Bioequivalence Strategies for Orally Disintegrating Tablets: Regulatory Considerations

Heather Boyce
Lead Pharmacokineticist
Division of Therapeutic Performance II, Office of Research and Standards
CDER | US FDA

Advancing Generic Drug Development (AGDD): Bioequivalence Challenges for Patient-Centric Oral Formulations – June 11, 2026

Learning Objectives

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Bioequivalence Strategies for Orally Disintegrating Tablets (ODTs): Regulatory Considerations

Upon completion of this presentation, participants will be able to:

- **Explain ODT pharmacokinetic and bioavailability differences**
- **Discuss patient-centric benefits of ODTs**
- **Evaluate water effects on ODT bioavailability**
- **Review product specific guidance (PSG) revisions related to water effect on ODT**

Bioequivalence (BE) Recommendations for Orally Disintegrating Tablets (ODTs)

Why 'Without Water' Is the Worst-Case Administration Condition — Evidence, Policy & Case Studies

CASE 1
Rizatriptan ODT

CASE 2
Alprazolam ODT

CASE 3
Vardenafil ODT

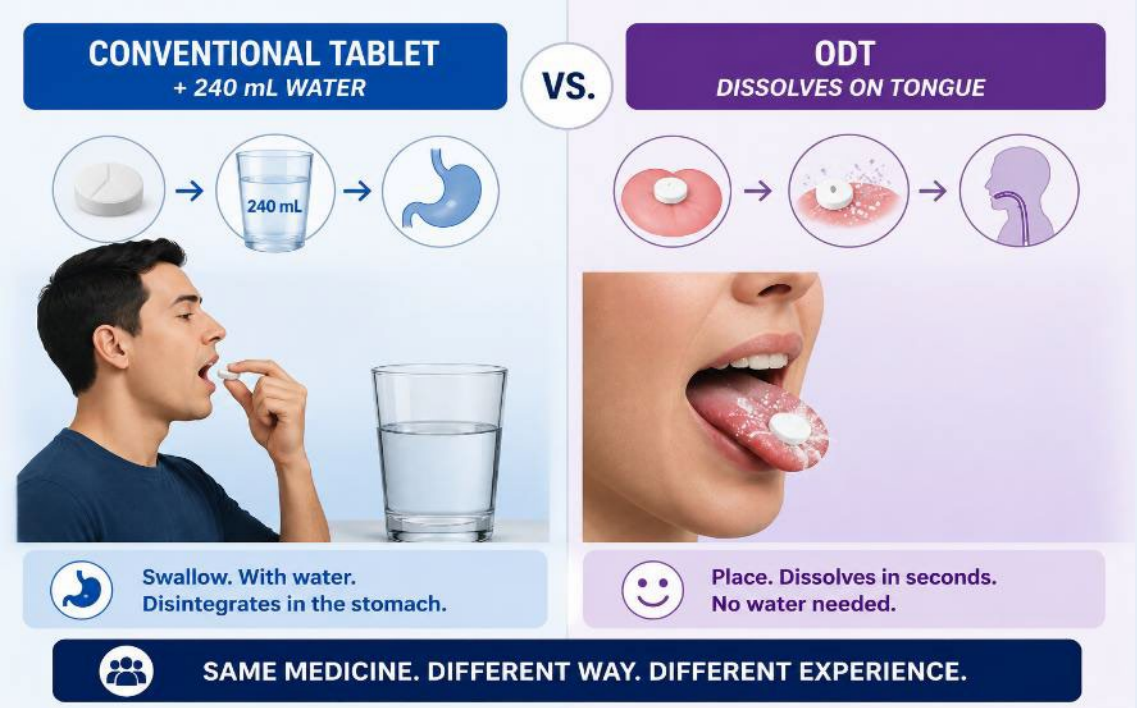
CASE 4
Donepezil HCl ODT

ODTs are Unique

Administration Condition Is Critical

BACKGROUND

- Rapidly disintegrates in oral cavity
- Supports dysphagic, pediatric, and geriatric patients
- May be administered with or without water
- Saliva dissolution differs from 240 mL water
- Absorption occurs with or without water



