

Dose Selection Considerations for Pharmacokinetic Bioequivalence Studies of Oral Suspension Products

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Disclaimer



This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Purpose

To outline considerations pertaining to the dose selection for pharmacokinetic (PK) bioequivalence (BE) studies of oral suspension products:

- Historical approach for dose recommendations in product-specific guidances (PSGs)
- Landscape of dose selection submitted in Abbreviated New Drug Applications (ANDAs)
- Current approach for dose recommendations in PSGs
- Case studies

Background

- Oral suspension formulations increase oral absorption and bioavailability by addressing poor water solubility and stability. From the patients' perspectives, oral suspensions improve swallowability and mask bitter taste.
- In PK BE studies, oral suspensions can be more easily adjusted in volume to deliver flexible doses.
- Historically, FDA did not specify a study dose in PSGs for oral suspension products to allow flexibility in dose selection, unless safety concerns require a maximum dose.
- FDA has received several inquiries on the appropriate study dose of oral suspension products, highlighting the need for clearer, more consistent guidance from FDA.

Dose Selection in Submitted ANDAs



- When the dose is not specified in the PSGs, the majority (65%) of the submitted PK studies in approved ANDAs were conducted using the labeled unit dose as the study dose.

Key Considerations for Dose Selection

-  *Safety for enrolled subjects*
-  *Sensitivity of bioanalytical methods*
-  *Alignment with clinical dose recommended in patients*
-  *Consistency with PSGs of other dosage forms with the same active pharmaceutical ingredient (API; if available)*
-  *Practicality in measuring with co-packaged dosing device (if applicable)*

Example 1: Specified Maximum Dose



RLD information

- Ganaxolone oral suspension 50 mg/mL
- Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator
- Indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder in patients 2 years of age and older

Relevant considerations

- Recommended dose (patients >28 kg): starting dose at 50 mg three times daily with food
- Severe central nervous system effects in healthy subjects at 300 mg

PSG

- Fed single-dose study in healthy males and non-pregnant, non-lactating females
- The dose should not exceed 250 mg

Example 2: Specified Dose Lower than Unit Dose



RLD information

- Baclofen oral suspension 25 mg/5 mL
- GABA-ergic agonist
- Indicated for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity

Relevant considerations

- Dose in relative bioavailability study in RLD program: 20 mg (4 mL)
- Recommended dose in patients: titrated to a maximum of 20 mg (4 mL) four times daily
- Recommended strength in PSGs for baclofen tablet, orally disintegrating tablet, and granules: 20 mg

PSG

- Fasting single-dose study in healthy males and non-pregnant, non-lactating females at 20 mg (4 mL)

Example 3: Specified Dose Higher than Unit Dose



RLD information

- Tasimelteon oral suspension 4 mg/mL
- Melatonin receptor agonist
- Indicated for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome in pediatric patients 3 years to 15 years of age

Relevant considerations

- Recommended dose in patients: weight-based to a maximum of 20 mg/day, to achieve exposures equivalent to 20 mg in adults
- Recommended strength in PSG for tasimelteon capsule: 20 mg (only strength)
- Co-packaged measuring device: 5 mL syringe

PSG

- Fasting single-dose study in healthy males and non-pregnant, non-lactating females at 20 mg (5 mL)

Example 4: Specified Dose Higher than Unit Dose



RLD information

- Ibrutinib oral suspension 70 mg/mL
- Kinase inhibitor
- Indicated for the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease after failure of one or more lines of systemic therapy

Relevant considerations

- Dose in relative bioavailability study in RLD program: 560 mg (8 mL)
- Recommended dose in patients: weight-based to a maximum of 420 mg/day
- Recommended strength in PSG for ibrutinib tablet: 420 mg (highest strength)
- Co-packaged measuring device: two 3 mL syringes

PSG

- Fasting single-dose study in healthy males and non-pregnant, non-lactating females at 420 mg (6 mL)

Summary

- FDA's current approach in PSGs for oral suspension products has evolved to provide more specific dose recommendations, balancing scientific rigor with study feasibility and subject safety.
- Key considerations for dose selection include safety profile, bioanalytical sensitivity, consistency with other PSGs of other dosage forms, and practicality in measuring with co-packaged dosing device.
- Case studies illustrate different scenarios: maximum dose specified, dose lower than unit dose, and dose higher than unit dose, each reflecting distinct regulatory and scientific rationales.

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