FDA Product-Specific Guidance Program Overview

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Generic Drug Forum - April 27, 2022

Learning Objectives

- Describe general principles of product-specific guidances (PSGs)
- Discuss the process of how PSGs are prioritized, developed and revised, and published
- Understand how PSGs and other pre-submission communications facilitate generic drug development
- Describe FDA's PSG webpage and the information available through that site

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**
- 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

ANDA: Abbreviated New Drug Application

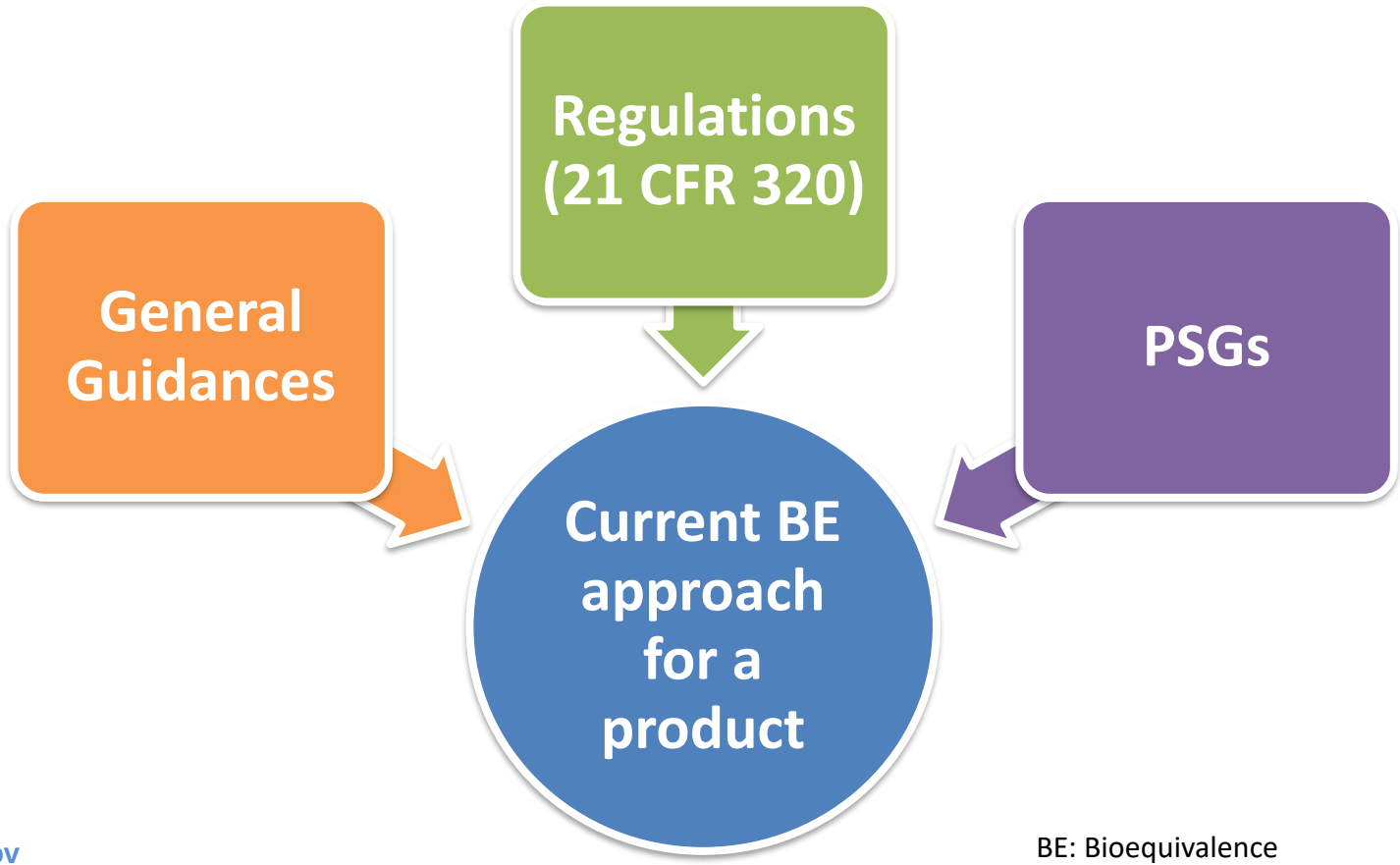
PSG is an Integral Part of the FDA's ANDA Program

