

Bioequivalence Strategies for Chewable Tablets: Regulatory Considerations

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Purpose

RLD labeling for chewable tablets may vary in administration instructions and tablets that can be chewed (e.g., "must chew" vs. "chew or swallow whole," with vs. without water).

This presentation provides guidance on recommended methodologies and regulatory considerations for BE study design.

- Chewable tablets: nomenclature and labeling from FDA guidance
- Recommended administration methods in BE studies: a decision tree approach with illustrative product-specific guidance (PSG) examples
- Formulation-specific considerations: immediate release (IR) and extended release (ER) chewable tablets
- BE study considerations for suitability petition-enabled chewable generics

Nomenclature and Labeling of Chewable Tablets



Guidance for Industry *Quality Attribute Considerations for Chewable Tablets (August 2018)*

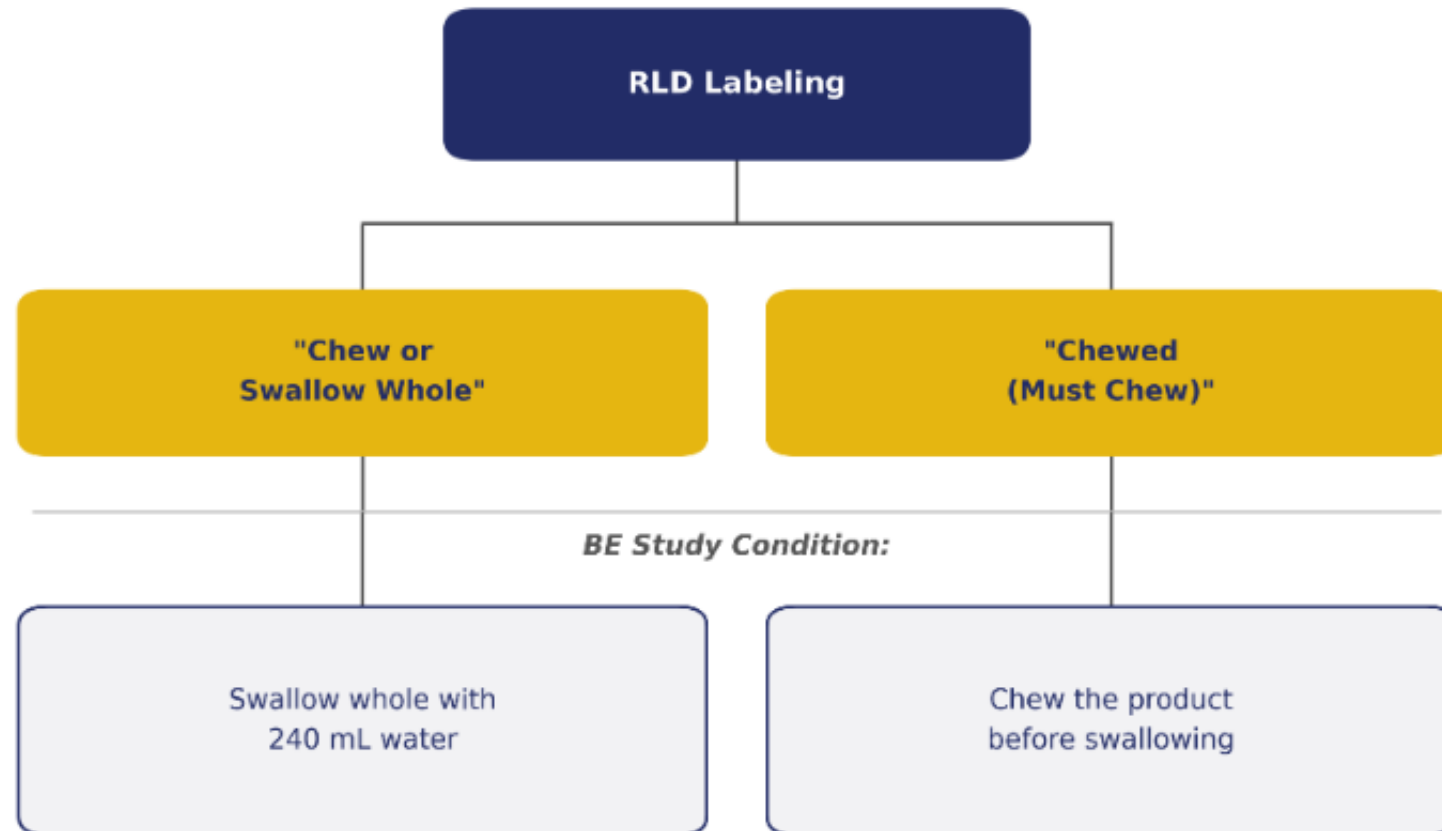
- *The text “[DRUG] **Tablets**” will be used for tablets that **MAY** be chewed or swallowed in their entirety. The labels and labeling for these products will also include a labeling statement indicating that the tablets **MAY** be chewed.*
- *The text “[DRUG] **Chewable Tablets**” will be used for tablets that **MUST** be chewed and for which there is no alternative route of administration. The labels and labeling for these products will also include a labeling statement indicating that the tablets **MUST** be chewed.*

