An Overview of the FDA Product-Specific Guidance (PSG) Program Under GDUFA III

Christine Le, PharmD, PMP
PSG Program Director
Office of Research and Standards
Office of Generic Drugs | CDER | U.S. FDA

Generic Drug Forum - April 12, 2023

Outline

- Provide an overview on general principles of FDA Product-Specific Guidances (PSGs)
- Discuss PSG process and communication
- Describe FDA's PSG database and other important information under GDUFA III
- Outline PSG teleconferences (T-cons) and PSG meetings; additional resources to fulfill GDUFA III commitments

GDUFA: Generic Drug User Fee Amendments

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

ANDA: Abbreviated New Drug Application

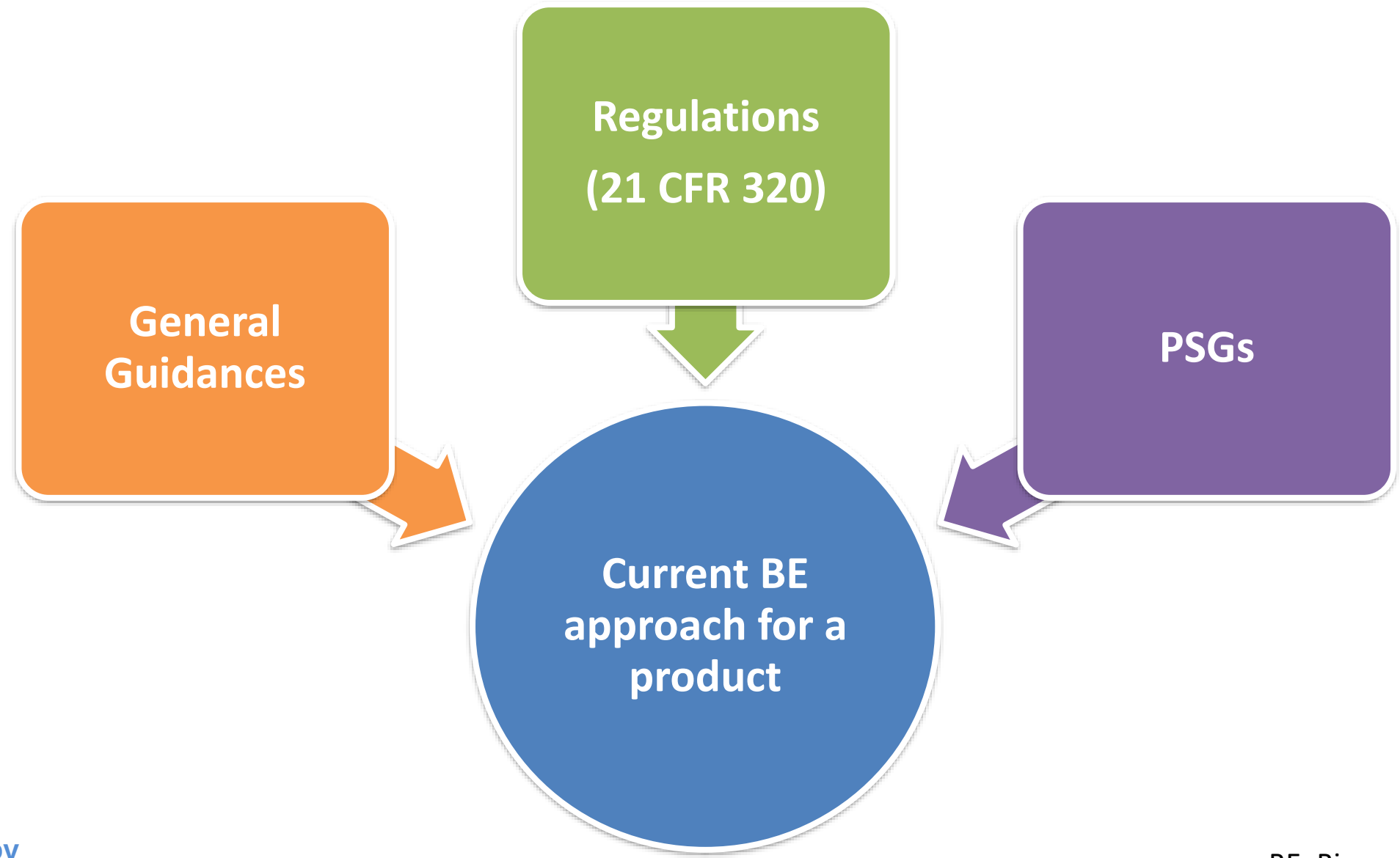
PSG is an Integral Part of the FDA's ANDA Program

