Overview of the FDA Product-Specific Guidance (PSG) Program

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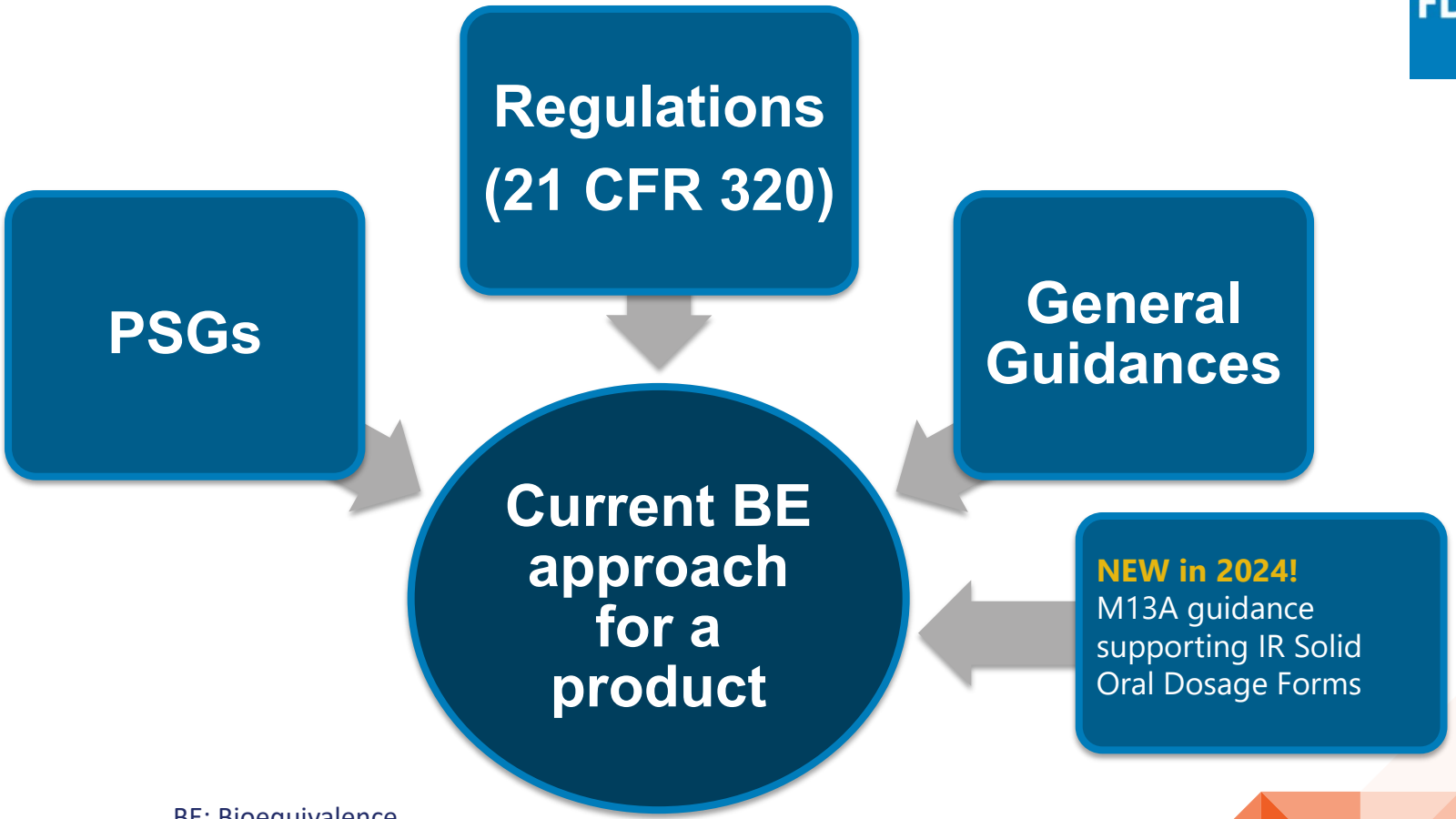
Generic Drug Forum - April 9th, 2025

Learning Objectives

- Understand the FDA's Product-Specific Guidance (PSG) program and its role in supporting Abbreviated New Drug Applications (ANDAs)
- Learn about the PSG process, GDUFA III commitments, and adoption of ICH M13A
- Identify available PSG online resources and forecasting to aid in drug development planning
- Understand how to utilize PSG public requests, public comments, and GDUFA III PSG teleconferences (T-Cons) and PSG meetings to engage with the FDA

What is a Product-Specific Guidance (PSG)?