ODTs are Recommended to Work Without Water:

Real-World Patient Scenarios Where Water Is Not Available

PATIENT NEED

BACKGROUND

Parkinson's Disease 1

Disease Progression → Loss of Swallowing Ability

- 80% of Parkinson's patients develop dysphagia.
- ODT enables therapy when swallowing becomes impossible

Neurological / Geriatric

Migraine Attack 2

Nausea & Vomiting Limit Water Intake

- Acute migraine associated with severe nausea.
- Water at co-administration may worsen symptoms.

Acute / PRN Therapy

Pediatric Oncology 3

Anticipatory Vomiting Prevents Water Use

- Conditioned anticipatory nausea before treatments.
- Antiemetic ODTs must dissolve without water to be clinically feasible in this population.

Pediatric / Oncology

Psychiatric Patients 4

Adherence Challenges & Covert Non-Compliance

- Rapid disintegration of ODT can improve adherence in treating psychiatric conditions
- Water can add a barrier and enable tablet disposal.

Psychiatric / Adherence

Emergency Dosing 5

Acute Situations Where Water Is Not Immediately Available

- Seizure, allergies, or acute pain require immediate dosing and effect.
- Water may or may not be available

Emergency / Acute Care

Resource-Limited Settings 6

No Reliable Access to Safe Drinking Water

In low- and middle-income countries or disaster relief scenarios, safe water may be unavailable. ODTs without water ensure therapeutic access regardless of infrastructure.

Global Health / Equity

ODTs are Recommended to Work Without Water:

Real-World Patient Scenarios Where Water Is Not Available

PATIENT NEED

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BACKGROUND

BE without water is not just a regulatory consideration; it is the condition that directly protects these populations.

The Core Regulatory Challenge

How to recommend a single worst-case condition that protects patients under ALL labeled uses

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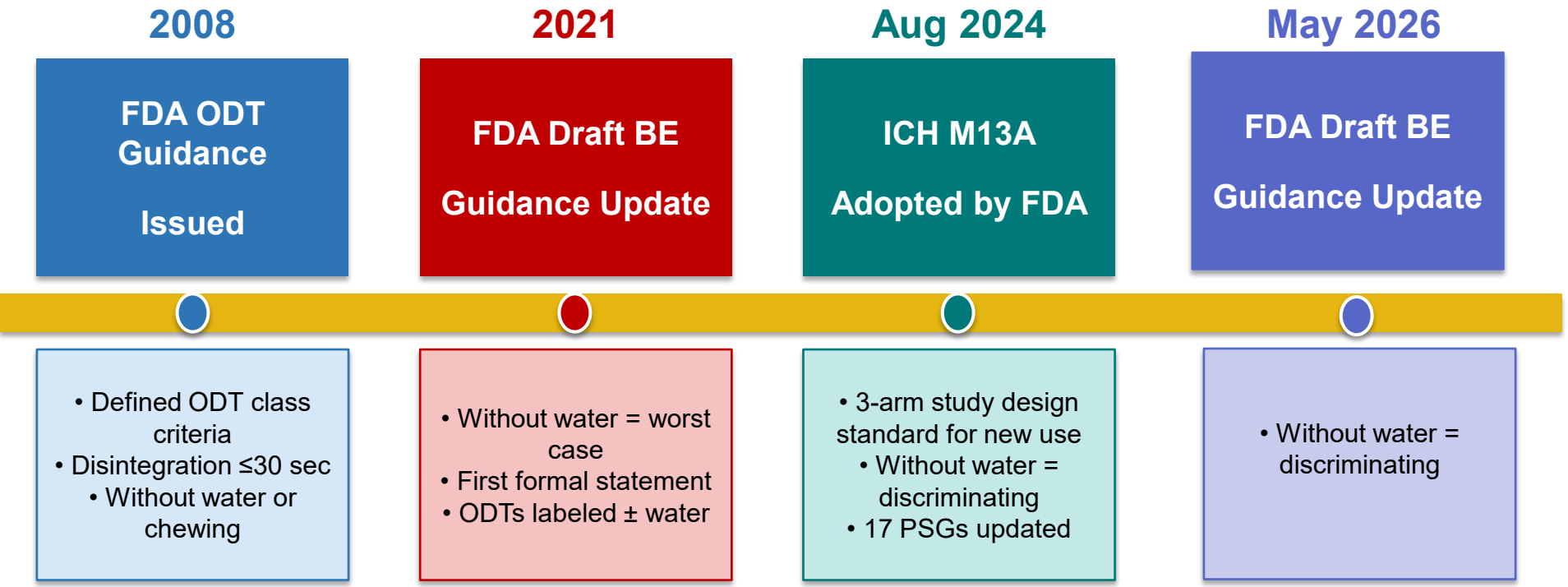
Policy