Administration methods recommended in BE studies: chew vs swallow whole



Guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021)

- *Applicants should administer chewable tablets according to the directions on in the RLD labeling.*



Administration methods recommended in BE studies: use of water

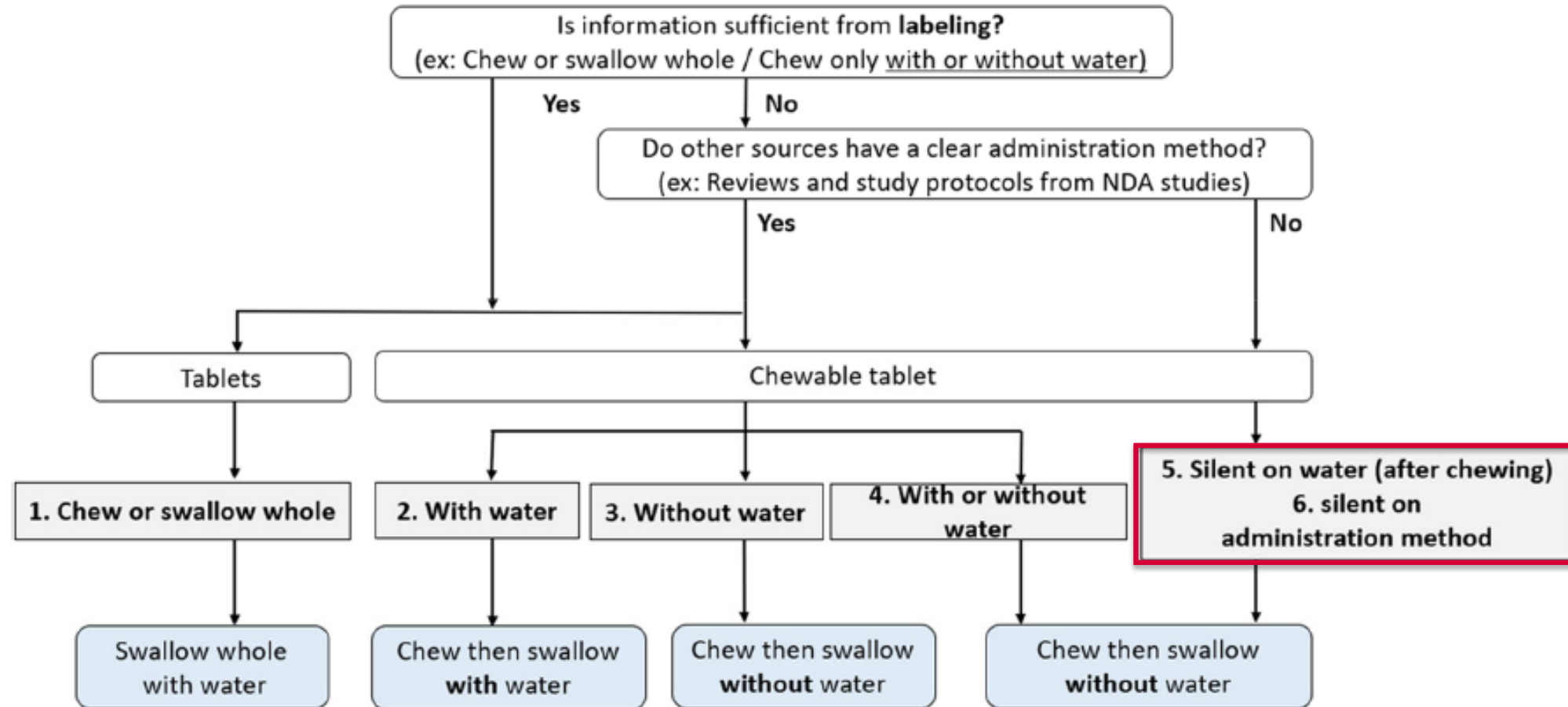


Guidance for industry *M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms* (October 2024)

