Product-Specific Guidance (PSG) Program: Updates and Overview of Available Resources

Joseph Kotsybar, Pharm.D.

Regulatory Health Project Manager
Office of Research and Standards (ORS) | Office of Generic Drugs (OGD) | Center for Drug Evaluation & Research (CDER)

SBIA Webinar: Facilitating Generic Drug Product Development through Product-Specific Guidances

April 25, 2024

Overview

- Product-Specific Guidance (PSG) background
- Overview of the FDA PSG program, GDUFA III commitments, PSG prioritization and Revisions
- Public Requests and Public Comments on PSGs
- PSG Online Resources

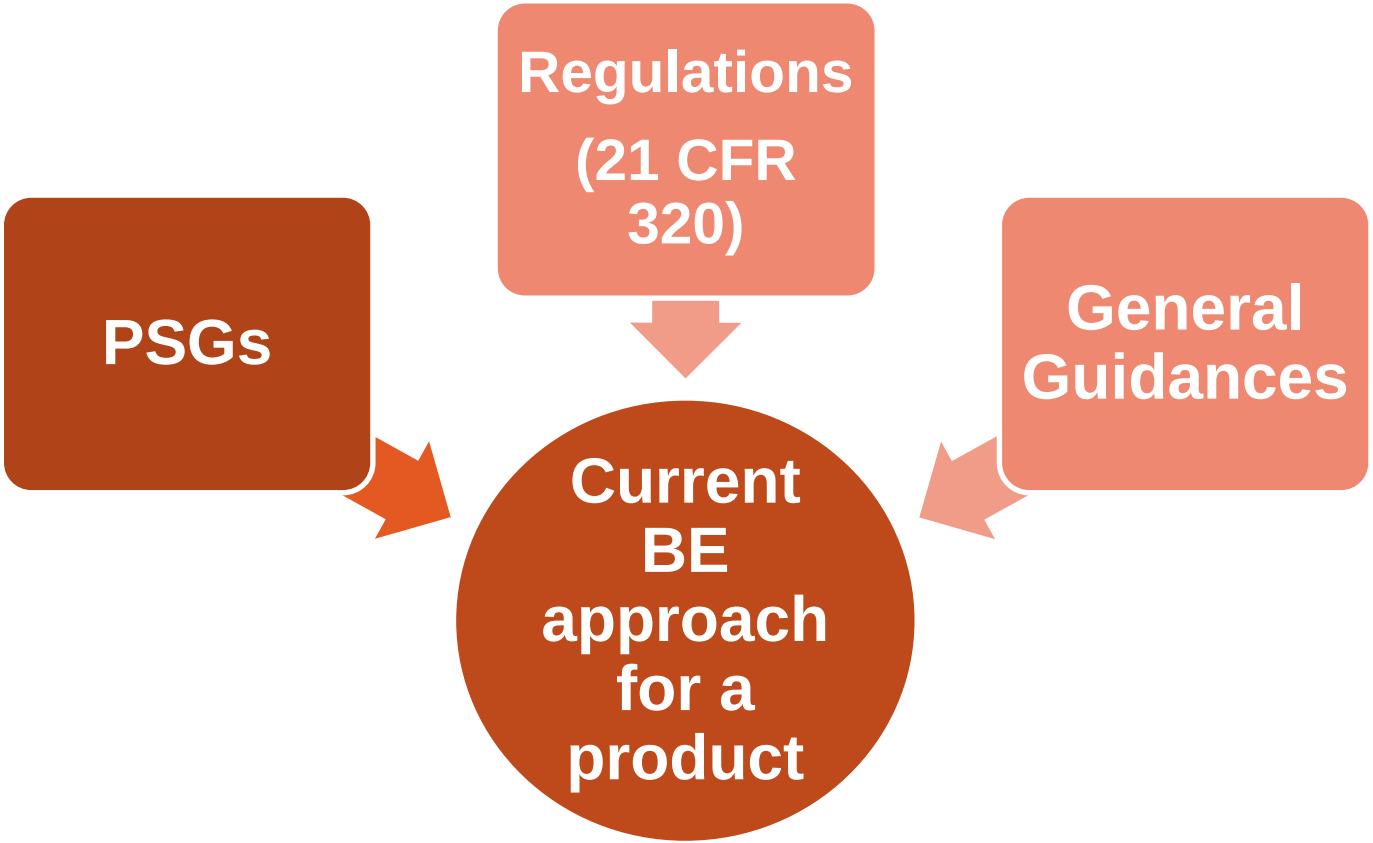
What is a PSG?