Pre-ANDA Program

- Pre-ANDA Meetings
- **Product-Specific Guidances (PSGs)**
- Controlled Correspondences

GDUFA: Generic Drug User Fee Amendments

Background on PSGs



BE: Bioequivalence

Background on PSGs (cont.)

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

- As of April 2022, the PSG database on the FDA PSG website includes almost 2,000 PSGs
  - Searchable and exportable

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Background on PSGs (cont.)

- GDUFA II commitment on PSG development
  - Issue PSGs for 90% of ***non-complex*** **NCE NDAs** that are approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA submission date
  - Strive to issue PSG for a ***complex product*** as soon as scientific recommendations are available

GDUFA: Generic Drug User Fee Amendments; NCE: new chemical entity; NDA: new drug application;
https://www.fda.gov/media/101052/download

Complex Products

Complex active pharmaceutical ingredient (API)	• Any drug product containing a complex API, regardless of administration routes and dosage forms. e.g., Conjugated Estrogen Tablet, Glatiramer Acetate Injection
Complex routes of delivery	• Any non-solution drug product with a non-systemic site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action) e.g., Cyclosporine Emulsion, Acyclovir Cream
Complex dosage forms/formulations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation e.g., Doxorubicin HCl Liposomes, Leuprolide Acetate for Depot Suspension
Complex drug-device combinations	• Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption e.g., Epinephrine Injection (autoinjector)
Other products	• Any solid oral opioid drug products with FDA approved labeling for that show properties (and thus gaining their labeling) to meaningfully deter drug abuse e.g., Hydrocodone Bitartrate ER Tablet

Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, Clinical Pharmacology & Therapeutics (CPT), 2019, Vol.105(4), p.878-885.

How PSGs Help Generic Drug Development

Timely PSGs help to enable access to generics in all product categories

- Provide guidance to applicants early in development
- Incorporate and communicate relevant research results
- Help to manage our pre-ANDA meeting capacity by making PSG available

Timely PSGs help to optimize ANDA assessments for all product categories

- Coordination between PSG development and ANDA assessments by incorporating what's learned from ANDA assessments into guidance recommendation
- Keep scientific guidance up to date

