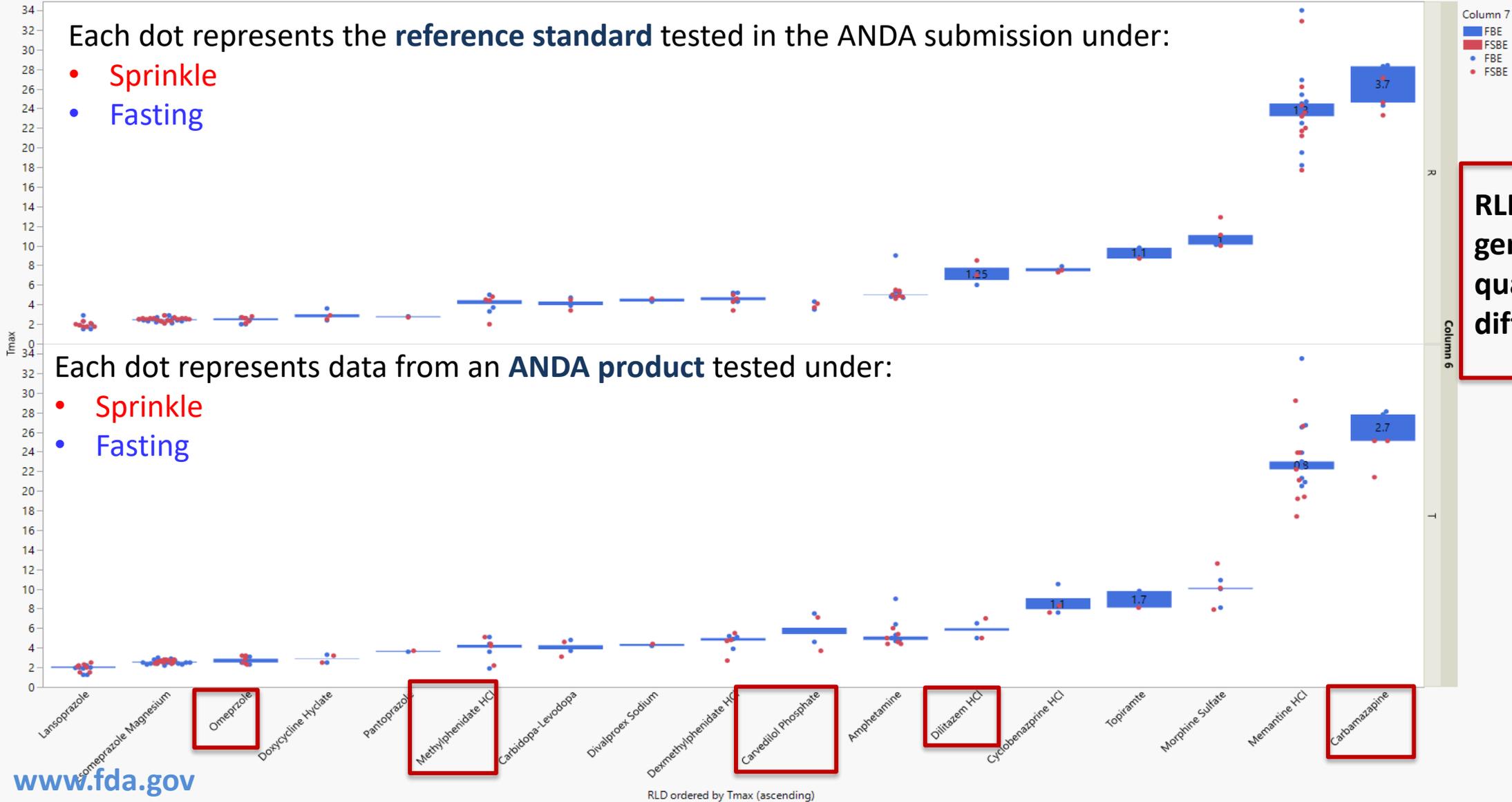
Median(Tmax) & Tmax vs. RLD

Each dot represents the **reference standard** tested in the ANDA submission under:

