Scientific and Regulatory Considerations for Sublingual Products

Wei-Jhe Sun, PhD
Division of Therapeutic Performance II/Office of Research and Standards/
Office of Generic Drugs/Center for Drug Evaluation and Research

Advancing Generic Drug Development Workshop: Patient-Centric Formulations
June 11, 2026

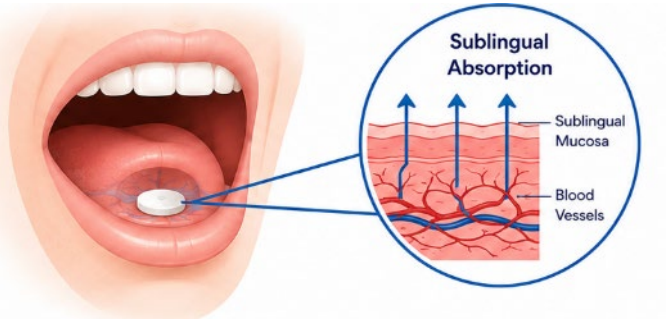
Disclaimer

This presentation reflects the views of the author only and should not be construed as representing FDA's views or policies

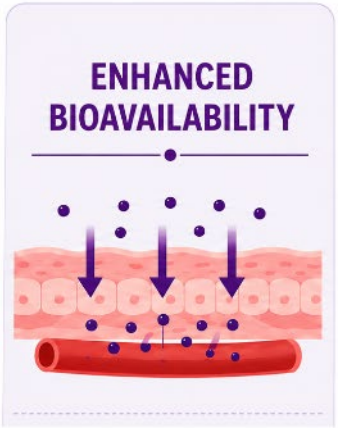
Overview

- Introduction to Sublingual Products
- Considerations of sublingual product development, BE study recommendations, and BE study design
- Case studies

Sublingual Drug Products



Dosage forms



Primary Therapeutic Applications

Cardiovascular

Nitroglycerin for immediate angina management

Substance Use Disorder

Buprenorphine for addiction

Sleep Aid

Zolpidem for insomnia

Pain Management

Fentanyl for severe pain management

Consideration in Sublingual Products Development

- Sublingual space and active pharmaceutical ingredients (API) dose limitations
- High API solubility and permeability requirements
- API taste and irritation tolerability
- Unsuitable for extended release system

Case Study 1: BE Study Consideration and Recommendation for Higher-than-RLD Strength via Suitability Petition

RLD Information & Suitability petition

RLD Information
- API: Y
- Dosage form: Tablet

Suitability petition: New strength (higher than the RLD strengths)

BE study consideration

- Sublingual space
- API solubility/permeability and dose proportionality data
- Any potential surface area impact

BE Recommendation

Two options for BE study:

a) 1 x Test product (petitioned strength) vs. 2 x RLD

b) 1 x Test product vs. 1 x RS (when an approved petitioned ANDA is designated as the RS)

Additional strengths: The in vivo testing are eligible to be waived when the required conditions are met

FDA Guidance for Sublingual Products

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

  "Other oral formulations such as orodispersible films, buccal tablets or films, and sublingual tablets may be handled in a similar way to that described above for ODTs."

- Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (May 2026)

  "Sublingual tablets should not be swallowed. The tablets should be placed under the tongue until they are dissolved. Follow the RLD labeling instruction or the applicable PSG for additional information on the method of administration."