- Reflects FDA's current thinking and expectations on how to develop a generic drug product therapeutically equivalent to a specific reference listed drug (RLD)
- Contains product-specific recommendations
  - Identifying the methodology for developing generic drugs and generating evidence recommended to support ANDA approval
  - Including key science and research output
- Unique to the generic drug development program



BE: Bioequivalence
IR: Immediate-Release

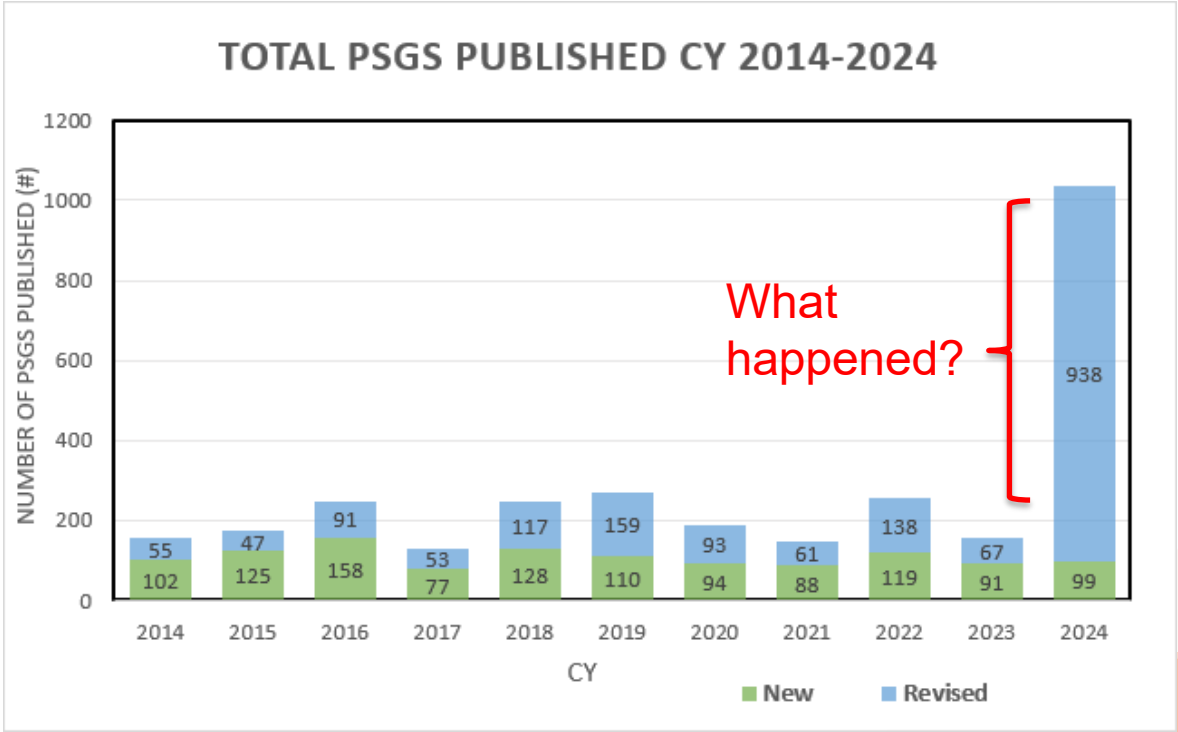
PSG is an Integral Part of the FDA's ANDA Program

- Pre-ANDA and ANDA Meetings
- Product-Specific Guidances
- Controlled Correspondences

Background on PSGs

- Starting in 2007, FDA has published PSGs to provide clear and direct recommendations to ANDA applicants

- As of 3/1/2025, 2,252 PSGs are published
  - ~30% of current published PSGs are for complex drug products*



**MAPP 5240.10 Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes*

GDUFA III Commitment on PSG Development

- For **Non-Complex, New Chemical Entity (NCE), New Drug Applications (NDAs)** approved on or after October 1, 2022, a PSG will be issued for 90% of such NDA products within 2 years after the date of approval.
  - No change from GDUFA II
- For **Complex Products** approved in **NDAs** on or after October 1, 2022, a PSG will be issued for 50% of such NDA products within 2 years after the date of approval, and for 75% of such NDA products within 3 years after the date of approval.
- FDA will continue to develop PSGs for Complex Products approved prior to October 1, 2022, for which no PSG has been published.