- Sprinkle
- Fasting

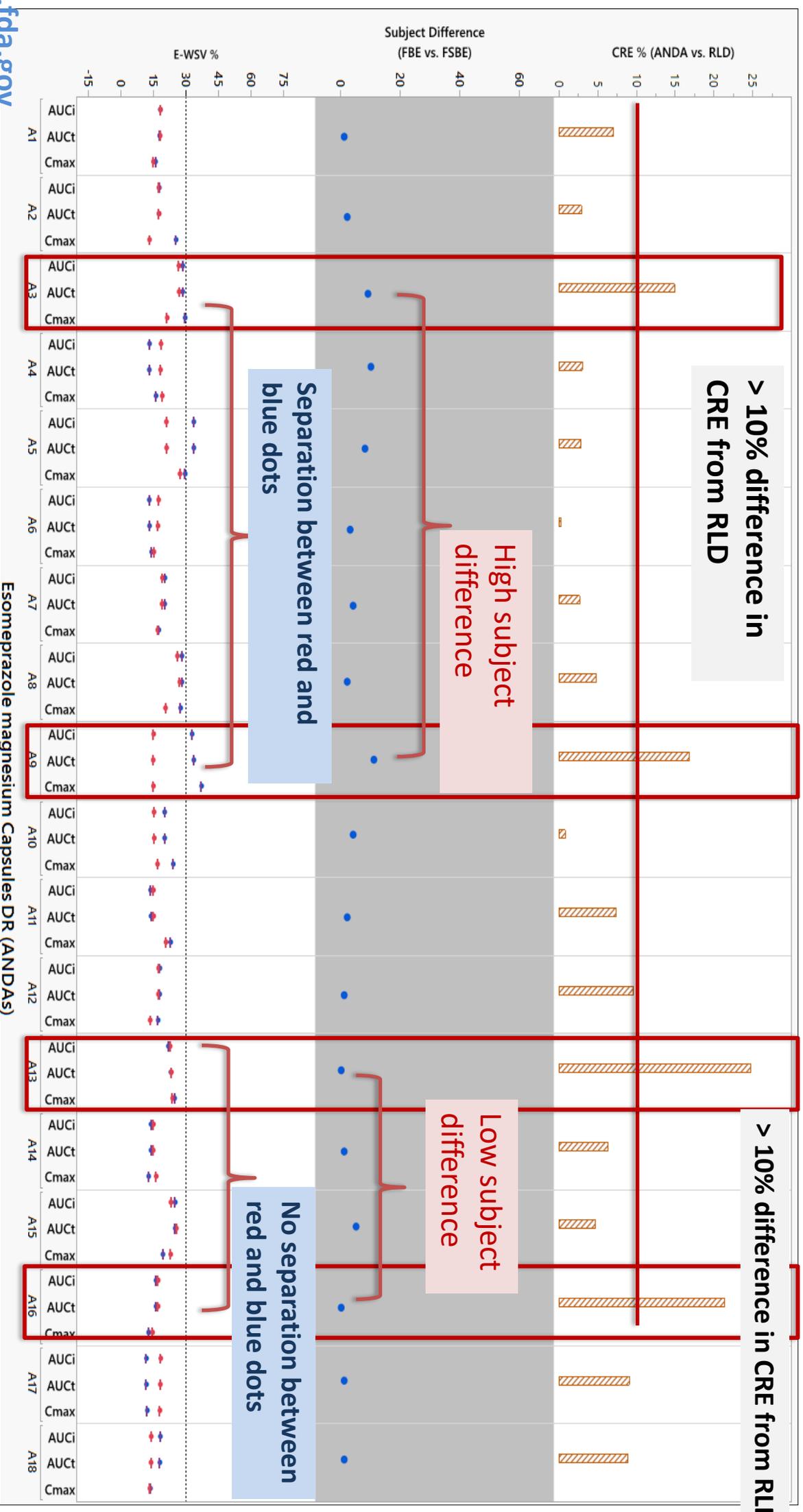
Each dot represents data from an **ANDA product** tested under:

- Sprinkle
- Fasting



RLD products with generics formulated qualitatively different

Inspection of Four ANDAs with Greatest Difference in CRE Show Subject Number may Drive PK Variability Between Studies



- Soft food does not appear to impact the PK of the products assessed and appears to reduce PK variability overall as shown by lower E-WSV parameters for fasting sprinkle PK studies
- The range of formulation variability in marketed generic products is small which limits our ability to understand when a generic formulation may fail when sprinkled on soft food
- The limited differences in PK variability appear to be driven by the highly variable nature of the drug substance or study design (i.e., number of subjects enrolled) rather than formulation differences

What We Still Do not Know and Ongoing Efforts

1. What conditions can cause different PK results when pellets are administered with versus without their capsule shell?
2. Based on this understanding, can we create a risk assessment to guide when an additional in vivo study may be necessary and where in vitro assessments in soft food may be more appropriate?

Possible scenario: in vivo sprinkle PK studies may be limited to capsule based products; granule-based products may be eligible for in vitro testing

Possible scenario: A sprinkle fasting study may still be recommended for acid labile drugs and those susceptible to first pass metabolism

3. If fasting sprinkle BE studies continue to be recommended, what efforts may be needed to harmonize soft food conditions globally as different regions prefer different soft food?

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