- M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021)

  "Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. "

- Product-specific guidance (PSG)

Case Study 2: BE Study Recommendation: M13A Guidance

RLD information & Original BE recommendation

RLD Information:

- API: X
- Dosage form: Tablet
- Food effect: Food decreases Cmax and AUC by 31% and 20%, respectively

BE Study Recommendation in PSG: Fasting and Fed

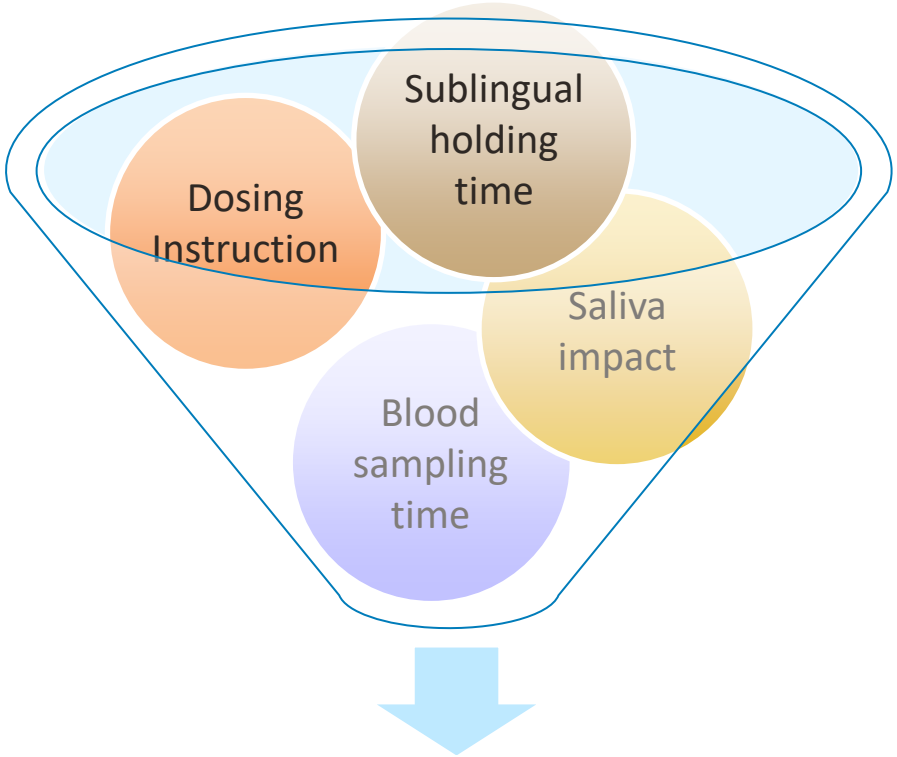
BE study consideration

- M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (October 2024)
  - Food effect is due to API property rather than formulation-dependent
  - A non-high-risk product

PSG revision

BE Study Recommendation: Fasting

In Vivo Study Design Considerations



PK performance may be impacted by several factors in study design:

- Dosing instruction: Administration methods in the labeling
- Sublingual holding time: Bioavailability impact
- Saliva impact: Sublingual API dissolution vs. GI tract swallowing
- Blood sampling time: Capturing quick onset

Case Study 3: BE Study Design for Sublingual Tablets

RLD information	**RLD Information:** • API: Z • Dosage form: Tablet • Tmax: ~ 1.5 hours **BE Study Recommendation in PSG**: Fasting
BE Study Design Consideration	**Dosing instruction consideration:** a) Instruct subject to keep the tablet under the tongue until it completely dissolved. b) Consider to include adequate holding time c) Consider to check sublingual space d) Instructed subjects to swallow **Blood sampling time**: Collect blood samples at an early time point, between 5 and 15 minutes after dosing, followed by additional sample collections, for example., two to five samples in the first hour after dosing

Summary

- Sublingual products provide rapid onset and high bioavailability, offering important clinical advantages for select therapies.
- BE recommendations are developed by integrating API properties, formulation design, and product-specific characteristics.
- Ensure reliable PK performance by tightly controlling critical study variables, such as sublingual holding time and early blood sampling, to accurately capture rapid onset.
- Generic drug applicants may seek correspondence with the Agency to clarify BE recommendation in PSGs or propose alternative BE approaches.

Acknowledgement

- Heather Boyce, Ph.D.
- Jihong Shon, M.D.
- Myong-Jin Kim, Pharm.D.
- Lei Zhang, Ph.D.
- Robert Lionberger, Ph.D.