- 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



BE: Bioequivalence

Background on PSGs

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

- 2,187 PSGs on the FDA PSG webpage as of April 2024
  - ~40% for complex products

MAPP 5240.10 Classifying Approved New Drug Products as Complex Products for Generic Drug Development Purposes

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 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.

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

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

Prioritization

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

Data to Support PSG Development

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

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

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

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 PSGs are published quarterly
  - February, May, August, and November
- 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
  - For example, three Level 2 PSG Revisions published in Nov 2023

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

Level 2 PSG Revision Example

Ruxolitinib Phosphate Topical Cream NDA 215309

h. Use within 7 days prior to baseline of 1) antihistamines, 2) topical antibiotics, 3) topical corticosteroids or 4) other topical drug products
i. Use within 24 hours prior to baseline of any topical product (e.g., sunscreens, lotions, creams bland emollient/moisturizer) in the areas to be treated
j. Known allergy or hypersensitivity to ruxolitinib ~~pimecrolimus~~ or any other component of the test product or reference standard
k. Not willing to minimize or avoid natural and artificial sunlight exposure during treatment

Recommended: 08/2023: Revised 11/2023

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
  - 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

Controlled Correspondence vs. Public Request

- Controlled Correspondences received are triaged as Public Requests for RLDs that:
  - Submitter is requesting or proposing general BE recommendation
  - Have no published PSG
- If a complex products, submitter may send pre-ANDA meeting request
- Public Request response:
  - The request for information related to product-specific recommendation for generic drug development was sent to ORS for further processing
  - ORS will take your request into consideration when publishing the PSG
  - You will not receive additional direction notification of guidance development from the Agency

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 (within or beyond 12 months)
- 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

fda.gov/cdersbia

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

Upcoming PSGs for Generic Drug Product Development (Forecast List)

Planned New PSGs for Complex and Non-Complex Generic Drug Products
Updated February 15, 2024