- Labeling allows ±water, which condition should BE studies test?
- Water may speed dissolution → faster Tmax
  (e.g., Case Study 1: rizatriptan and Case Study 2: alprazolam)
- Water may inhibit buccal absorption → lower AUC
  (e.g., Case Study 3: vardenafil)
- When to be taken without water

Regulatory Framework: FDA & ICH M13A Guidance Evolution

How ODT BE Administration Conditions Have Been Codified Over Time

Policy



Case Study 1: Rizatriptan Benzoate ODT: Water Accelerates Absorption

Labeling: No liquid is needed to take the orally disintegrating tablet.

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CASE 1: The Foundation

Rizatriptan Benzoate (NDA 020865 Maxalt-MLT)

5-HT1B/1D agonist
Migraine treatment
ODT approved:1998

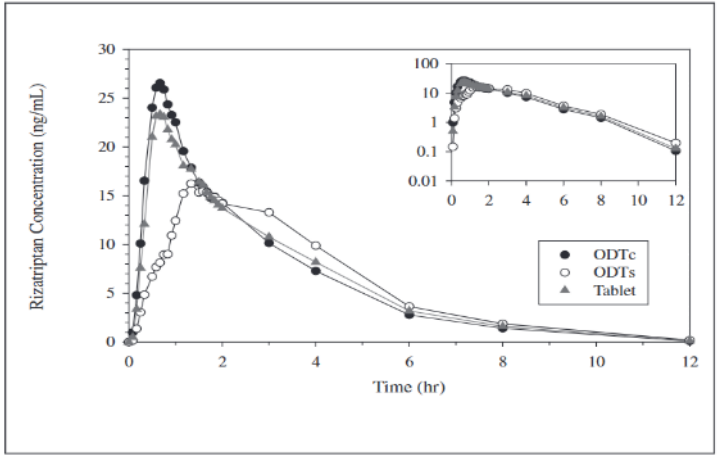
EQ 5 mg Base | EQ 10 mg Base

Study Design: Open-Label, Randomized, Single-Dose, 3-Period Crossover

Arm A: ODTc (ODT + Water)

Arm B: ODTs (ODT, No Water)

Arm C: Tablet (Reference)



Parameter	ODTc (With Water)	ODTs (Without Water)	Tablet (Ref)
AUC0-1h (h·ng/mL)	9.9	5.23	8.27
AUC0-2h (h·ng/mL)	33.1*	18.85	32.5
AUC0-∞ (h·ng/mL)	Similar	Lower	Ref
Tmax – Median (h)	0.67*	1.33	0.67
Cmax (ng/mL)	45.1	41.9	44.4

** p<0.001 vs. ODTs (without water) — AUC0-2h and Tmax differences statistically significant*

Swan SK et al. J Clin Pharmacol. 2006;46(2):172-8. doi:10.1177/0091270005284194 | PMID: 16432269 | Funded by Merck & Co., Inc.