- Chewable tablets should be administered in BE studies according to the comparator product labeling with regard to intake of water.*

RLD Labeling	BE Study Recommendation
Chew with water	With water
Chew without water	Without water
Chew with or without water	Without water

Decision Tree for Selecting BE Administration Methods for Chewable Tablet



PSG Examples: Chewable Tablets and Tablets Instructing Chewing



API	RLD Labeling	PSG Recommendation	Rationale
Ethinyl estradiol; norethindrone	Chew or swallow whole	Swallow whole with water	Swallowing whole more discriminating
Cetirizine hydrochloride (HCl)	Chew then swallow with or without water	Chew then swallow without water	Without water more discriminating
Lanthanum carbonate	Chew before swallowing (silent on water)	Chew then swallow with water	NDA study protocol specified water

Additional Considerations: ER Chewable Tablets

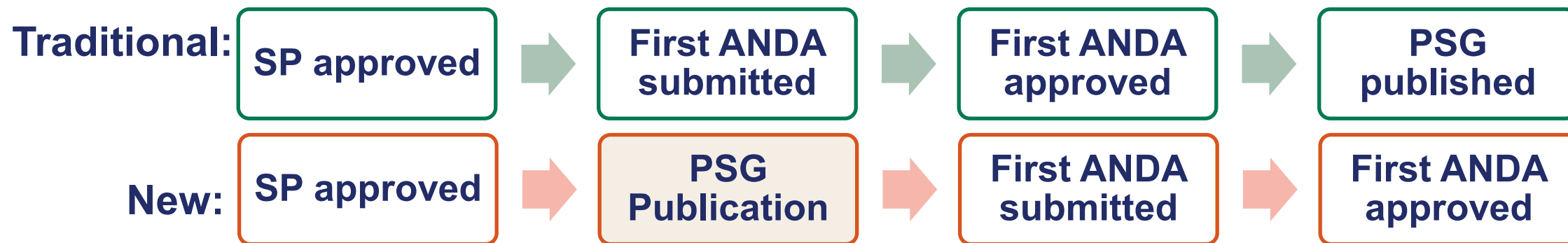


- 1. Must be chewable while maintaining ER mechanism throughout GI transit.
- 2. Chewing is the critical test condition to assess ER mechanism survival after chewing.
- 3. Swallowing whole does not test ER mechanism survival.
- 4. PSG recommendations available on a case-by-case basis.

An Overview: Chewable Tablet PSGs and Suitability Petitions



- Suitability petitions enable generic applicants to develop chewable tablets as an alternative dosage form to the RLD.
- Increased controlled correspondence (CC) inquiries following GDUFA III highlighted key questions on BE study design for petitioned dosage forms, including chewable tablet products.



PSG Strategies for Petitioned Dosage Forms



Study Design Considerations			Alternative dosage form	PSG Resolution
BE Approach	In vivo BE	Formulation information known?	No	2 Options Option 1 (First petitioned ANDA): • Compare to RLD per intended label use • Fed waiver: feasible for BCS I Option 2 (After first approved petitioned ANDA): • Fed waiver: Risk-based approach per M13A
		Data on food effect available?	No	
	Waiver	Strength waiver applicable?	Yes	
		BCS waiver applicable?	No	
		Fed waiver applicable?	Yes	

Chewable Tablet as a Petitioned Dosage form: Metformin HCl Example



RLD:

Metformin HCl tablets

Petitioned:

Metformin HCl chewable tablets

- PSG for RLD tablet NDA 020357 (RLD): one single BE study
- No approved ANDA for the petitioned dosage form
- CCs received to inquire BE study design.

The Two-Option Recommendations for Metformin HCl PSG



	Option 1	Option 2
When?	Before first petitioned ANDA approval	After first petitioned ANDA approval
Comparator	RLD, metformin HCl tablets	Approved petitioned metformin HCl chewable tablets (RS)
BE Study Design	Fasting, three-arm (1) RLD tablet with water (2) Test chewable tablet with water (3) Test chewable tablet without water Fed, two-arm (1) RLD tablet with water (2) Test chewable tablet without water	Fasting, two-arm (1) RS Chewable without water (2) Test Chewable without water

Summary



- Tablets with chewing instructions should be swallowed whole in BE studies.
- Chewable tablets in BE studies should be chewed, and the use of water is based on RLD labeling and FDA M13A guidance.
- When the labeling is unclear, the worst scenario is generally recommended which is chewing without water.
- Monitor relevant PSGs and consult the Agency for BE study design for chewable tablets approved through suitability petitions.

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