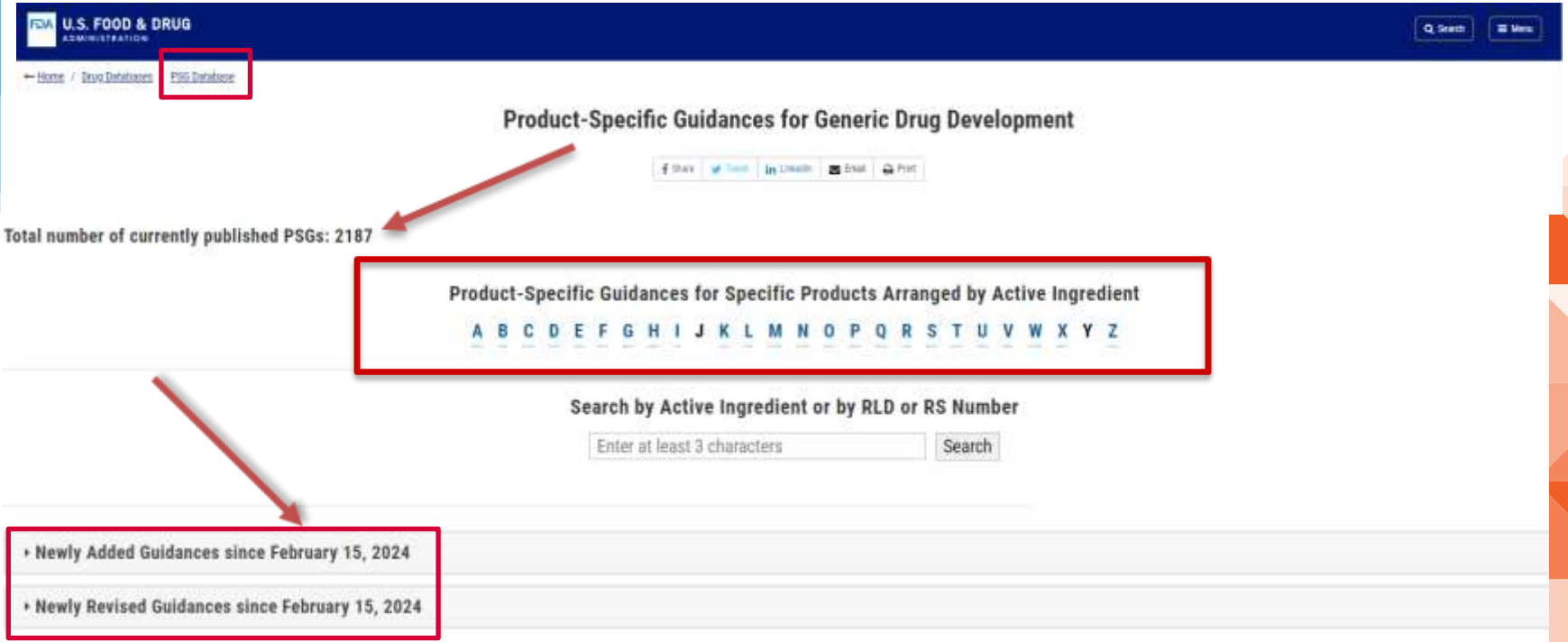
Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Product Complexity	Planned Publication
Air Polymer-Type A	Intrauterine	Foam	212279	Complex	08/2024
Amikacin Sulfate	Inhalation	Suspension, Liposomal	207356	Complex	05/2024
Aripiprazole	Oral	Tablet	207202	Complex	Within the next 12 months
Atorvastatin Calcium	Oral	Suspension	213260	Non-Complex	05/2024
Baclofen	Oral	Suspension	215662	Non-Complex	05/2024
Bexagliflozin	Oral	Tablet	214373	Non-Complex	05/2024
Clobetasol Propionate	Topical	Cream	209483	Complex	Beyond 12 months
Dapropdustat	Oral	Tablet	216951	Non-Complex	05/2024
Desmopressin Acetate	Nasal	Spray, Metered	201656	Complex	11/2024
Elacestrant Dihydrochloride	Oral	Tablet	217639	Non-Complex	05/2024

Planned Revised PSGs for Complex and Non-Complex Generic Drug Products
Updated February 15, 2024

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Planned Revision Category with Description	Product Complexity	Planned Publication
Acetaminophen; Butalbital	Oral	Capsule	088831	Minor Revision: Remove recommendation on a strength due to safety concerns	Non-Complex	Within the next 12 months
Albuterol Sulfate	Inhalation	Aerosol, Metered	020503; 020983; 021457	Editorial Revision: Update the language Minor Revision: Clarify in vitro study design; Revise recommendations for device comparisons	Complex	08/2024
Albuterol Sulfate; Ipratropium Bromide	Inhalation	Spray, Metered	021747	Editorial Revision: Update the language Minor Revision: Clarify in vitro study design; Revise recommendations for device comparisons	Complex	08/2024
Allopurinol	Oral	Tablet	016084	Minor Revision: Add information on newly approved (lower or middle) strengths of the RLD/RS	Non-Complex	08/2024

PSG Online Resources

PSG Website


U.S. FOOD & DRUG
Home / Drug Databases / PSG Database
Product-Specific Guidances for Generic Drug Development
Total number of currently published PSGs: 2187
Product-Specific Guidances for Specific Products Arranged by Active Ingredient
A B C D E F G H I J K L M N O P Q R S T U V W X Y Z
Search by Active Ingredient or by RLD or RS Number
Enter at least 3 characters
Search
Newly Added Guidances since February 15, 2024
Newly Revised Guidances since February 15, 2024

Locating PSGs

Newly Added Guidances since February 15, 2024

Excel | CSV | PDF

Show 10 entries

Active Ingredient (link to Specific Guidance)	Type
Abacavir Sulfate; Dolutegravir Sodium; Lamivudine	
Adagrasib	Draft
Amoxicillin; Clarithromycin; Vonoprazan Fumarate	Draft
Amoxicillin; Vonoprazan Fumarate	Draft
Baclofen	Draft
Budesonide; Formoterol Fumarate; Glycopyrrolate	Draft
Caffeine; Ergotamine Tartrate	Draft
Durlobactam Sodium; Durlobactam Sodium; Sulbactam Sodium	Draft
Elagolix Sodium, Estradiol, Norethindrone Acetate; Elagolix Sodium	Draft
Ferric Derisomaltose	Draft