Case Study 1: Rizatriptan Benzoate ODT: Water Accelerates Absorption

Conclusions

Without Water = Worst Case PK

AUC0-2h 43% lower & Tmax 1 hour later vs. ODT+ water

With Water = Best Delivery Method

AUC & Tmax match conventional tablet — fastest absorption

Total Bioavailability Similar (AUC0-∞)

ODTc and tablet BE for overall exposure; ODTs consistently lower

PSG Update

Generic rizatriptan
ODTs now recommended to test WITHOUT water (per M13A)

Swan SK et al. J Clin Pharmacol. 2006;46(2):172-8. doi:10.1177/0091270005284194 | PMID: 16432269 | Funded by Merck & Co., Inc.

Case Study 2: Alprazolam ODT (Niravam®) BE With/Without Water

CASE 2

Labeling: Administration with liquid is not necessary

Alprazolam
(NDA 021726 Niravam®)
Benzodiazepine
Anxiety/Panic Disorder
NDA approved: January 2005

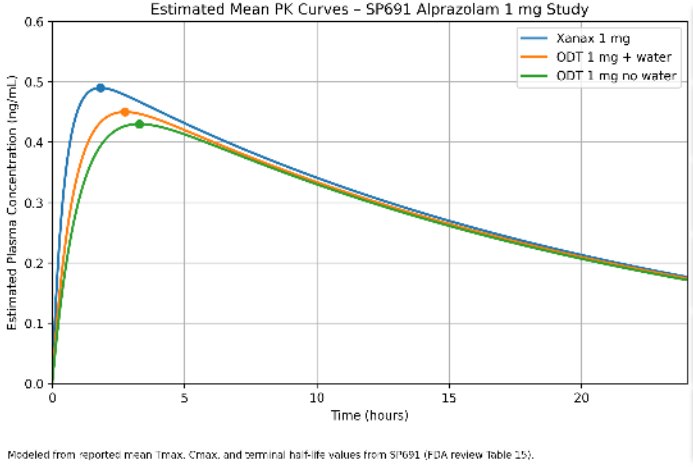
0.25 mg | 0.5 mg | 1 mg | 2 mg

Study Design: 3-Way Crossover BE Studies (SP691 & SP765) vs. Xanax® (Reference)

ODT + Water vs. Xanax Tablet

ODT without Water vs. Xanax Tablet

Both conditions tested at 0.5 mg & 1 mg



Modeled from reported mean Tmax, Cmax, and terminal half-life values from SP691 (FDA review Table 15).

Parameter / Strength	ODT + Water vs. Xanax	ODT without Water vs. Xanax	Conclusion
Cmax ratio (1 mg)	~92.5–95% of Ref	~92.5–95% of Ref	BE (80–125%)
AUC ratio (1 mg)	~92.5–95% of Ref	~92.5–95% of Ref	BE (80–125%)
Cmax ratio (0.5 mg)	~89–96% of Ref	~89–96% of Ref	BE (80–125%)
AUC ratio (0.5 mg)	~89–96% of Ref	~89–96% of Ref	BE (80–125%)
Tmax difference	~15 min earlier	Reference	Not clinically significant

Case Study 2: Alprazolam ODT (Niravam®): BE With/Without Water

Conclusions

CASE 2

Both Conditions Achieved BE

Cmax & AUC within 80–125% under BOTH ±water conditions

Only Tmax Differs (15 min, not clinically significant)

Water slightly speeds absorption but no PK impact on BE

PSG Update

Generic alprazolam ODTs now recommended to test WITHOUT water (per M13A)

Case Study 3: Vardenafil ODT (Staxyn®) Water Reduces Bioavailability

Labeled to be taken explicitly WITHOUT water

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CASE 3:
The Twist

Vardenafil (Staxyn®)

PDE5 inhibitor
Erectile Dysfunction
FDA Approved: 2011

10 mg

Study Design: Open-Label, Randomized, Single-Dose, 4-Period Crossover

Arm A: ODTc (ODT + Water)

Arm B: ODTs (ODT, No Water)

Arm C: Tablet (Reference)