Additional Resources

Pre-ANDA Meetings

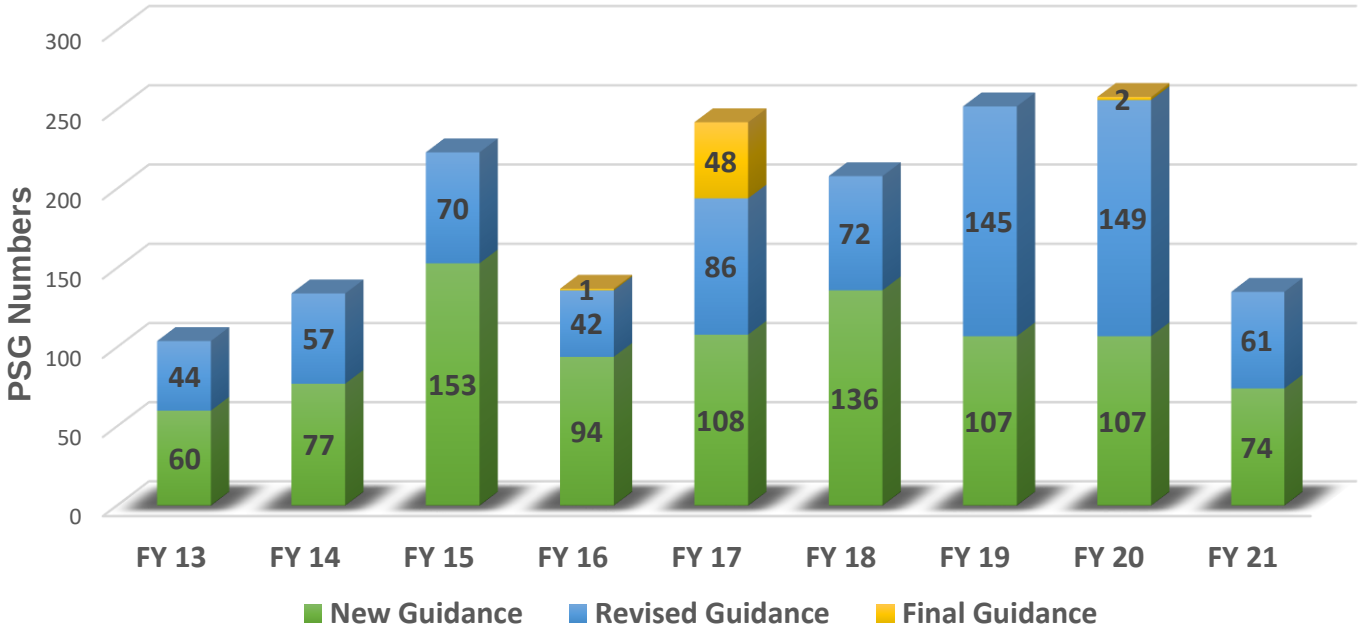
- Complex drug products without PSGs
- Complex drug products: alternative proposal(s) to PSG recommendations

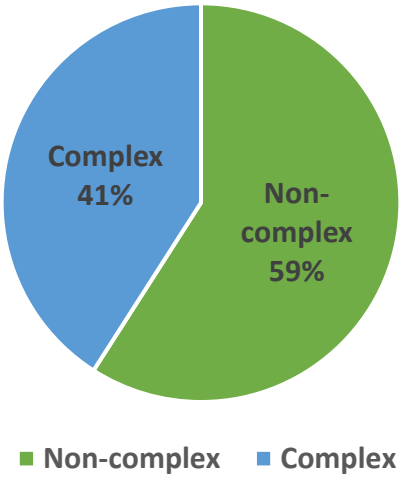
Controlled Correspondences

- Inquiries regarding existing PSGs
- Alternative proposal(s) to PSG recommendations

- *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA, Nov 2020*
- *Controlled Correspondence Related to Generic Drug Development, Dec 2020*

PSGs Published (FY 2013-FY 2021)