Showing 1 to 10 of 29 entries

Next

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Abacavir Sulfate; Dolutegravir Sodium; Lamivudine

February 2024

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: Abacavir sulfate; Dolutegravir sodium; Lamivudine

Dosage Form: Tablet, for suspension

Route: Oral

Strength: EQ 60 mg Base; EQ 5 mg Base; 30 mg

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 60 mg Base; EQ 5 mg Base; 30 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments: None

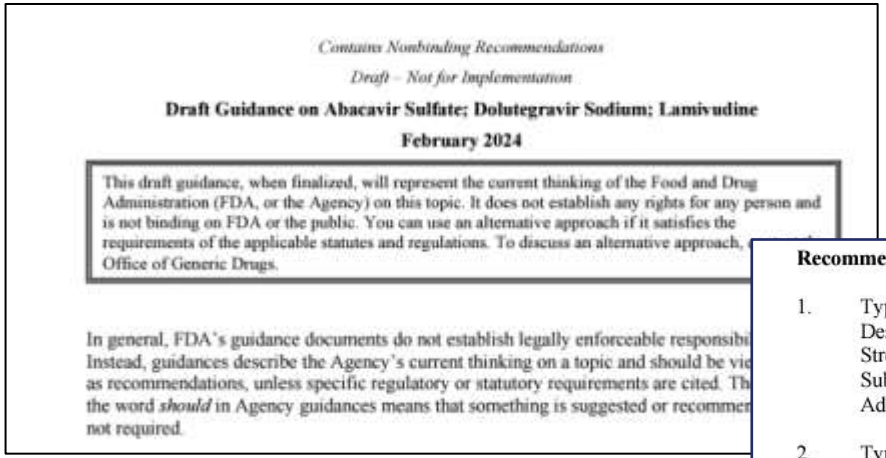
2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg Base; EQ 5 mg Base; 30 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments: None

Analytes to measure: Abacavir, dolutegravir, and lamivudine in plasma

Bioequivalence based on (90% CI): Abacavir, dolutegravir, and lamivudine

Waiver request of in vivo testing: Not applicable

Navigating a PSG



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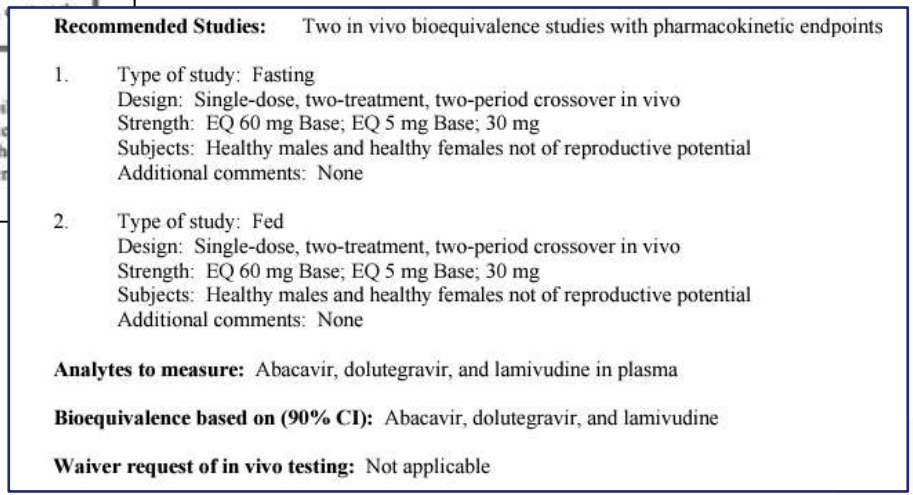
Regulatory Preface