Vardenafil ODT PK: Without vs. With Water

Parameter	Without Water (Labeled Use)	With Water (Off-Label)
AUC0-∞	+21 to +44% vs. FCT	−29% vs. no-water ODT
Tmax	~1.5 h	~0.5 h (60 min earlier)
Cmax	Similar to FCT	Similar (unaffected)
BE vs. FCT	NOT BE (suprabioavailable)	N/A

Case Study 3: Vardenafil ODT (Staxyn®) Water Reduces Bioavailability

Mechanism: Why Water Impacts Vardenafil ODT

- Buccal absorption bypasses first-pass metabolism thereby increasing absorption and bioavailability
- Water likely removes drug before mucosal absorption
- Water lowers AUC 29%, faster Tmax by 60 min

Staxyn® (vardenafil) Prescribing Information (Bayer/GSK) | **Heinig, R. et al.** (2011) Clin Drug Investig. | FDA approved 2011

Case Study 3: Vardenafil ODT (Staxyn®) Water Reduces Bioavailability

Conclusions

CASE 3:
The Twist

REGULATORY OUTCOME & POLICY IMPLICATION

▸ **Labeled 'Without Water Only:'**	Staxyn labeling explicitly requires administration without water because water compromises the intended buccal absorption pathway
▸ **NOT Interchangeable with Levitra® FCT:**	ODT and film-coated tablet are not bioequivalent — AUC 21–44% higher for ODT without water; separate drugs for regulatory purposes

PSG Recommendation Justified

Generic vardenafil
ODTs continue to recommended to test WITHOUT water (per M13A)

Three Cases, One Recommendation

How Rizatriptan, Alprazolam & Vardenafil Together Support the 'Without Water = Worst Case' Recommendation

Drug / Formulation	AUC (effect of water)	Cmax (effect of water)	Tmax (effect of water)	BE Without Water?	Study Utility
Rizatriptan ODT *(Maxalt-MLT)*	↑ AUC0-2h +43%	↔ Similar	↓ 1h earlier	**YES**	**Worst case;** discriminating condition
Alprazolam ODT *(Niravam / generics)*	↔ No change	↔ No change	↓ ~15 min earlier	**YES**	**Current PSG standard;** robust BE
Vardenafil ODT *(Staxyn)*	↓ AUC -29%	↓ Lower	↓ 60 min earlier	**NOT BE** **vs. FCT**	**Labeled use &** distinct PK state

Special Case: Donepezil HCl ODT (Aricept ODT®) The only ODT Labeled to be Taken With Water

CASE 3:
The Twist

Labeling: Administration WITH water

Donepezil HCl
(NDA 021720 Aricept ODT®)

Acetylcholinesterase Inhibitor
Alzheimer's Disease Dementia
NDA approved: October 2004

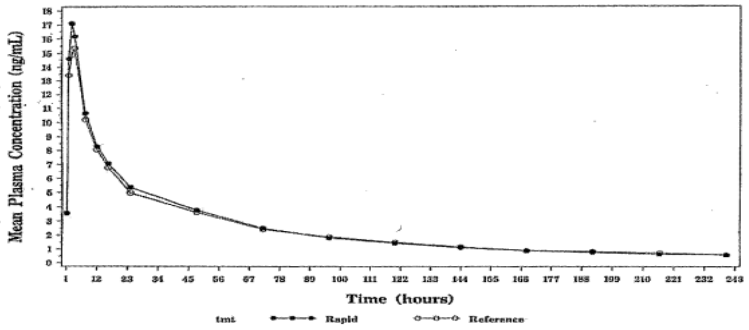
5 mg | 10 mg

Study Design: 505(B)(2) BE Study — ODT vs. Aricept® Conventional Tablet (Reference)

ODT + Water (100 mL) vs. Aricept Tablet

No without-water data submitted
⚠ Gap identified by FDA

Figure* 1: Mean donepezil plasma concentration-time in healthy volunteers (study E2020-A001-015) receiving single 10 mg donepezil hydrochloride dose as ODT or tablet (fasted state)