Pre-ANDA Program

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

GDUFA: Generic Drug User Fee Amendments

Background on PSGs



BE: Bioequivalence

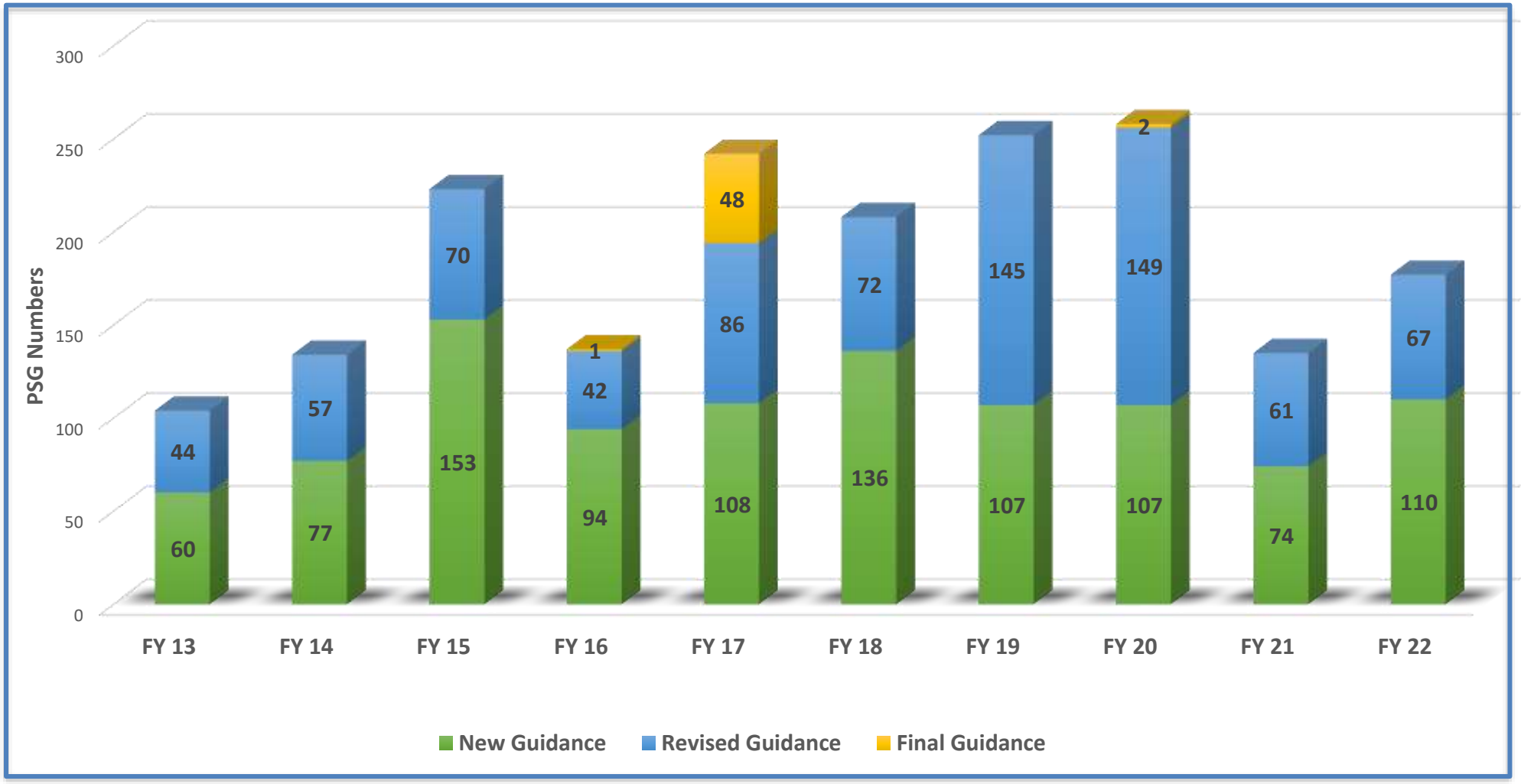
Background on PSGs (cont.)

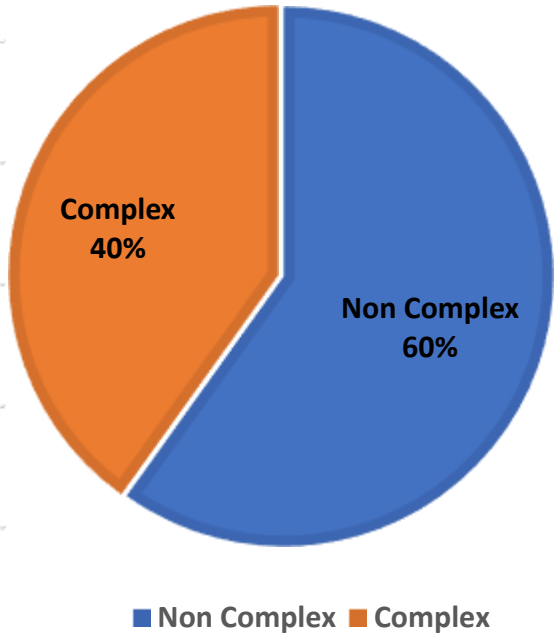
- Started in 2007, the FDA has published PSGs to provide clear and direct recommendations to ANDA applicants

- More than 2,000 PSGs on the public PSG webpage as of April 2023
  - Searchable and exportable

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

PSGs Published (FY 2013 - FY 2022)





