

Bioequivalence Strategies for Orally Disintegrating Tablets: Regulatory Considerations

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

Learning Objectives

FDA

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

CONVENTIONAL TABLET
+ 240 mL WATER



**Swallow. With water.**
Disintegrates in the stomach.

VS.

ODT
DISSOLVES ON TONGUE



**Place. Dissolves in seconds.**
No water needed.

**SAME MEDICINE. DIFFERENT WAY. DIFFERENT EXPERIENCE.**

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

FDA

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

Policy

- ❖ Labeling allows $\pm$ water, which condition should BE studies test?
- ❖ Water may speed dissolution $\rightarrow$ faster T_{max}
(e.g., Case Study 1: rizatriptan and Case Study 2: alprazolam)
- ❖ Water may inhibit buccal absorption $\rightarrow$ lower AUC
(e.g., Case Study 3: vardenafil)
- ❖ When to be taken without water

Regulatory Framework: FDA & ICH M13A Guidance Evolution



Policy

How ODT BE Administration Conditions Have Been Codified Over Time

2008

**FDA ODT
Guidance
Issued**

2021

**FDA Draft BE
Guidance Update**

Aug 2024

**ICH M13A
Adopted by FDA**

May 2026

**FDA Draft BE
Guidance Update**

- Defined ODT class criteria
- Disintegration ≤ 30 sec
 - Without water or chewing

- Without water = worst case
- First formal statement
- ODTs labeled $\pm$ water

- 3-arm study design standard for new use
 - Without water = discriminating
- 17 PSGs updated

- Without water = discriminating

Case Study 1: Rizatriptan Benzoate ODT: Water Accelerates Absorption

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

CASE 1:
The Foundation

Rizatriptan Benzoate (NDA 020865 Maxalt-MLT)

5-HT_{1B/1D} agonist
Migraine treatment
ODT approved: 1998

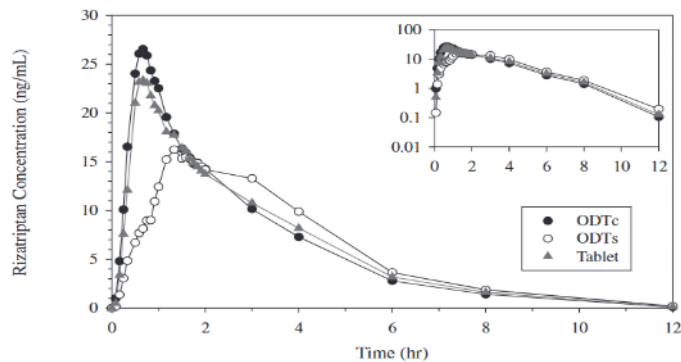
EQ 5 mg Base | EQ 10 mg Base

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)
AUC _{0-1h} (h·ng/mL)	9.9	5.23	8.27
AUC _{0-2h} (h·ng/mL)	33.1*	18.85	32.5
AUC _{0-∞} (h·ng/mL)	Similar	Lower	Ref
T _{max} – Median (h)	0.67*	1.33	0.67
C _{max} (ng/mL)	45.1	41.9	44.4

* $p < 0.001$ vs. ODTs (without water) — AUC_{0-2h} and T_{max} differences statistically significant

Case Study 1: Rizatriptan Benzoate ODT: Water Accelerates Absorption

Conclusions



CASE 1:
The Foundation

**Without Water =
Worst Case PK**

AUC_{0-2h} 43% lower &
T_{max} 1 hour later vs.
ODT+ water

**With Water = Best
Delivery Method**

AUC & T_{max} match
conventional tablet —
fastest absorption

**Total Bioavailability
Similar (AUC_{0-∞})**

ODT_c and tablet BE
for overall exposure;
ODTs consistently lower

PSG Update

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

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

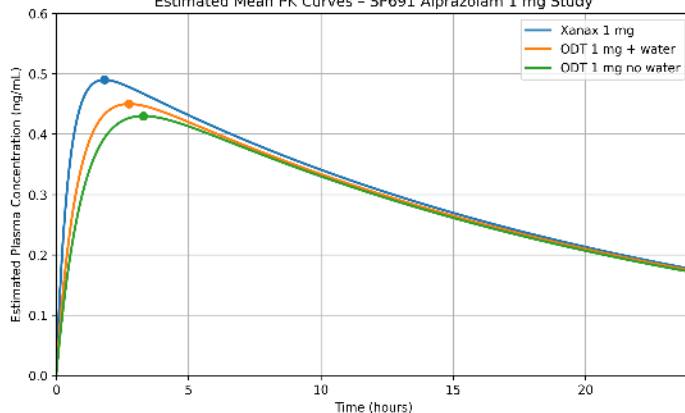
Study Design: 3-Way Crossover BE Studies (SP691 & SP765) vs. Xanax® (Reference)

ODT + Water
vs. Xanax
Tablet

ODT without
Water
vs. Xanax Tablet

Both conditions
tested at 0.5 mg
& 1 mg

Estimated Mean PK Curves – SP691 Alprazolam 1 mg Study



Modeled from reported mean T_{max}, C_{max}, and terminal half-life values from SP691 (FDA review Table 15).

Parameter / Strength	ODT + Water vs. Xanax	ODT without Water vs. Xanax	Conclusion
C _{max} 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%)
C _{max} 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%)
T _{max} difference	~15 min earlier	Reference	Not clinically significant

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



CASE 2

Conclusions

**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



CASE 3:
The Twist

Labeled to be taken explicitly WITHOUT water

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)
AUC_{0-∞}	+21 to +44% vs. FCT	-29% vs. no-water ODT
T_{max}	~1.5 h	~0.5 h (60 min earlier)
C_{max}	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 T_{max} by 60 min

Case Study 3: Vardenafil ODT (Staxyn®)

Water Reduces Bioavailability

Conclusions

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

Labeling: Administration *WITH* water

Donepezil HCl (NDA 021720 Aricept ODT®)

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

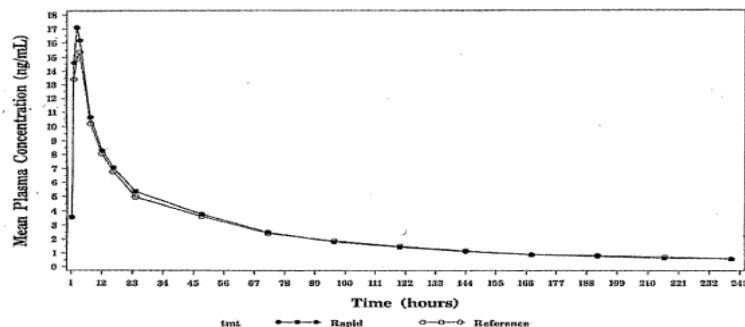
5 mg | 10 mg

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

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

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

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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Questions?

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