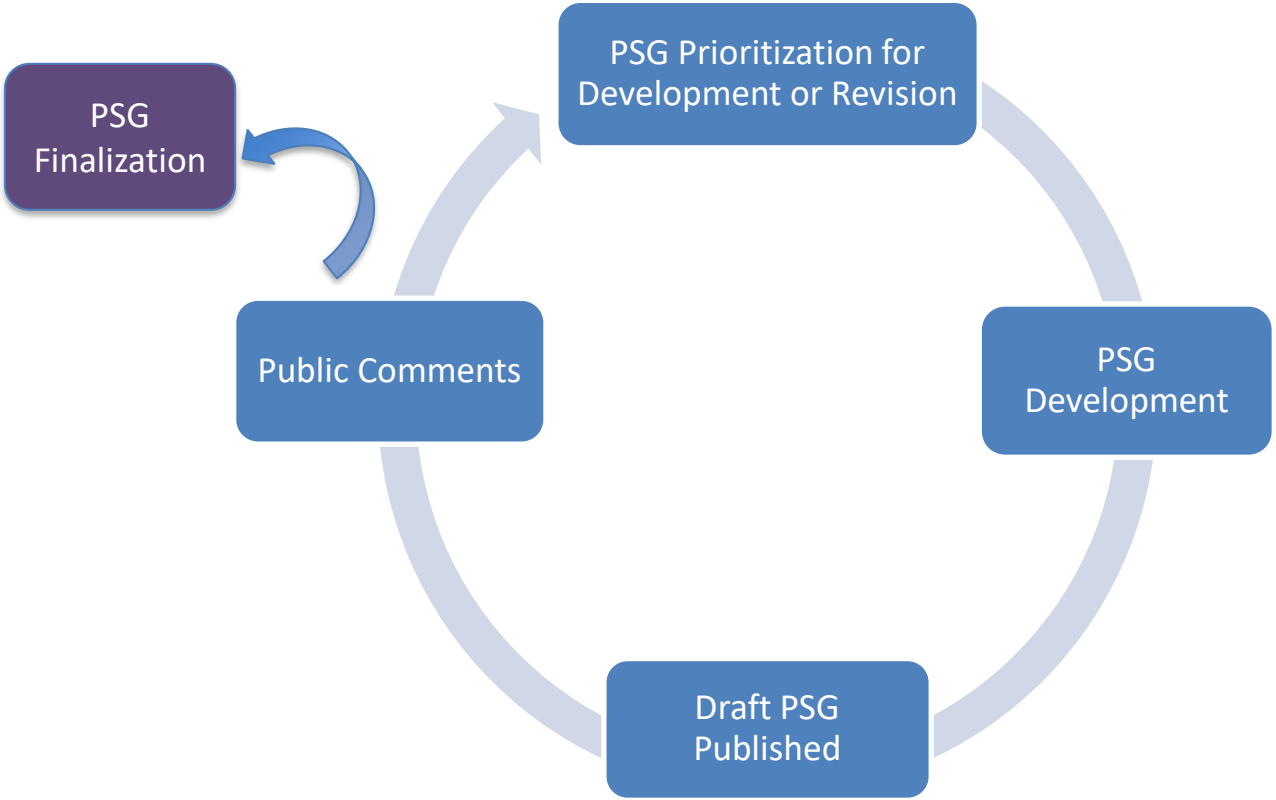




FDA's Ongoing Efforts on PSGs

- FDA commits to develop new PSGs in a timely manner
  - GDUFA II sets up goal date on PSGs for ***non-complex NCEs***
- FDA provides transparency through PSG development and revisions to incorporate FDA's latest science-driven thinking and understanding for assembling evidence in support of generic drug applications
  - Improve efficiency and quality of generic product development
- FDA provides information regarding current plans for developing PSGs for complex generic drug products
  - Upcoming PSGs for Complex Generic Drug Product Development

PSG Process



Quarterly Batch/
Standalone

Prioritization for New PSG Development

- GDUFA commitments: Non-Complex NCEs
- Complexity of the product
- External interests: Pre-ANDA meetings, Controlled Correspondences, ANDAs without PSGs, Public Requests
- Public health priorities: e.g., opioid epidemic
- Drug availability and accessibility
  - Drug shortage, number of available products in market
  - Market share of the reference listed drug products
- Completion of research projects related to scientific gaps

Public Requests for PSGs

- Public requests for PSGs can be submitted using the CDER Direct NextGen Collaboration Portal
  - FDA receives approximately 100-150 requests annually
  - FDA reviews these requests and takes appropriate action

How Revised PSGs are Planned?

Identification of Needs for PSG Revision

- Changes to the reference products: 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