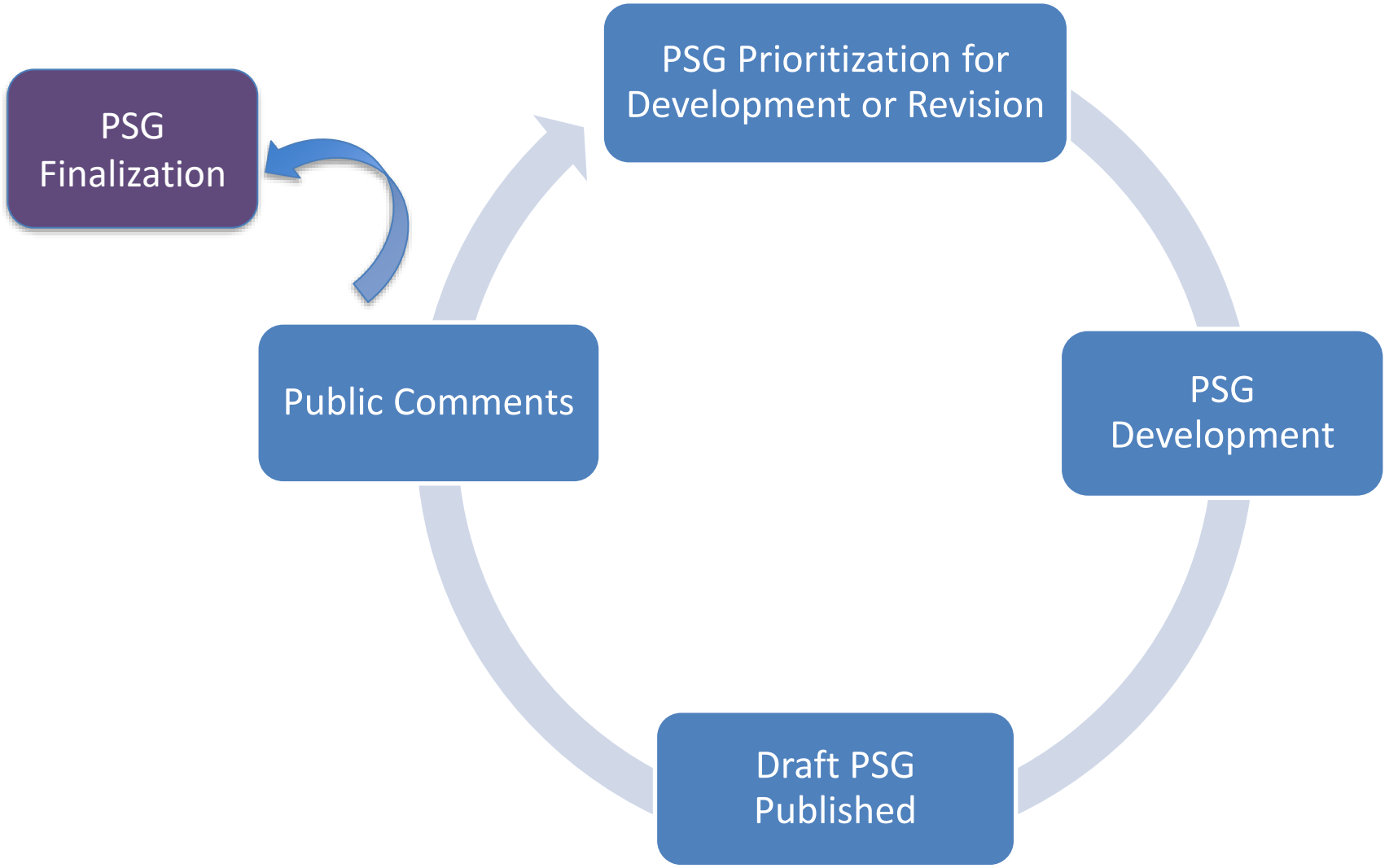
GDUFA III Commitment on PSG Development

- For **Non-Complex 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 compared to 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

GDUFA: Generic Drug User Fee Amendments; NCE: New Chemical Entity; NDA: New Drug Application; GDUFA III Commitment Letter

PSG Process



Quarterly Batch/
Standalone

Prioritization of PSG Development

- GDUFA commitments
- External interests: Pre-ANDA meetings, Controlled Correspondences, ANDA submissions, Public Requests
- Public health priorities
- 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 requests annually
  - FDA reviews these requests and takes appropriate action

How are Revised PSGs Planned?

Identification of Needs for PSG Revision

- Changes to the Reference Listed Drug (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

