Improving Administration Method Consistency of Product-Specific Guidances for Chewable Tablets and Tablet Products with Chewing in Labeling

PRESENTER

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BACKGROUND:

- *Chewable tablets* are an oral dosage form to be chewed and then swallowed by the patient.
- There are also *tablets*, not chewable tablets, for which several administration methods such as “chew,” “chew or swallow,” or “chew or disperse,” are observed from the labeling.
- The FDA recommends that if the reference listed drug (RLD) labeling states that the tablet must be chewed before swallowing, the product should be chewed when administered in bioequivalence (BE) studies.[1]
- Administration of water with the chewable tablet is not always specified in the RLD labeling.
- Several product-specific guidances (PSGs) for BE studies of chewable tablets or tablets with chewing described in the labeling do not provide a specific administration method recommendation in BE studies.
- The objective of this work was to align the administration method recommended in PSGs for these products to the recommendations outlined in RLD labeling and the FDA draft guidance.

METHODS

1. FDALabel database search for oral drug products that contains instructions for **chewing** under **Dosage and Administration Section** of the labeling*

Search keywords: “new drug application (NDA)” and “oral,” and key words (e.g., “chew,” “chewing”, “chewed”, “chewable”)

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2. Determine the number of oral products that meet the definition of “chewable tablet” vs “tablet” with chewing administration option

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3. Categorize by the administration method

- Chew OR swallow
- Chew and swallow with water
- Chew and swallow with or without water, or silent on water intake
- Labeling is silent

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4. PSG search for chewable tablets and tablets with chewing administration

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A comparison of the PSG recommendation to the RLD labeling recommendation was made to identify the number of PSGs that should be reviewed to have consistent recommendations

*Information collected: active pharmaceutical ingredients, drug products, dosage forms, and administration methods

RESULTS:

- A total of 38 drug products that instruct patients to chew the tablet in the Dosage and Administration Section of the labeling were identified.
- RLD labeling identifies these products as either *chewable tablets* (n= 33) or *tablets* (n= 5).
- Twenty-six PSGs were obtained (see table 1 on the right panel).
  - Three PSGs instructed chew the tablet or were silent on administration method in BE studies when RLD labeling recommended chew or swallow whole.
  - Two PSGs were silent on the administration method when RLD labeling recommended chew the tablet with water.
  - Two PSGs were silent on water after chewing in BE studies when RLD labeling recommended chew the tablet with or without water, or silent on intake of water.
  - One PSG was silent on administration method and the RLD labeling was also silent on the administration method (e.g., no instruction on chewing or swallowing whole).

25% of chewable tablet PSGs were identified to not have consistent recommendations regarding how a chewable tablet should be administered in bioequivalence studies. We updated these PSGs to ensure that administration methods in bioequivalence studies for chewable tablet products are consistent.

Definitions of tablets and chewable tablets[2]

- *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.*

Reference: 2. U.S. Food and Drug Administration. (2021). *Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an abbreviated new drug application.*

Administration method of chewable tablets recommended in the FDA guidance[1]

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

(1) RLD labeling ‘chew’ OR ‘swallow whole’	(2) RLD labeling ‘chewed’*
If the label gives the option of <u>either</u> chewing the product <u>or</u> swallowing it whole	*The tablet must be <u>chewed</u> before swallowing*
Then in the BE studies,	Then in the BE studies,
The product should be <u>swallowed</u> whole, with 240 mL of water	*The product <u>should be chewed</u>*

- *We also recommend that you conduct in vitro dissolution testing on intact, whole tablets of the chewable drug product.*

Reference: 1. U.S. Food and Drug Administration. (2021). *Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an abbreviated new drug application.*

Overview of drug products that can be chewed

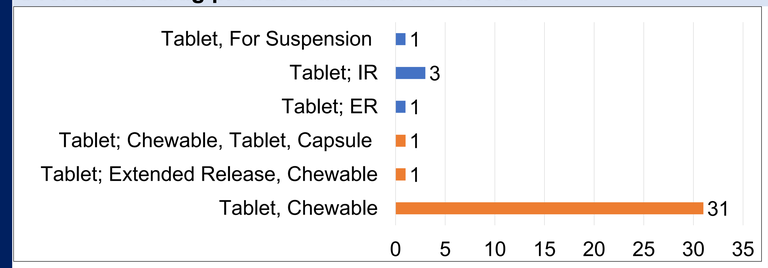

Table 1. A summary of PSGs (n=8) that were recently revised

Categories	Administration method in Labeling	Administration method in PSG	API	Revised administration method
Chew OR swallow (n=3)	Chew OR swallow	Not available (NA)	Lamotrigine	Swallow with water
	Chew OR swallow	NA	Ethinyl estradiol/Norethindrone	Swallow with water
	Chew OR swallow	Chew and swallow with water	Ethinyl estradiol/Norethindrone	Swallow with water
Chew and swallow with water (n=2)	Chew and swallow with water	NA	Methylphenidate	Chew and swallow with water
	Chew before swallowing	NA	Lanthanum carbonate	Chew and swallow with water
Chew and swallow with or without water, or silent on water intake (n=2)	with or witout water	NA	Cetirizine	Chew and swallow without water
	Chew before swallowing	NA	Loratadine	Chew and swallow without water
Labeling is silent (n=1)	Silent	NA	Amoxicillin/Clavulanate Potassium	Chew and swallow without water

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