PSG Prioritization and Development

Initiating Events

- Recently approved NDAs and supplemental NDAs
- FDA analysis of products without PSGs
- Pre-ANDA meetings
- Public requests
- Comments submitted to PSG docket
- Controlled correspondences
- Citizen petitions

Data to Support PSG Development

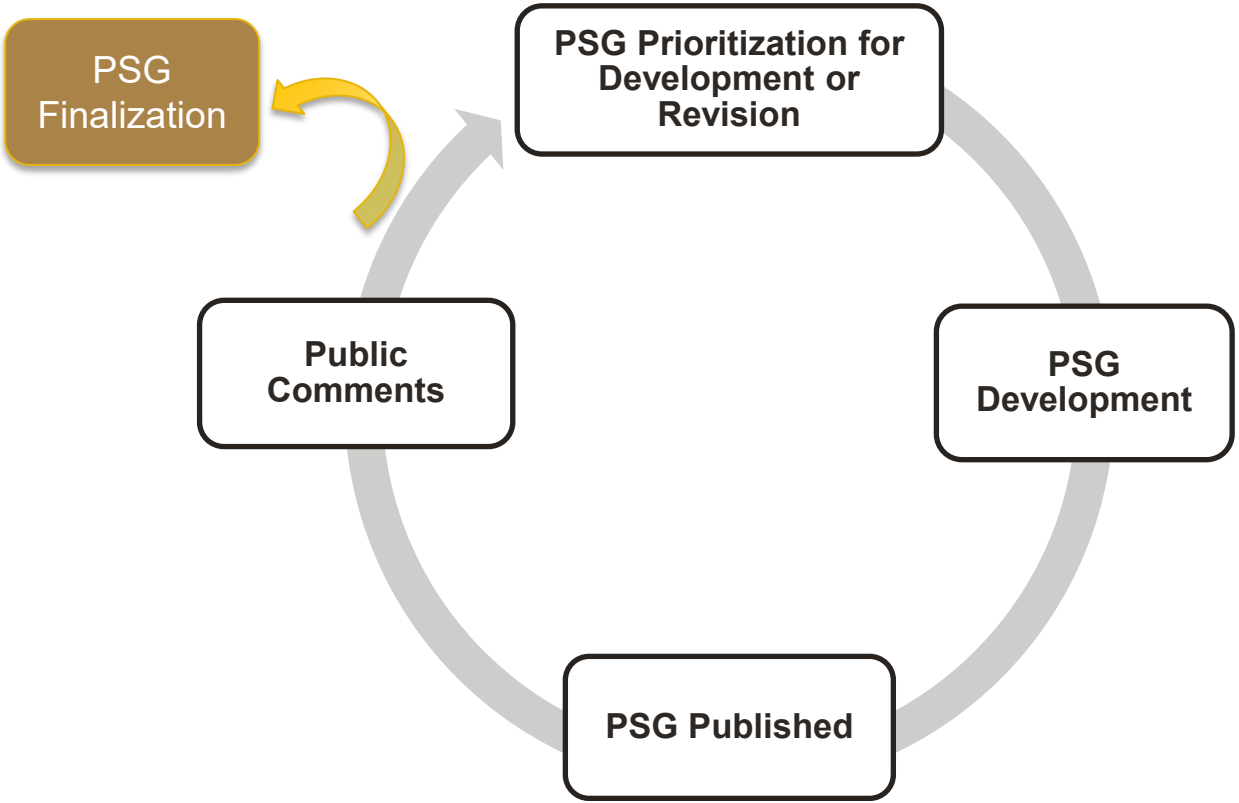
- Pharmacokinetic (PK) and pharmacodynamic (PD) modeling
- Previous BE studies
- NDA review and labeling
- Pharmacovigilance
- GDUFA-funded research outcomes

Prioritization

- GDUFA commitments
- Stakeholder interest in ANDA submission
- Drug availability and access
- Public requests from generic drug industry and other stakeholders
- Public health priorities

PSG Snapshot: *www.fda.gov/media/150142/download?attachment*

PSG Process



Quarterly Batch or as Standalone

How are Revised PSGs Planned?