Notification of PSG Revision*

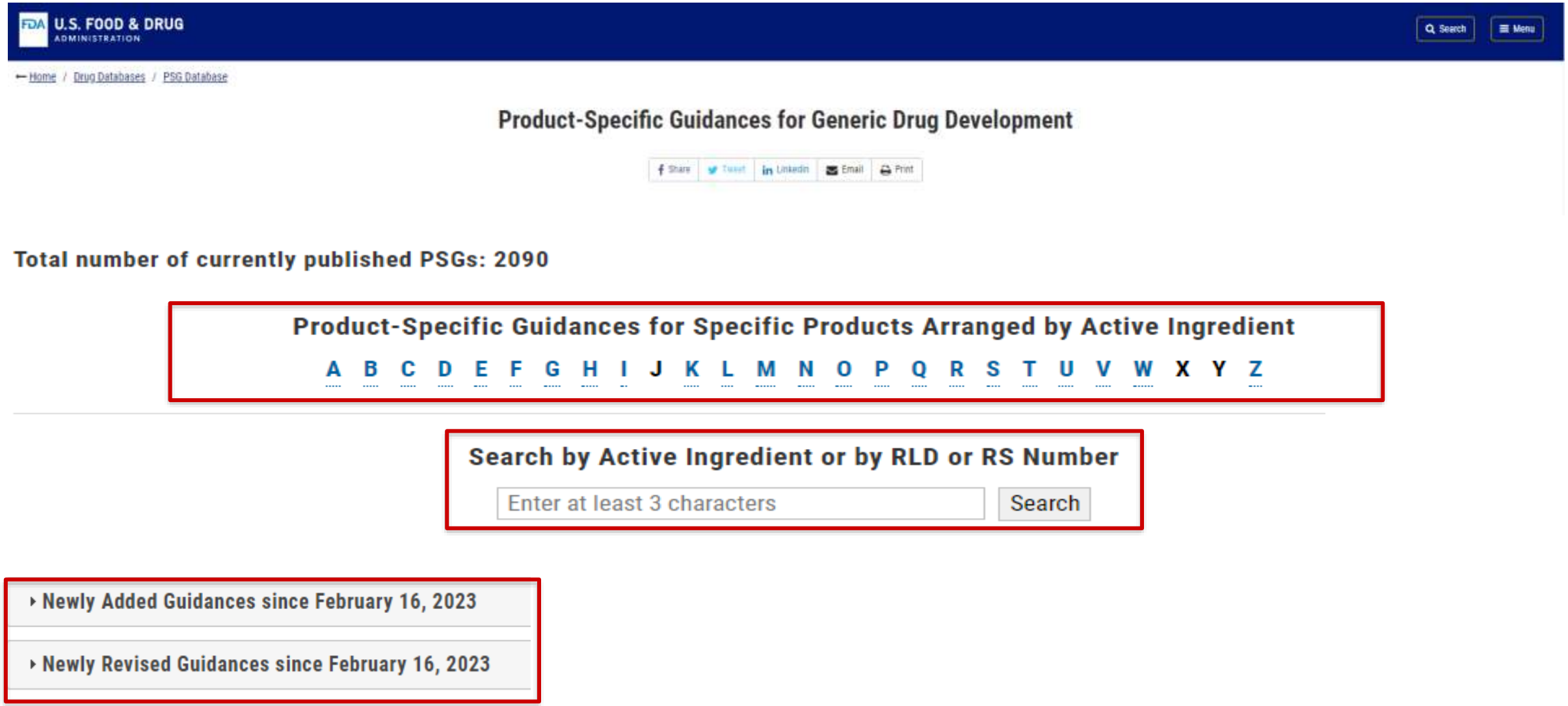
Category	Description
Critical	PSG revision includes additional bioequivalence studies or evidence recommended to support FDA approval that reflect a change in the safety or effectiveness of the drug product. The critical revision has a potential impact on all ANDAs including the approved applications.
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

*Upcoming PSGs for 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 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
- The FDA will issue a notice in the Federal Register for every batch and stand-alone posting

FDA PSG Database



www.fda.gov

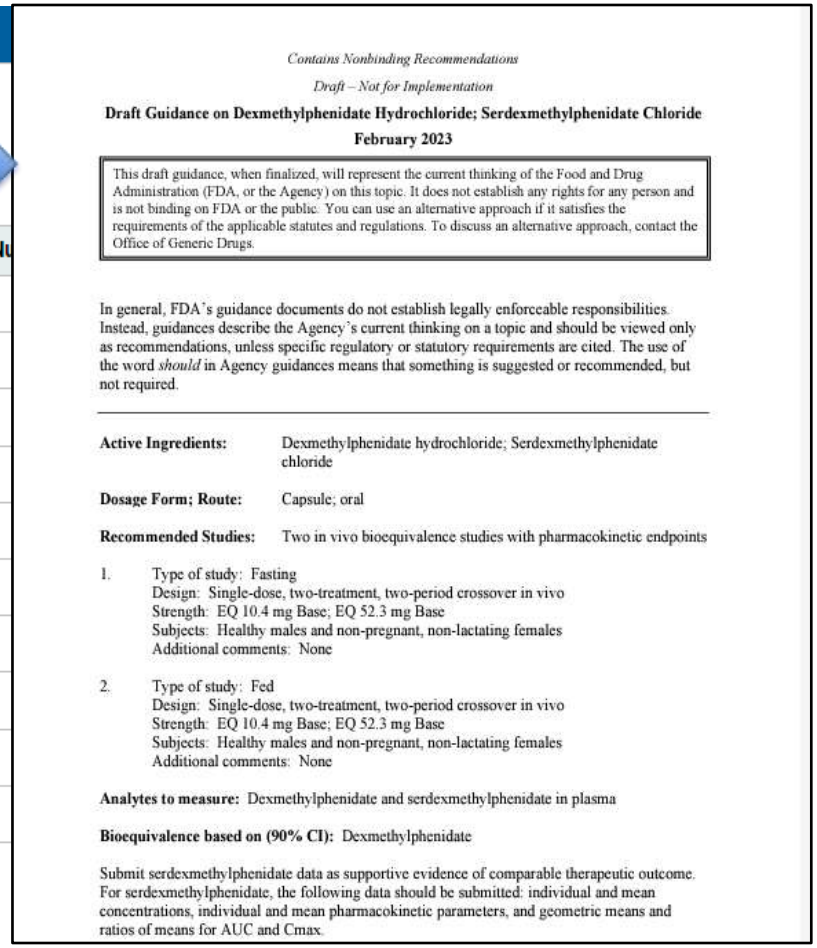
Locating PSGs

Newly Added Guidances since February 16, 2023

Excel | CSV | PDF

Show 10 entries

Active Ingredient (link to Specific Guidance)	Type	Route	Dosage Form	RLD or RS Nu
Afamelanotide	Draft	Subcutaneous	Implant	210797
Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride	Draft	Oral	Tablet, Chewable, Tablet, Capsule	050719
Cabotegravir; Rilpivirine	Draft	Intramuscular	Suspension, Extended Release	212888
Dexmethylphenidate Hydrochloride; Serdexmethylphenidate Chloride	Draft	Oral	Capsule	212994
Dihydroergotamine Mesylate	Draft	Nasal	Spray, Metered	213436
Donepezil Hydrochloride	Draft	Transdermal	System	212304
Fexinidazole	Draft	Oral	Tablet	214429
Glucagon	Draft	Nasal	Powder	210134
Golodirsen	Draft	Intravenous	Solution	211970
Ibrexafungerp Citrate	Draft	Oral	Tablet	214900