Notification of PSG Revision*

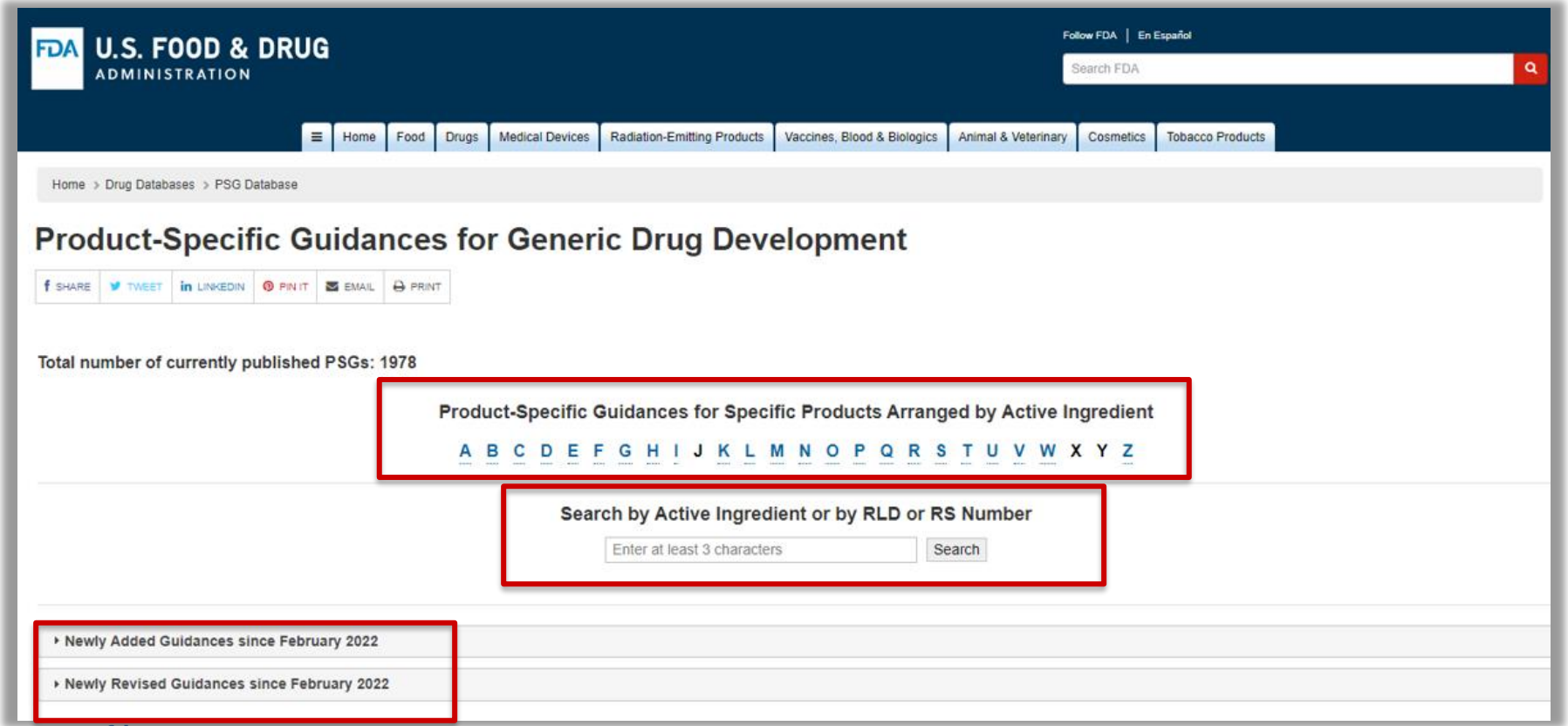
Category	
Major	Additional BE studies or evidence recommended to support FDA approval
Minor	Any revision that is not considered major
Editorial	Non-substantive changes

*Upcoming PSGs for Complex Generic Drug Product Development: https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development

When are PSGs published?