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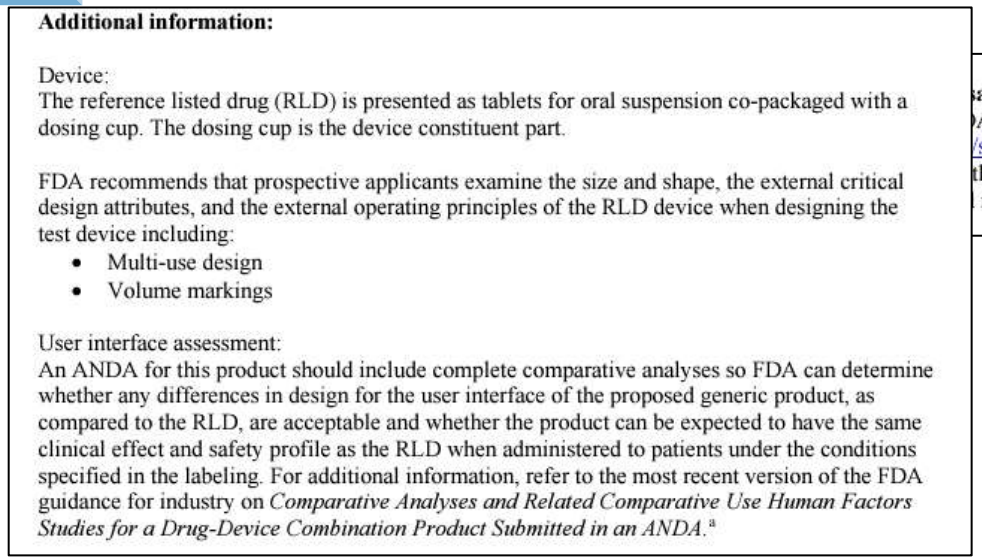
Bioequivalence Recommendation(s)

Navigating a PSG



Additional information:

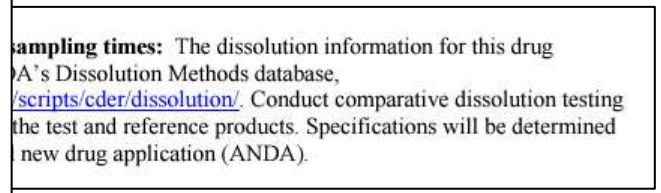
Device:
The reference listed drug (RLD) is presented as tablets for oral suspension co-packaged with a dosing cup. The dosing cup is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Multi-use design
- Volume markings

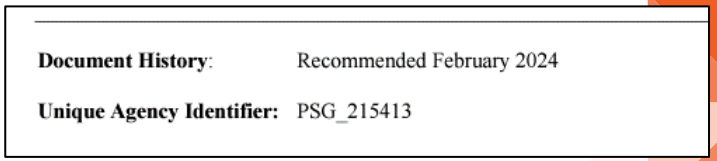
User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Drug-Device Recommendation and/or Additional Product Development Recommendations



ampling times: The dissolution information for this drug
A's Dissolution Methods database,
/scripts/cder/dissolution/. Conduct comparative dissolution testing
the test and reference products. Specifications will be determined
new drug application (ANDA).

Dissolution Recommendation



Document History: Recommended February 2024

Unique Agency Identifier: PSG_215413

Administrative Tracking

How to Use RLD/RS on the PSG Webpage?

TRIUMEQ PD (ABACAVIR SULFATE; DOLUTEGRAVIR SODIUM; LAMIVUDINE)
EQ 60MG BASE;EQ 5MG BASE;30MG
Marketing Status: Prescription

Active Ingredient: ABACAVIR SULFATE; DOLUTEGRAVIR SODIUM; LAMIVUDINE
Proprietary Name: TRIUMEQ PD
Dosage Form; Route of Administration: TABLET, FOR SUSPENSION; ORAL
Strength: EQ 60MG BASE;EQ 5MG BASE;30MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N215413
Product Number: 001
Approval Date: Mar 30, 2022
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription
Patent and Exclusivity Information

Filter:

RLD or RS Number	Date Recommended
020977	05/01/2008
215413	02/15/2024
205551	08/28/2020
021652	11/01/2007
021205	05/01/2008
206966	10/21/2022
208716	09/13/2018
202379	07/20/2018
210308	06/03/2020
213871	08/21/2023

