# 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

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| RLD information | • Ganaxolone oral suspension 50 mg/mL<br>• Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator<br>• 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<br>• 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<br>• The dose should not exceed 250 mg |

# Example 2: Specified Dose Lower than Unit Dose

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| RLD information | • Baclofen oral suspension 25 mg/5 mL<br>• GABA-ergic agonist<br>• 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)<br>• Recommended dose in patients: titrated to a maximum of 20 mg (4 mL) four times daily<br>• 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

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|---|---|
| RLD information | • Tasimelteon oral suspension 4 mg/mL<br>• Melatonin receptor agonist<br>• 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<br>• Recommended strength in PSG for tasimelteon capsule: 20 mg (only strength)<br>• 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

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| RLD information | • Ibrutinib oral suspension 70 mg/mL<br>• Kinase inhibitor<br>• 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)<br>• Recommended dose in patients: weight-based to a maximum of 420 mg/day<br>• Recommended strength in PSG for ibrutinib tablet: 420 mg (highest strength)<br>• 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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