- New and revised, draft PSGs are generally published quarterly in batches
- A PSG may be published as a stand-alone PSG
  - Coordinate with citizen petition responses
  - Meet the GDUFA goal date
- The FDA will issue a notice in the Federal Register

FDA PSG Webpage



Locating PSGs

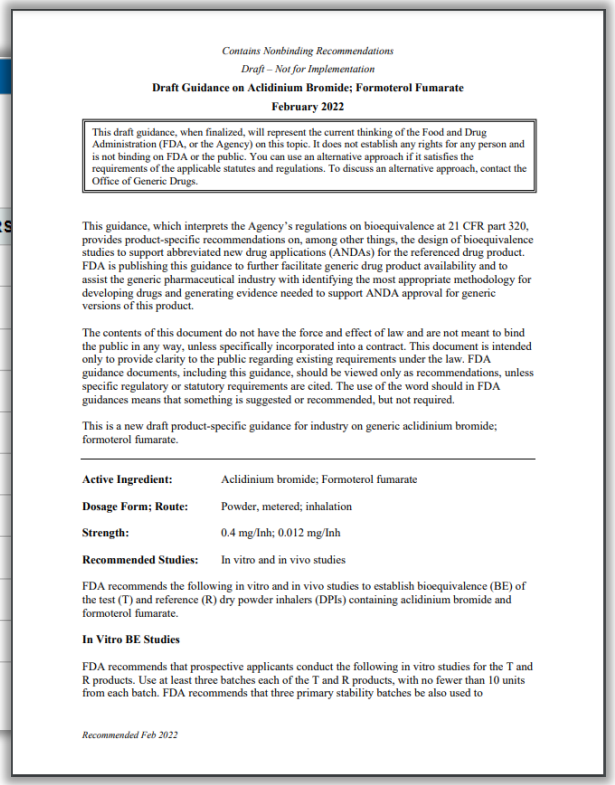
Newly Added Guidances since February 2022

Excel | CSV | PDF

Show 10 entries

Active Ingredient (link to Specific Guidance)	Type	Route	Dosage Form	RLD or RS
Aclidinium Bromide; Formoterol Fumarate	Draft	Inhalation	Powder, Metered	210595
Apomorphine Hydrochloride	Draft	Sublingual	Film	210875
Atropine Sulfate	Draft	Ophthalmic	Solution/Drops	206289
Capmatinib Hydrochloride	Draft	Oral	Tablet	213591
Cladribine	Draft	Oral	Tablet	022561
Dicyclomine Hydrochloride	Draft	Oral	Capsule	007409
Dolutegravir Sodium	Draft	Oral	Tablet, For Suspension	213983
Enzalutamide	Draft	Oral	Tablet	213674
Estradiol	Draft	Transdermal	Gel, Metered	021813
Estradiol	Draft	Transdermal	Spray	022014

Showing 1 to 10 of 29 entries



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Aclidinium Bromide; Formoterol Fumarate

February 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic aclidinium bromide; formoterol fumarate.