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Dexmethylphenidate Hydrochloride; Serdexmethylphenidate Chloride

February 2023

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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients: Dexmethylphenidate hydrochloride; Serdexmethylphenidate chloride

Dosage Form; Route: Capsule; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 10.4 mg Base; EQ 52.3 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

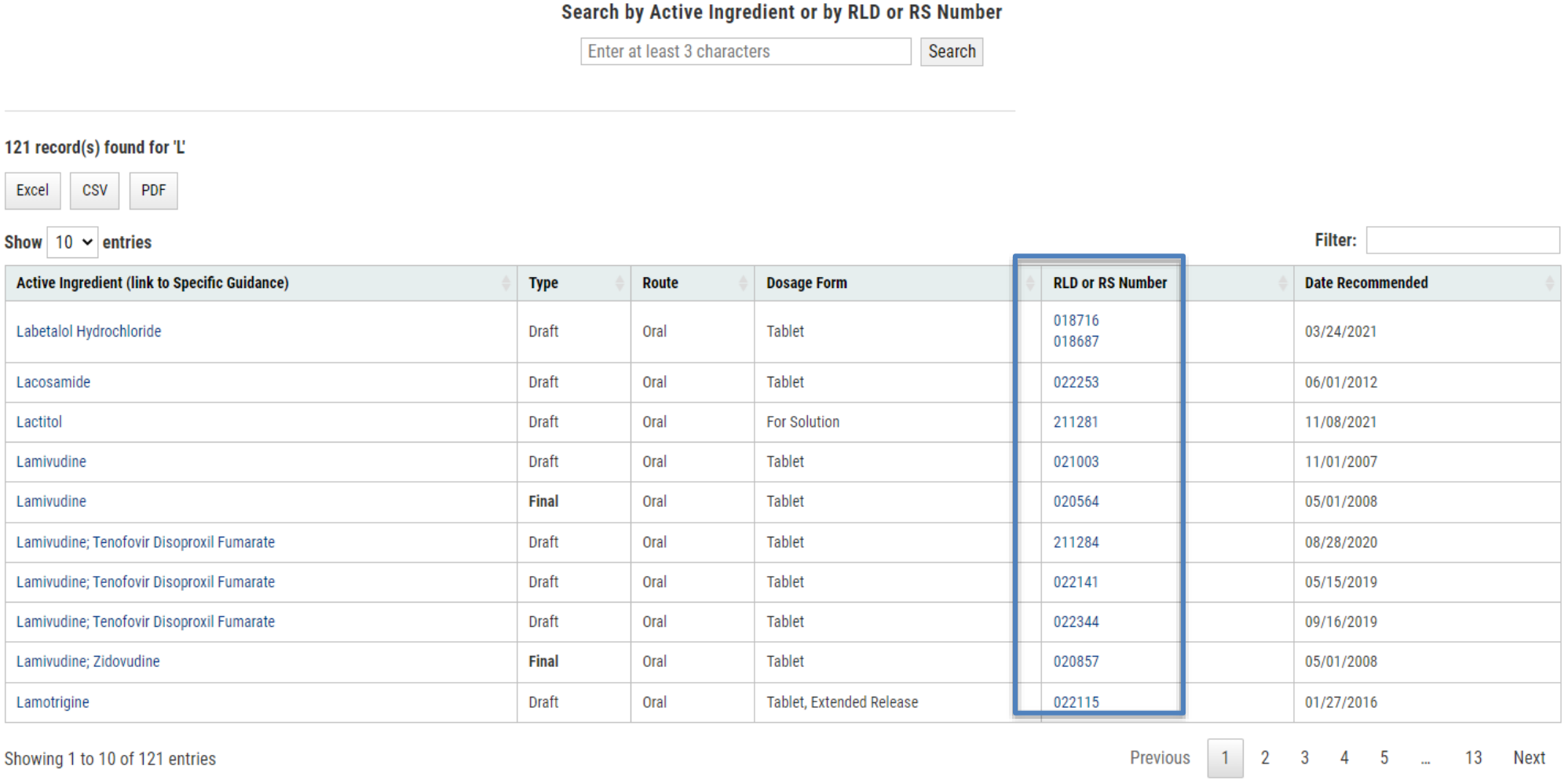
2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 10.4 mg Base; EQ 52.3 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

Analytes to measure: Dexmethylphenidate and serdexmethylphenidate in plasma

Bioequivalence based on (90% CI): Dexmethylphenidate

Submit serdexmethylphenidate data as supportive evidence of comparable therapeutic outcome. For serdexmethylphenidate, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