Showing 1 to 10 of 205 entries

Previous 1 2 3 4 5 … 21 Next

How to Use RLD/RS on the PSG Webpage

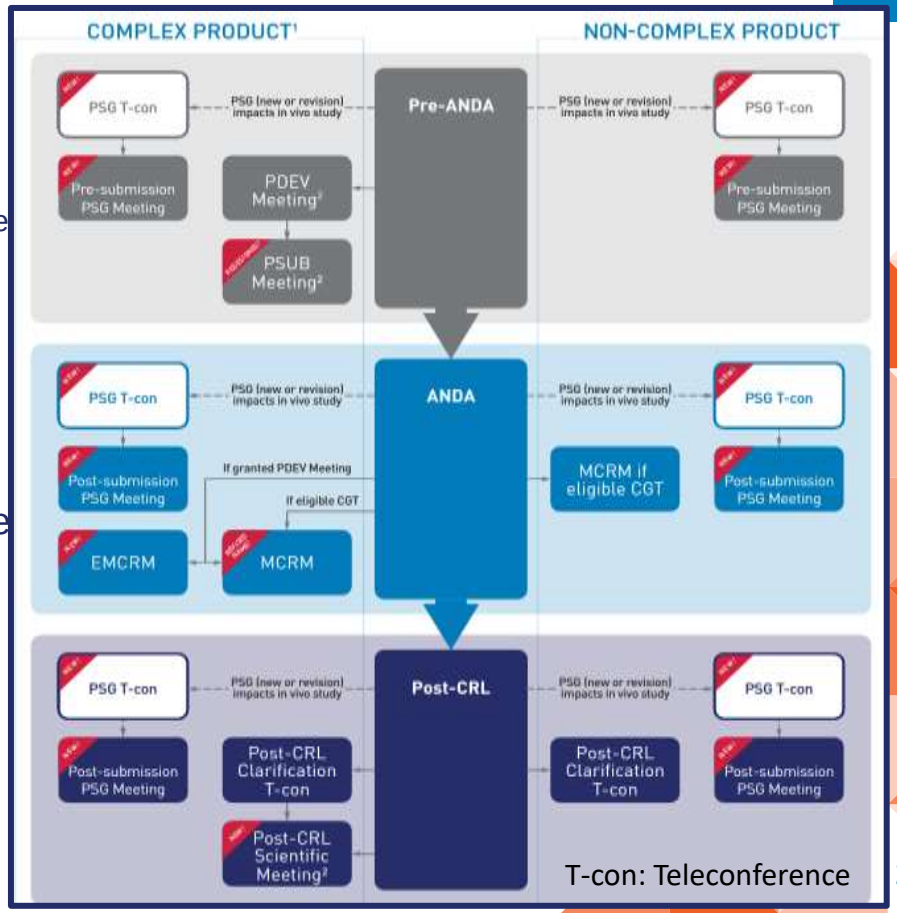
- RLD/RS information on the FDA PSG webpage helps identify the product related to a specific PSG
  - Not a substitute for the Orange Book
  - Information is current when the PSG is posted but the RS may change over time

- Applicant(s) should use the Orange Book for:
  - Correct basis of ANDA submission
  - Current RS

Referencing Approved Drug Products in ANDA Submissions Guidance for Industry (October 2022)

GDUFA III Meetings

- PSG meetings (pre-submission or post-submission) can be requested following the 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
  - Pre-submission PSG meetings can be requested if the ANDA has not been submitted
  - Post-submission PSG meetings can be requested if the ANDA has been submitted
- Controlled correspondence is an alternative way for applicants to follow up with FDA on the remaining issues following the PSG T-con
- Other pre-ANDA and ANDA scientific meetings are available as alternative to PSG meetings



T-con: Teleconference

fda.gov/cdersbia Summary of T-cons & Meetings

Resources

- CDER Guidances Webpage
- MAPP 5240.10: Classifying Approved New Drug Products as Complex Products for Generic Drug Development Purposes (April 2022)
- Guidance for Industry on Bioequivalence Recommendations for Specific Products (June 2010)
- Guidance for Industry Referencing Approved Drug Products in ANDA Submissions (October 2020)
- Product-Specific Guidances for Generic Drug Development
- Upcoming Product-Specific Guidances for Generic Drug Product Development
- PSG Snapshot
- The ABCs of Product Specific Guidances
- SBIA webinar on PSGs (May 2021): FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs
- Guidance for Industry Product-Specific Guidance Meetings Between FDA and ANDA Applicants Under GDUFA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