Active Ingredient: Aclidinium bromide; Formoterol fumarate

Dosage Form; Route: Powder, metered; inhalation

Strength: 0.4 mg/Inh; 0.012 mg/Inh

Recommended Studies: In vitro and in vivo studies

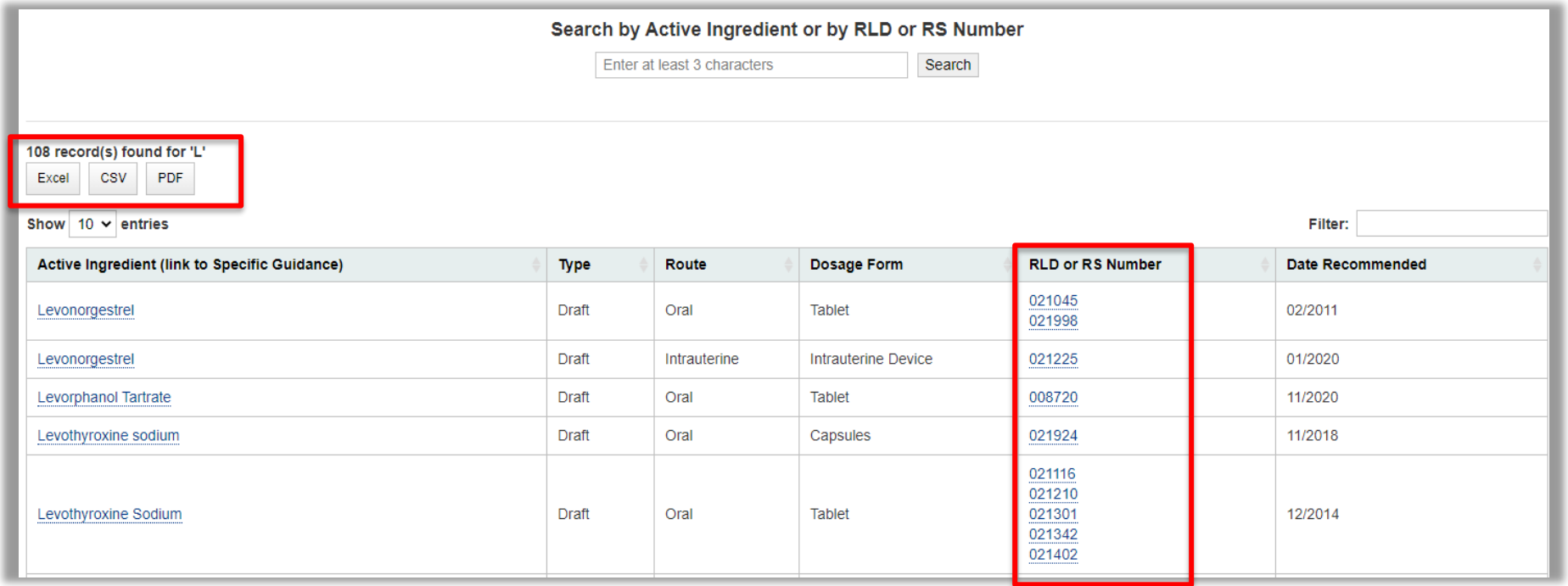
FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing aclidinium bromide and formoterol fumarate.

In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro studies for the T and R products. Use at least three batches each of the T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to

Recommended Feb 2022

How to Use RLD/RS on the PSG Webpage?



Search by Active Ingredient or by RLD or RS Number

Enter at least 3 characters | Search

108 record(s) found for 'L'

Excel | CSV | PDF

Show 10 entries | Filter:

Active Ingredient (link to Specific Guidance)	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Levonorgestrel	Draft	Oral	Tablet	021045 021998	02/2011
Levonorgestrel	Draft	Intrauterine	Intrauterine Device	021225	01/2020
Levorphanol Tartrate	Draft	Oral	Tablet	008720	11/2020
Levothyroxine sodium	Draft	Oral	Capsules	021924	11/2018
Levothyroxine Sodium	Draft	Oral	Tablet	021116 021210 021301 021342 021402	12/2014

RLD: Reference Listed Drug
RS: Reference Standard

How to Use RLD/RS on the PSG Webpage?

- RLD/RS information on the FDA PSG webpage helps to identify the product related to a specific PSG
  - Not a substitute for the Orange Book
  - Information is current when the PSG is posted but the RS may change over time
- Use the Orange Book for:
  - Correct basis of ANDA submission
  - Current RS

Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions (Oct. 2020)

Upcoming PSGs for Complex Generic Drug Product Development Webpage

- Describes the FDA's plans for issuing new and revised PSGs for complex generic drug products (as defined in the GDUFA II Commitment Letter) in the next 12 months
- Enhances transparency in PSG development or revision plan for complex products
- Assists applicants in planning their development of complex generic drug products, which are typically more difficult to develop
- Updated quarterly when a new PSG batch is posted

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development

Upcoming PSGs for Complex Generic Drug Product Development Webpage

New and Revised PSGs for Complex Generic Drug Products

Below is the list of PSGs for complex generic drug products that FDA plans to issue and the list of PSGs that FDA plans to revise in the coming year. While this list reflects FDA's effort to be transparent regarding current plans for developing PSGs for complex generic drug products, it should be noted that timing may be subject to change.