Identification of Needs for PSG Revision

- Changes to the RLD: e.g., labeling update, supplements, new strength
- Newly identified safety concerns
- Consistency with revision to general guidances
- Responses to the received BE comments
- Citizen petitions
- New BE approaches from research: e.g., addition of the in vitro option
- New knowledge from ANDA assessments, Pre-ANDA meetings and controlled correspondences

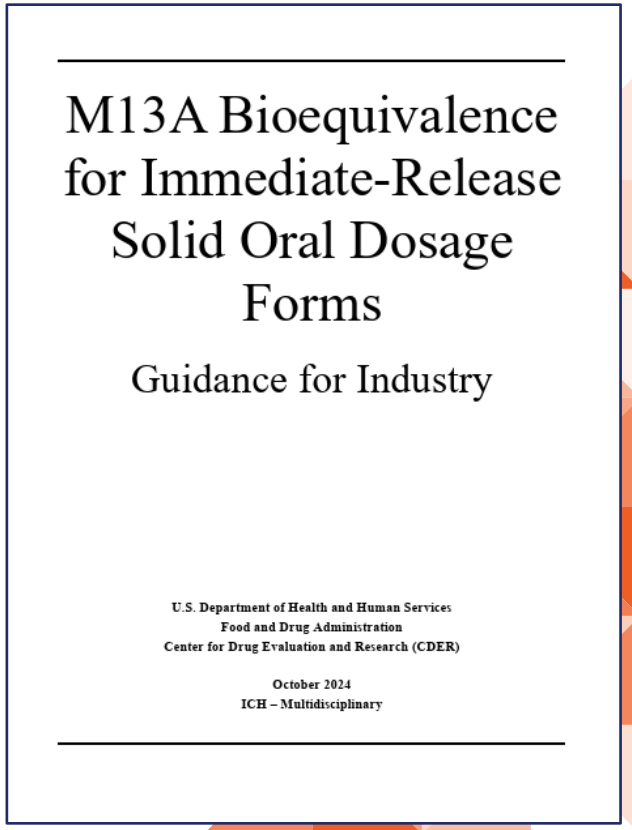
Category	Description
Critical	PSG revision includes additional bioequivalence studies or evidence recommended to support FDA approval that reflect a change in the safety or effectiveness of the drug product. The critical revision has a potential impact on all ANDAs including the approved applications.
In Vivo Major	PSG revision includes additional in vivo bioequivalence studies or evidence recommended that is necessary to establish BE and support FDA approval
In Vitro Major	PSG revision includes additional in vitro bioequivalence studies or evidence recommended that is necessary to establish BE and support FDA approval
Minor	PSG revision includes in vivo and/or in vitro changes that is not considered critical or major
Editorial	PSG revision includes non-substantive changes

What is ICH M13A?

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines.
- Since 1990, ICH has gradually evolved, to respond to increasing global developments in the pharmaceutical sector.
- ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective and high-quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.
- **M13A** is the first ICH generic drug guideline to harmonize BE standards for oral IR solid dosage form drugs.

M13A: Risk-Based* Approach to Determine BE Study Conditions with Regards to Meals

- **Non-High-Risk Products**
  - A single BE study is sufficient to ensure there is no clinically significant difference in BE under different meal conditions
  - BE testing under only one condition (fasting or fed)
  - Fasting condition is generally recommended due to being the most sensitive condition to detect formulation impact on bioavailability
- **High-Risk Products**
  - For certain products, differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa
  - BE studies should be conducted under **both** fasting and fed conditions



fda.gov/cdersbia

*Risk of Bioinequivalence

Before M13A

- Different regulatory agencies have different recommendations for BE study designs and criteria to support generic drug approval
  - For IR oral products FDA generally recommended both fasting and fed BE studies
- Several other regulatory agencies including European Medicines Agency (EMA), generally recommended a BE study under fasting conditions only
  - Differences in general BE guidances had led to different PSG recommendations
  - Multiple BE studies to meet recommendations from multiple jurisdictions