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

121 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
Labetalol Hydrochloride	Draft	Oral	Tablet	018716 018687	03/24/2021
Lacosamide	Draft	Oral	Tablet	022253	06/01/2012
Lactitol	Draft	Oral	For Solution	211281	11/08/2021
Lamivudine	Draft	Oral	Tablet	021003	11/01/2007
Lamivudine	**Final**	Oral	Tablet	020564	05/01/2008
Lamivudine; Tenofovir Disoproxil Fumarate	Draft	Oral	Tablet	211284	08/28/2020
Lamivudine; Tenofovir Disoproxil Fumarate	Draft	Oral	Tablet	022141	05/15/2019
Lamivudine; Tenofovir Disoproxil Fumarate	Draft	Oral	Tablet	022344	09/16/2019
Lamivudine; Zidovudine	**Final**	Oral	Tablet	020857	05/01/2008
Lamotrigine	Draft	Oral	Tablet, Extended Release	022115	01/27/2016

Showing 1 to 10 of 121 entries

Previous 1 2 3 4 5 … 13 Next

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

RLD= Reference Listed Drug; RS= Reference Standard

Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions (October 2020)

Upcoming PSGs for Generic Drug Product Development (Forecast List)

- Describes the FDA's plans for all upcoming new and revised PSGs of generic drug products in the next 12 months
  - New in GDUFA III: The forecast list includes both complex and non-complex products
- Enhances transparency in PSG development or revision plan for generic drug products
  - New in GDUFA III: Updates include projected PSG publication dates in MM/YYYY or descriptive timeline
- Ensure consistency in FDA recommendations/decisions following previous iterations of the PSG and establish principles for PSG revisions to reflect "most accurate, sensitive, and reproducible" approaches
  - New in GDUFA III: Redefine revision classification (category with description)
- Updated quarterly with each PSG batch posting

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

Upcoming PSGs for Generic Drug Product Development Webpage

New and Revised PSGs for Generic Drug Products

Below is the list of PSGs for both complex and non-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 generic drug products, it should be noted that timing may be subject to change.

Planned New PSGs for Complex and Non-Complex Generic Drug Products Updated February 16, 2023

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Product Complexity	Planned Publication
ABROCITINIB	ORAL	TABLET	213871	NON-COMPLEX	08/2023
AMOXICILLIN; CLARITHROMYCIN; VONPRAZAN FUMARATE	ORAL	CAPSULE, TABLET, TABLET	215152	NON-COMPLEX	11/2023
AMOXICILLIN; VONOPRAZAN FUMARATE	ORAL	CAPSULE, TABLET	215153	NON-COMPLEX	11/2023
APREPITANT	INTRAVENOUS	EMULSION	216457	COMPLEX	08/2023
ARIPIPRAZOLE	ORAL	TABLET	207202	COMPLEX	Within the next 12 months

Planned Revised PSGs for Complex and Non-Complex Generic Drug Products Updated February 16, 2023

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application	Planned Revision Category with Description	Product Complexity	Planned Publication
ALBUTEROL SULFATE	INHALATION	AEROSOL, METERED	020503, 021457, 020983	Editorial Revision: Update the language	COMPLEX	08/2023
AZELAIC ACID	TOPICAL	GEL	021470	Minor Revision: Add an in vitro BE option	COMPLEX	Beyond 12 months
AZELASTINE HYDROCHLORIDE; FLUTICASONE PROPIONATE	NASAL	SPRAY, METERED	202236	Minor Revision: Add in vivo and in vitro BE options	COMPLEX	05/2023
BALOXAVIR MARBOXIL	ORAL	TABLET	210854	Minor Revision: Add information on newly approved strengths of the RLD	NON-COMPLEX	05/2023
BECLOMETHASONE DIPROPIONATE	INHALATION	AEROSOL, METERED	207921	Editorial Revision: Update the language	COMPLEX	08/2023
BECLOMETHASONE DIPROPIONATE	INHALATION	AEROSOL, METERED	020911	Editorial Revision: Update the language	COMPLEX	08/2023
BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE	INHALATION	AEROSOL, METERED	021929	Editorial Revision: Update the language	COMPLEX	08/2023

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 https://www.regulations.gov/support
- FDA will consider comments on draft PSGs while developing final BE recommendations