* In figure rapid refers to ODT and reference refers to Aricept tablet

Parameter	ODT + Water vs. Tablet	Without Water (Not Studied)	Conclusion
Cmax ratio	~100–107% of Ref	No data	BE (80–125%) ✓
AUC ratio	~93–104% of Ref	No data	BE (80–125%) ✓
Tmax	~3 h (similar to tablet)	No data	Not significantly different

Special Case: Donepezil HCl ODT (Aricept ODT®) The only ODT Labeled to be Taken With Water

Conclusion

PSG Update

Generic donepezil
ODTs now recommended to
disintegrate and swallow with water (per M13A)
No administration instruction provided prior

PSG Harmonization: The 39-Product Review

Identifying & Resolving Inconsistencies Between ODT Labeling and BE Study Recommendations

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PSG Review

43
ODT products identified in Orange Book

4
Already aligned with M13A (post-guidance) **Indication**

39
Products requiring assessment (pre-M13A PSGs)

17
PSGs with inconsistent water instructions

17
PSGs subsequently updated to align with M13A **PSG (Post-M13A)**

PSG Harmonization: The 39-Product Review

Identifying & Resolving Inconsistencies Between ODT Labeling and BE Study Recommendations

FDA

PSG Review

	Drug (API)	Indication	Labeling Instruction	PSG (Pre-M13A)	PSG (Post-M13A)
●	**Alprazolam**	Anxiety / Panic Disorder	With or Without water*	Follow with 240 mL water	**Without water**
●	**Rizatriptan Benzoate**	Migraine	Without water (no liquid necessary)	Follow with 240 mL water	**Without water**
●	**Zolmitriptan**	Migraine	Without water	Follow with 240 mL water	**Without water**
●	**Carbidopa / Levodopa**	Parkinson's Disease	Without water	Follow with 240 mL water	**Without water**
●	**Clozapine**	Treatment-Resistant Schizophrenia	Without water	Silent (no instruction)	**Without water**
●	**Methylphenidate**	ADHD	Without water	Silent (no instruction)	**Without water**
●	**Ondansetron**	Nausea/Vomiting (chemo, post-op)	Without water	Silent (no instruction)	**Without water**
●	**Donepezil**	Alzheimer's Disease	With water	Silent (no instruction)	**With water**
●	**Metoclopramide**	Gastroparesis / Nausea	Without water	Silent (no instruction)	**Without water**
●	**Loratadine**	Allergic Rhinitis	With OR without water	Silent (no instruction)	**Without water**
●	**Mirtazapine**	Major Depressive Disorder	With OR without water	Silent (no instruction)	**Without water**
●	**Olanzapine**	Schizophrenia / Bipolar I	With OR without water	Silent (no instruction)	**Without water**
●	**Risperidone**	Schizophrenia / Autism	With OR without water	Silent (no instruction)	**Without water**
●	**Desloratadine**	Allergic Rhinitis / Urticaria	With OR without water	Silent (no instruction)	**Without water**
●	**Lansoprazole**	GERD / Ulcers	With OR without water	Silent (no instruction)	**Without water**
●	**Cetirizine HCl**	Allergy Symptoms	With OR without water	Follow with 240 mL water	**Without water**
●	**Aripiprazole**	Anxiety Disorder	Without water or whole with water	Silent (no instruction)	**Without water**

Bagde S, Xi X, Boyce H, Kim M-J. AAPS Open. 2026;12:2. https://doi.org/10.1186/s41120-025-00138-y | Table 1 | FDA M13A Guidance (Aug 2024)

Summary & Conclusions

The FDA Position

When an ODT label permits use with OR without water, bioequivalence is recommended to be demonstrated without water. This condition:

- Is the pharmacokinetically more discriminating scenario
- Tests the condition patients most often use (no water available)
- Ensures generics perform at least as well as RLD under the most sensitive condition
- If BE passes without water → BE with water is assured

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U.S. FOOD & DRUG ADMINISTRATION

Questions?

Heather Boyce
Lead Pharmacokineticist
Division of Therapeutic Performance II, Office of Research and Standards
CDER | US FDA

Heather.Boyce@fda.hhs.gov