M13A Assessment

- FDA published the final M13A guidance in October 2024 following ICH adoption of final M13A guideline in July 2024
- ~1,150 published PSGs of oral IR drug products: ~160 PSGs were excluded from the FDA's initial efforts for PSG revision to align with M13A
  - Narrow therapeutic index drugs
  - Locally acting drug products
  - Products with PSGs recommending BE studies in patients
  - Products with PSGs recommending only one BE study
- ~150 PSGs of oral IR drug products considered as "High-Risk" products were not revised and continue to recommend two BE studies
  - Solid dispersions; lipid-based formulations (e.g., self-emulsifying drug delivery system)
  - Nanotechnologies (e.g., micro/nano-emulsions)
  - Gastro-retentive formulation; polymer-based (e.g., functional coating)
  - Critical excipients

After M13A

- Initial revision efforts to align with M13A revised **814 PSGs** and posted in October 2024
  - ~72% of FDA's existing PSGs for oral IR products; **~37%** of **total** number of FDA published PSGs
- Significant impact of M13A on ANDA Submissions to the U.S.
  - Primary focus assessed risk evaluation for "High-Risk" and "Non-High-Risk" oral IR drug products to reduce the need for additional in vivo BE studies compared FDA's prior recommendations
  - Estimated savings of 50 million dollars per year based on numbers of ANDAs FDA received (200 ANDA approvals in FY2024 for products impacted by these BE recommendation changes)
- Additional PSGs to align with M13A are being posted in quarterly batches (e.g., Nov 2024)

SBIA webinar: M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms - Implementing the Final Guidance (Nov 2024)

Wait there's more!

PSG Online Website and Resources

Product-Specific Guidances for Generic Drug Development

New in Generic Drug User Fee Amendments (GDUFA) III

When a new or revised PSG is published and an applicant or prospective applicant has already commenced an in vivo bioequivalence study (i.e., the study protocol has been signed by the study sponsor and/or the contract research organization), the applicant or prospective applicant may request a PSG Teleconference to obtain agency feedback on the potential impact of the new or revised PSG on its development program. Pre-submission or post-submission PSG meetings may be requested following feedback received at the PSG teleconference. Refer to the GDUFA III Enhancements to the Pre-ANDA Program web page for additional details.

Resources

- GDUFA III Enhancements for the Pre-ANDA Program
- FDA Product Specific Guidance Snapshot (PDF - 150 KB)
- FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs (pre-recorded webinar)
- How to Submit Comments on a Product-Specific Guidance
- Upcoming Product-Specific Guidances for Generic Drug Product Development
- Drug-Related General Guidances
- Bioequivalence Recommendations for Specific Products Final Guidance (June 2010) (PDF - 80 KB)
- Dissolution Methods Database
- Withdrawn CDER Product Specific Guidances (PDF - 90 KB)

When are PSGs published?

- New and revised PSGs are generally published quarterly in four batches a year
- A PSG may be published as a stand-alone guidance or a stand-alone batch outside the quarterly batches, e.g.,
  - Coordinate with citizen petition responses
  - Meet the GDUFA goal date
  - Efficiency in developing PSGs for products in the same class
  - Level 2 Revision(s)
- The FDA will issue a notice in the Federal Register for every batch and stand-alone posting, except Level 2 Revisions

What is a Level 2 PSG Revision?