PSGs Withdrawn

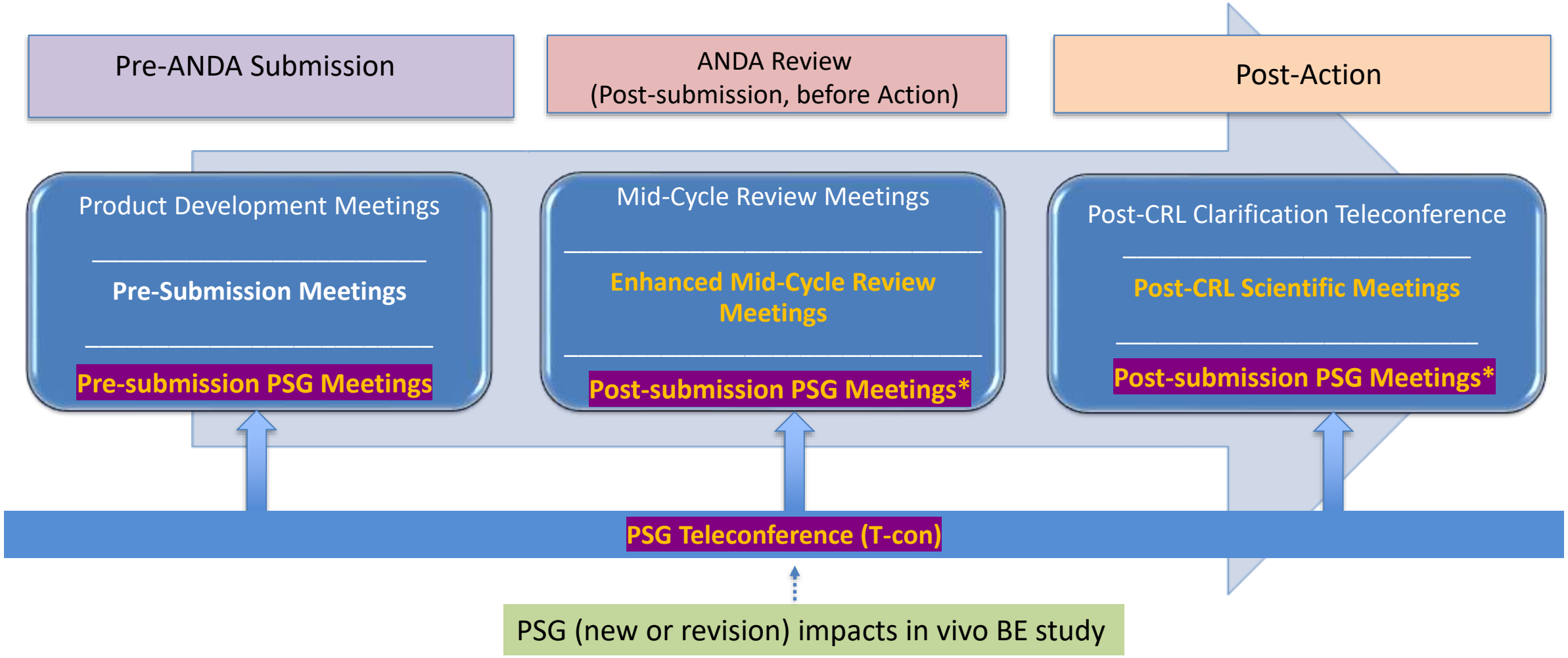
- Recommendations in a PSG are withdrawn when they no longer reflect the FDA's current thinking
- List of withdrawn PSGs can be accessed via: https://www.fda.gov/media/90032/download
- Once a PSG has been re-posted, it will be removed from the withdrawn list

CDER Product-Specific Guidances Withdrawn Listing

Updated May 20, 2022

ACTIVE INGREDIENT	TYPE OF GUIDANCE	ROUTE AND DOSAGE FORM	RLD	DATE PSG POSTED OR REVISED	FEDERAL REGISTER NOTICE DATE
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	3/4/2021
LORCASERIN HYDROCHLORIDE	Draft	Oral Tablet, ER	208524	5/1/2017	3/4/2021
LOVASTATIN; NIACIN	Draft	Oral Tablet, ER	021249	7/1/2009	4/18/2016
NIACIN; SIMVASTATIN	Draft	Oral Tablet, ER	022078	10/1/2011	4/18/2016

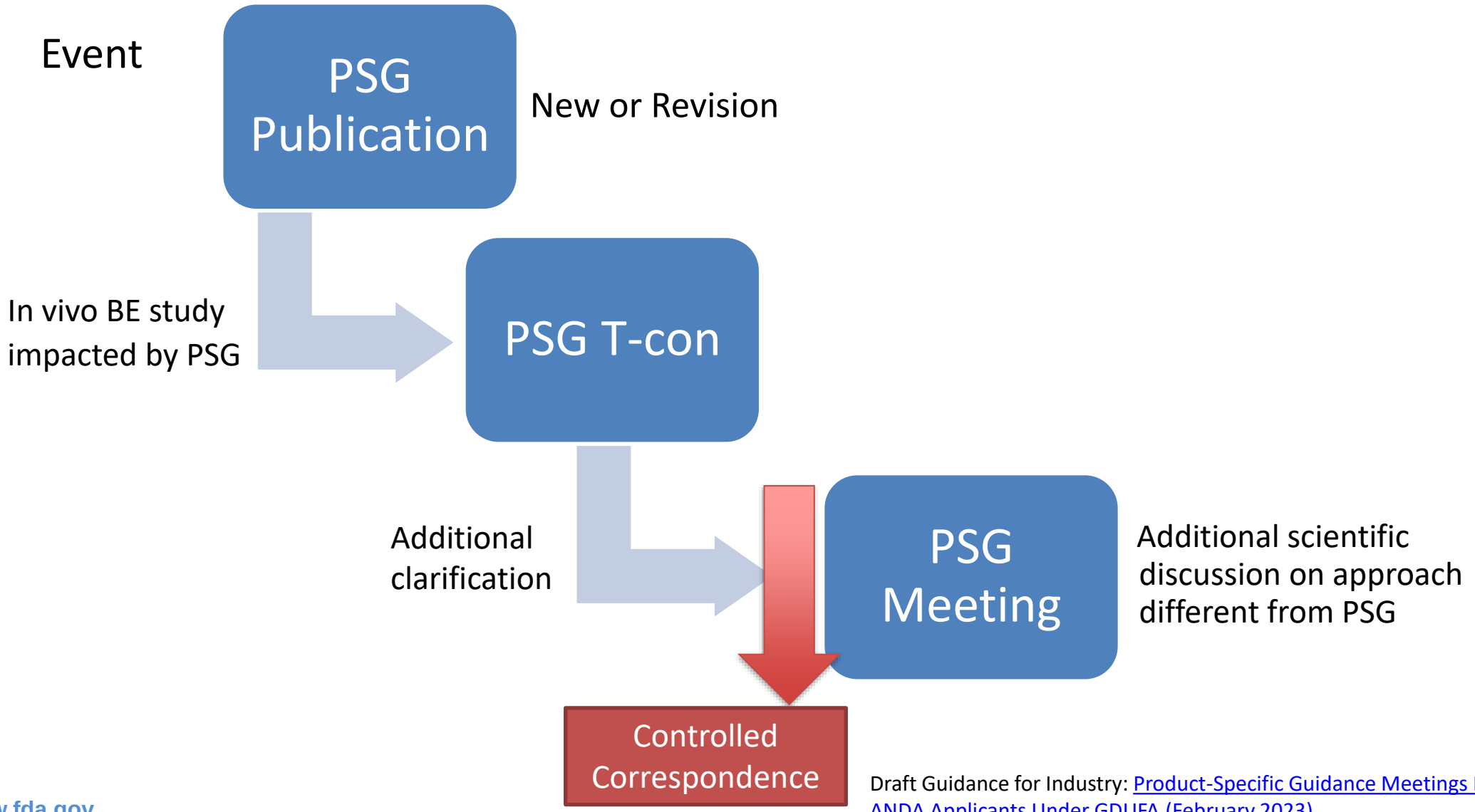
New in GDFUA III: PSG Teleconferences and Meetings