Planned New PSGs for Complex Generic Drug Products Updated Februrary 17th, 2022

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS A Number
ABAMETAPIR	TOPICAL	LOTION	206966
ACETAMINOPHEN	RECTAL	SUPPOSITORY	018337
ACYCLOVIR; HYDROCORTISONE	TOPICAL	CREAM	022436
AFAMELANOTIDE	SUBCUTANEOUS	IMPLANT	210797

Planned Revised PSGs for Complex Generic Drug Products Updated Februrary 17th, 2022

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Planned Revision Category (Brief Reason)
ACARBOSE	ORAL	TABLET	020482	Minor Revision: Change the study design for in vivo BE studies
ACYCLOVIR	BUCCAL	TABLET	203791	Editorial Revision: Correct typos
ACYCLOVIR	TOPICAL	CREAM	021478	Editorial Revision: Harmonize the language for BE recommendations across similar PSGs in alignment with the general guidances; Reorganize information on physicochemical and structural characterization studies Minor Revision: Add links or references to general guidance; Expand the eligibility for an in vitro-based BE option; Comply with Clinical Data Interchange Standards Consortium (CDISC)

Public Comments on PSGs

- FDA issues a Federal Register notice announcing the availability of new and revised PSGs (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 https://www.regulations.gov/support
- FDA will consider comments on draft PSGs while developing final BE recommendations

PSGs Withdrawn

- Recommendations in a PSG are withdrawn when they no longer reflect the FDA's current thinking
- List of withdrawn PSGs can be accessed via: https://www.fda.gov/media/90032/download
- Once a PSG has been re-posted, it will be removed from the withdrawn list

CDER Product-Specific Guidances Withdrawn Listing
Updated September 9, 2021

ACTIVE INGREDIENT	TYPE OF GUIDANCE	ROUTE AND DOSAGE FORM	RLD	DATE PSG POSTED OR REVISED	DATE WITHDRAWN
BUTENAFINE HYDROCHLORIDE	Draft	Topical Cream	21408	3/1/2012	2/1/2015
LEVONORGESTREL	Draft	IUD	203159	4/1/2014	10/1/2014
LORCASERIN HYDROCHLORIDE	Draft	Oral Tablet	022529	3/1/2015	3/19/2021
LORCASERIN HYDROCHLORIDE	Draft	Oral Tablet, ER	208524	5/1/2017	3/19/2021
LOVASTATIN; NIACIN	Draft	Oral Tablet, ER	021249	7/1/2009	5/10/2021
NIACIN; SIMVASTATIN	Draft	Oral Tablet, ER	022078	10/1/2011	5/10/2021
THEOPHYLLINE	Draft	Oral Tablet, ER	081236, 089763, 089807, 089808	2/1/2010	8/28/2020

Resources

- CDER Guidances Webpage: https://www.fda.gov/drugs/guidance-compliance-regulatory information/guidances-drugs
- Guidance for Industry on Bioequivalence Recommendations for Specific Products (June 2010)
- Guidance for Industry Referencing Approved Drug Products in ANDA Submissions (October 2020)
- PSGs for Generic Drug Development: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- Upcoming PSGs for Complex Generic Drug Product Development: https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development
- FDA Product-Specific Guidance Snapshot
- The ABCs of Product Specific Guidances
- SBIA webinar on PSGs (May 2021): FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs

Challenge Question #1

If a prospective ANDA applicant is developing a generic version of a ***complex*** drug product and there is ***no*** PSG available, they can request feedback from the FDA on their proposed bioequivalence approach by:

a) Submitting a controlled correspondence

b) Submitting a pre-ANDA product development meeting request

c) Either a or b

Challenge Question #2

What is **NOT** one of the factors FDA takes into consideration while prioritizing PSG development or revision?

a) ANDA assessment goal dates

b) Complexity of the product

c) External interests: Pre-ANDA meetings, Controlled Correspondences, ANDAs without PSGs, Public Requests

d) Drug availability and accessibility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