- **Level 1** guidance documents set forth the Agency's initial interpretations of statutory or regulatory requirements; describe changes in FDA's earlier interpretation or policy that are of more than a minor nature; and deal with complex scientific or highly controversial issues.
- **Level 2** guidance documents address existing practices or minor changes in FDA's interpretation or policy.
- Level 2 PSG Revisions
  - Typographical errors found in PSGs
  - No change in BE recommendation or Agency thinking

https://www.fda.gov/about-fda/reports/background-fda-good-guidance-practices

Upcoming PSGs for Generic Drug Product Development (Forecast List)

Planned New PSGs for Complex and Non-Complex Generic Drug Products
Updated: November 19, 2024

Search: Export Excel Show 10 entries

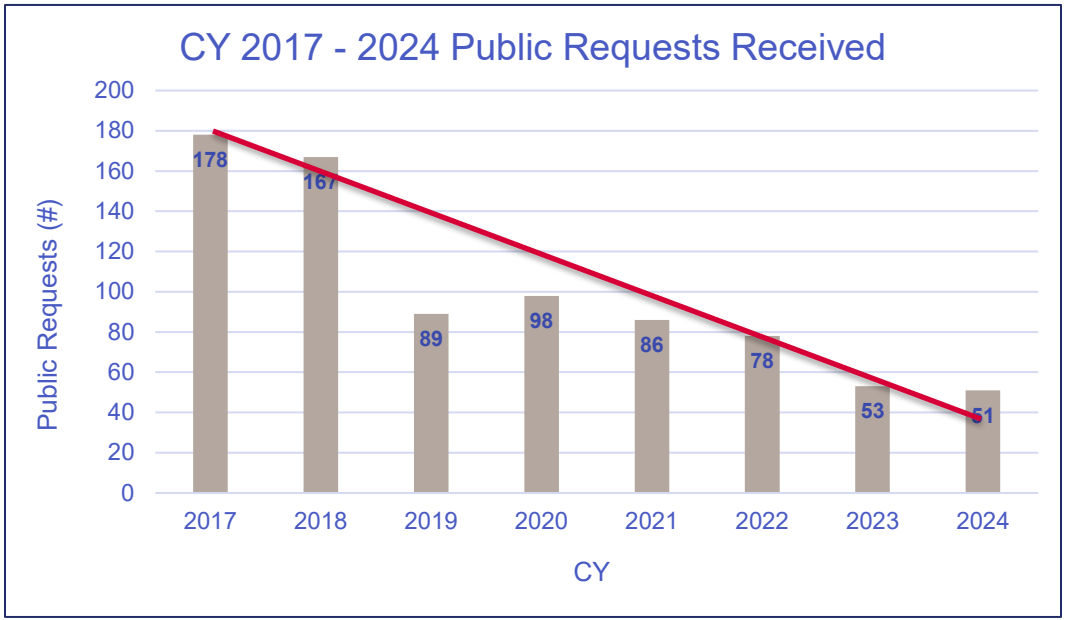
Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Product Complexity	Planned Publication	Updates
Gepirone Hydrochloride	Oral	Tablet, Extended Release	021164	Non-Complex	02/2025	Planned publication date assigned
Givinostat Hydrochloride	Oral	Suspension	217865	Non-Complex	08/2025	No Change
Ibrutinib	Oral	Suspension	217003	Non-Complex	05/2025	Newly Added
Iptacopan Hydrochloride	Oral	Capsule	218276	Non-Complex	02/2025	Planned publication date change to an earlier date
Lanreotide Acetate	Subcutaneous	Solution	215395	Complex	Within the next 12 months	No change
Levacetylleucine	Oral	Suspension	219132	Non-Complex	11/2025	Newly Added

Public Comments on PSGs

- FDA issues a Federal Register Notice announcing the availability of new and revised PSGs via Docket Number FDA-2007-D-0369
- The notice will identify a comment period for the draft recommendations
  - Comment can be submitted electronically to the docket or by mail
  - Users can request additional assistance with a Help Desk ticket: https://www.regulations.gov/support
- FDA will consider comments on draft PSGs while revising the PSGs

Public Requests for PSGs

- Public requests for PSGs can be submitted using the CDER Direct NextGen Collaboration Portal
  - ➢ FDA reviews requests and takes appropriate action