CR: Complete Response; TA: Tentative Approval; AP: Approval; RTR: Refuse to Receive

*Depend on the ANDA status, i.e., whether ANDA is under review, post-CRL or TA Action: CR, TA or AP, (during filing, RTR)

PSG T-cons and Meetings



Draft Guidance for Industry: Product-Specific Guidance Meetings Between FDA and ANDA Applicants Under GDUFA (February 2023)

PSG T-cons and Meetings

	PSG T-con (Pre- or Post-Submission)	Pre-submission PSG Meeting	Post-submission PSG Meeting
New in GDUFA III?	Yes	Yes	Yes
Eligible Products	Both complex and non-complex if PSG (new or revision) impacts in vivo BE study	Both complex and non-complex if PSG (new or revision) impacts in vivo BE study; **follow up from prior PSG T-con**	
When to Request a Meeting	When applicants has already commenced an in vivo BE study that is different from FDA newly published PSGs (new or revision)	Following PSG T-con, this meeting can be requested for further scientific discussion	
Format of the Meeting	T-con or WR[1]	In person face-to-face, Videoconference, T-con[2] or WR[2]	
Grant/Deny Decision Timeline	14 days	14 days*	
Days to Conduct the Meeting	30 days from meeting request receipt	120 days from meeting request receipt	90 days from meeting request receipt
When to Send a Controlled Correspondence (CC) in Lieu of a Meeting Request	Seek further feedback from the FDA after a PSG T-con; Clarification questions or questions outside of the scope of the meeting	Clarification questions or questions outside of the scope of the meeting. Applicants can send CC after meetings if they are seeking further clarification or have new questions	

* In the Commitment Letter

[1] If applicant requests a Written Response (WR) instead of T-con, it may be granted as WR

[2] FDA can provide a T-con or WR, if requested by the applicant or if FDA grants the meeting above and beyond the Commitment Letter

Upcoming SBIA Webinar on PSG T-Cons and Meetings

- **Title:** "A Deep Dive: GDUFA III Scientific Meetings"
- **Date:** May 15, 2022, 1-4:30 PM EDT
- **Objectives:**
  - Provide an in-depth look into the enhancements and new features of GDUFA III scientific meetings
  - Describe how and when to utilize these meetings to support generic drug development
  - Provide clarification and best practices in meeting request and conduct
- **Topics covered:**
  - Pre-Submission Meetings
  - Post-Complete Response Letter Scientific Meetings
  - Product-Specific Guidance (PSG) Teleconferences, and Pre- and Post-submission PSG Meetings

CDER Small Business & Industry Assistance (SBIA) Webinar Page

Challenge Question #1

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

a) ANDA assessment goal dates

b) Public health priorities

c) Public requests

d) Drug availability and accessibility

Challenge Question #2

The generic applicant or prospective applicant may request a PSG Teleconference to obtain FDA feedback on the potential impact of the new or revised PSG on its development program:

a) If has already commenced in vivo bioequivalence study

b) If has already commenced in vitro bioequivalence studies

c) Both a and b

Resources (1)

- GDUFA III Commitment Letter
- MAPP 5240.10: Classifying Approved New Drug Products as Complex Products for Generic Drug Development Purposes (April 2022)
- GDUFA III Enhancements to the Pre-ANDA Program: https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii-enhancements-pre-anda-program
- ANDA Assessment Program – GDUFA III Performance Goals and Program Enhancements: https://www.fda.gov/industry/generic-drug-user-fee-amendments/anda-assessment-program-gdufa-iii-performance-goals-and-program-enhancements
- Draft Guidance for Industry: Product-Specific Guidance Meetings Between FDA and ANDA Applicants Under GDUFA (February 2023)
- GDUFA III T-Cons and Meetings Infographic

Resources (2)

- 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 on Referencing Approved Drug Products in ANDA Submissions (October 2020)
- PSGs for Generic Drug Development Upcoming PSGs for 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