PSGs Withdrawn

CDER Product-Specific Guidances Withdrawn Listing
Updated November 19th, 2024

Active Ingredient	Type of Guidance	Route and Dosage Form	RLD	Date PSG posted, or revised	FEDERAL REGISTER Notice Date
Butenafine Hydrochloride	Draft	Topical Cream	021408	03/01/2012	02/01/2015
Hydroxyprogesterone Caproate	Draft	Subcutaneous Solution	021945	09/16/2019	04/06/2023
Lorcaserin Hydrochloride	Draft	Oral Tablet, Extended Release	022529	03/01/2015	03/04/2021
Lorcaserin Hydrochloride	Draft	Oral Tablet, Extended Release	208524	05/01/2017	03/04/2021
Lovastatin; Niacin	Draft	Oral Tablet, Extended Release	021249	07/01/2009	04/18/2016
Melphalan Flufenamide Hydrochloride	Draft	Intravenous Powder	214383	11/17/2022	04/18/2024
Mobocertinib Succinate	Draft	Oral Capsule	215310	08/21/2023	07/15/2024
Niacin; Simvastatin	Draft	Oral Tablet, Extended Release	022078	10/01/2011	04/18/2016
Oxymorphone Hydrochloride	Draft	Oral Tablet, Extended Release	201655	10/04/2016	12/23/2020

Note: If a PSG is re-posted, it will be removed from the withdrawn list

- Recommendations in a PSG are withdrawn when they no longer reflect the FDA's current thinking
- Withdrawn PSGs could also be due to a withdrawn RLD for safety or efficacy reasons
  - List of withdrawn PSGs can be accessed: https://www.fda.gov/media/90032/download

PSG T-Cons

- ANDA applicant(s) can request a PSG T-con at any time during their product development (pre-submission or post-submission) when FDA publishes a new or revised guidance that introduces or revises a recommendation if:
  - BE recommendation is for an **in vivo** BE study
  - ANDA applicant has already commenced an in vivo BE study that may be different from PSG recommendations as of the published date for the new or revised PSG
- A prospective ANDA applicant should submit a request for a pre-submission PSG T-con or pre-submission PSG meeting electronically through the CDER Direct NextGen Collaboration Portal
- An ANDA applicant should submit a request for a post-submission PSG T-con or post-submission PSG meeting electronically through the Electronic Submissions Gateway
- In CY 2024, 3 PSG T-cons were requested (2 pre-submission and 1 post submission)
  - 1 PSG T-con was granted

Guidance for Industry on PSG T-cons and Meetings (Aug 2024): www.fda.gov/media/165468/download

PSG Meetings

- PSG meetings (pre-submission or post-submission) can be requested following a PSG T-con if additional discussion is needed
  - Allows a forum to discuss the scientific rationale for an approach other than the approach recommended in the PSG
- Potential applicants may submit additional questions following the PSG T-con via controlled correspondences for any remaining issues
- Applicants may submit a pre-ANDA or ANDA scientific meeting as an alternative to PSG meetings
  - Applicants may ask additional questions that are not in the PSG meeting scope, if applicable
  - FDA recommends that applicants not submit a controlled correspondence and a request for a meeting at or around the same time with the same or similar questions
- In CY 2024, FDA did not receive any PSG meeting requests

Guidance for Industry on PSG T-cons and Meetings (Aug 2024): www.fda.gov/media/165468/download

Summary

- PSGs reflects FDA's current thinking and expectations on how to develop a generic drug product therapeutically equivalent to a specific RLD
- PSGs are generally published quarterly or as a standalone batch with future forecasting at Upcoming Product-Specific Guidances for Generic Drug Product Development
- M13A reduced the need for additional in vivo BE studies for IR oral products compared to what FDA recommended prior to support streamlined global generic drug development
- Potential ANDA applicants are encouraged to submit Public Requests, request PSG T-con and PSG meetings, and/or leave public comments on published PSGs, as applicable

Resources

- Product-Specific Guidances for Generic Drug Development: https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development
- GDUFA III Commitment Letter
- MAPP 5240.10: Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes (April 2022)
- Product-Specific Guidances for Generic Drug Development (*PSG Database*): https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- GDUFA III Enhancement to the Pre-ANDA Program: https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii-enhancements-pre-anda-program
- FDA Guidance for Industry: Product-Specific Guidance Meetings Between FDA and ANDA Applicants Under GDUFA (August 2024)
- FDA Guidance for Industry: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms Questions and Answers (Oct 2024)
- SBIA webinar: M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms - Implementing the Final Guidance (Nov 2024)
- SBIA webinar: Facilitating Generic Drug Product Development through Product-Specific Guidances (April 2024)

Questions?

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