U.S. FOOD & DRUG ADMINISTRATION

Product-Specific Guidances

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Learning Objectives

- Describe general principles of product-specific guidances (PSGs)
- Discuss the process of how PSGs are developed and revised
- Describe how PSG revision efforts are prioritized and share a recent example of significant PSG revisions
- Describe the upcoming PSGs for complex generic drug product development webpage

Background on PSGs

- How do you know the best current bioequivalence (BE) approach?
  - Regulations (21 CFR 320)
  - General Guidances
  - PSGs

Background on PSGs (cont.)

- Since 2007, FDA has published PSGs to provide clear and direct recommendations to abbreviated new drug application (ANDA) applicants

- PSGs identify the methodology for developing generic drugs and generating evidence recommended to support ANDA approval and are a key science and research output

- As of March 2020, more than 1,800 PSGs have been published

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

Background on PSGs (cont.)

- PSGs and general BE guidance provide FDA's current thinking and expectations for generic drug development

- GDUFA II commitment on PSG development
  - Issue PSGs for 90% of 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

PSG Recommendations

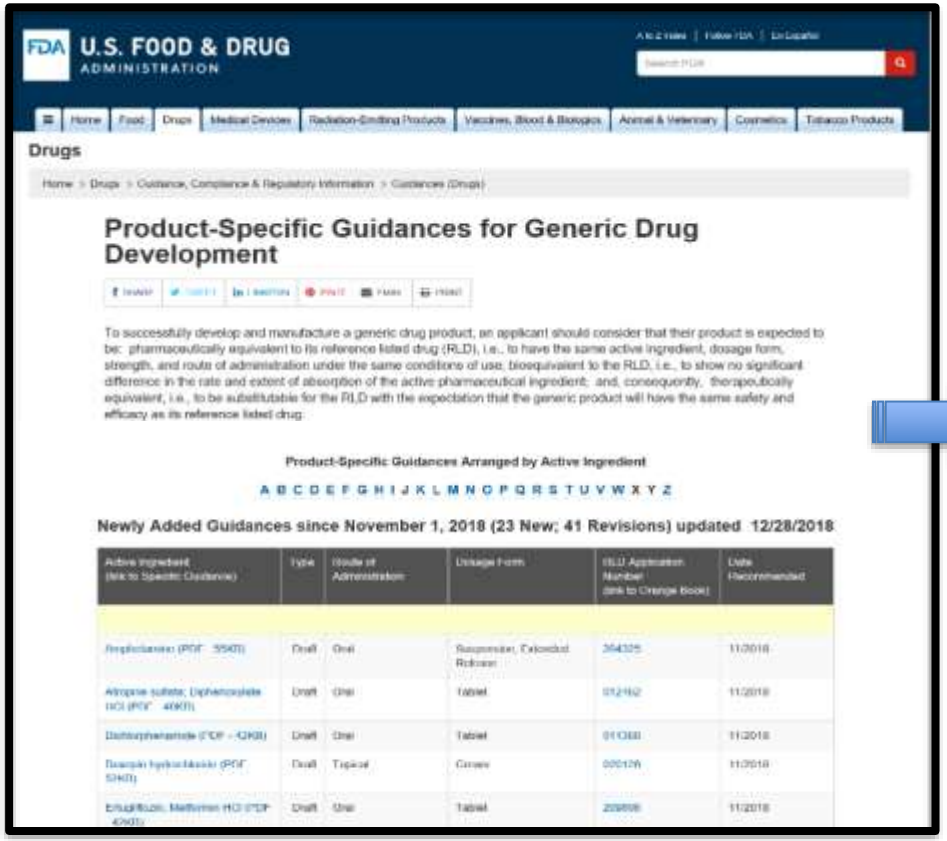
Category	General Examples
Subjects	General population (males/females), patients
Design	Single-dose, multiple-dose, crossover, parallel, partial or fully replicate
Type of BE study	Fasting, fed, fasting sprinkle
Analyte(s) to measure, biological matrix	Parent, active metabolite, or both in plasma, serum, whole blood, or urine
Dissolution methods	FDA database, split tablets if appropriate
Waiver	For additional strength(s), BCS 1 or 3
Special considerations	Alcohol dose-dumping, enteral feeding tube, drugs with partial AUC evaluation, NTI drugs, highly variable drugs, endogenous, baseline adjustment, sampling approach, concomitant drugs, safety measurements, etc.

BCS: biopharmaceutical classification system; AUC: area under the curve; NTI: narrow therapeutic index

PSG Development and Issuance

- New and revised draft PSGs are generally posted quarterly
- Non-Complex NCE NDAs
- Complex NDAs
- Requests from industry
- Public health priorities

Locating PSGs



Contains Nonbinding Recommendations

Draft Guidance on Diltiazem Hydrochloride

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.

Active Ingredient: Diltiazem hydrochloride

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 120 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 120 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

Analyte to measure (in appropriate biological fluid): Diltiazem in plasma

Bioequivalence based on (90% CI): Diltiazem

Waiver request of in vivo testing: 30 mg, 60 mg, and 90 mg based on (i) acceptable bioequivalence studies on the 120 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Diltiazem tablets, 60 mg, 90 mg, and 120 mg are scored. For additional information on the evaluation of scored tablets, refer to the FDA Guidance *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.

Recommended Mar 2020

Locating PSGs (cont.)

Product-Specific Guidances for Generic Drug Development

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Disclaimer: Due to April 2019 systemwide upgrades to www.fda.gov, the filenames for product-specific guidances on this web page may not match the corresponding guidance titles. In such cases, the name on the document correctly identifies the title of the guidance. These discrepancies will be corrected as soon as possible.

To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use; bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.
Read more >>

Total number of currently published PSGs: 1832

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 March 2020
- Newly Revised Guidances since March 2020

https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Comments on Draft 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
- FDA will consider comments on draft PSGs in developing final BE recommendations

Study Designs; Study Population; Study Types; Bioanalytical Methodology

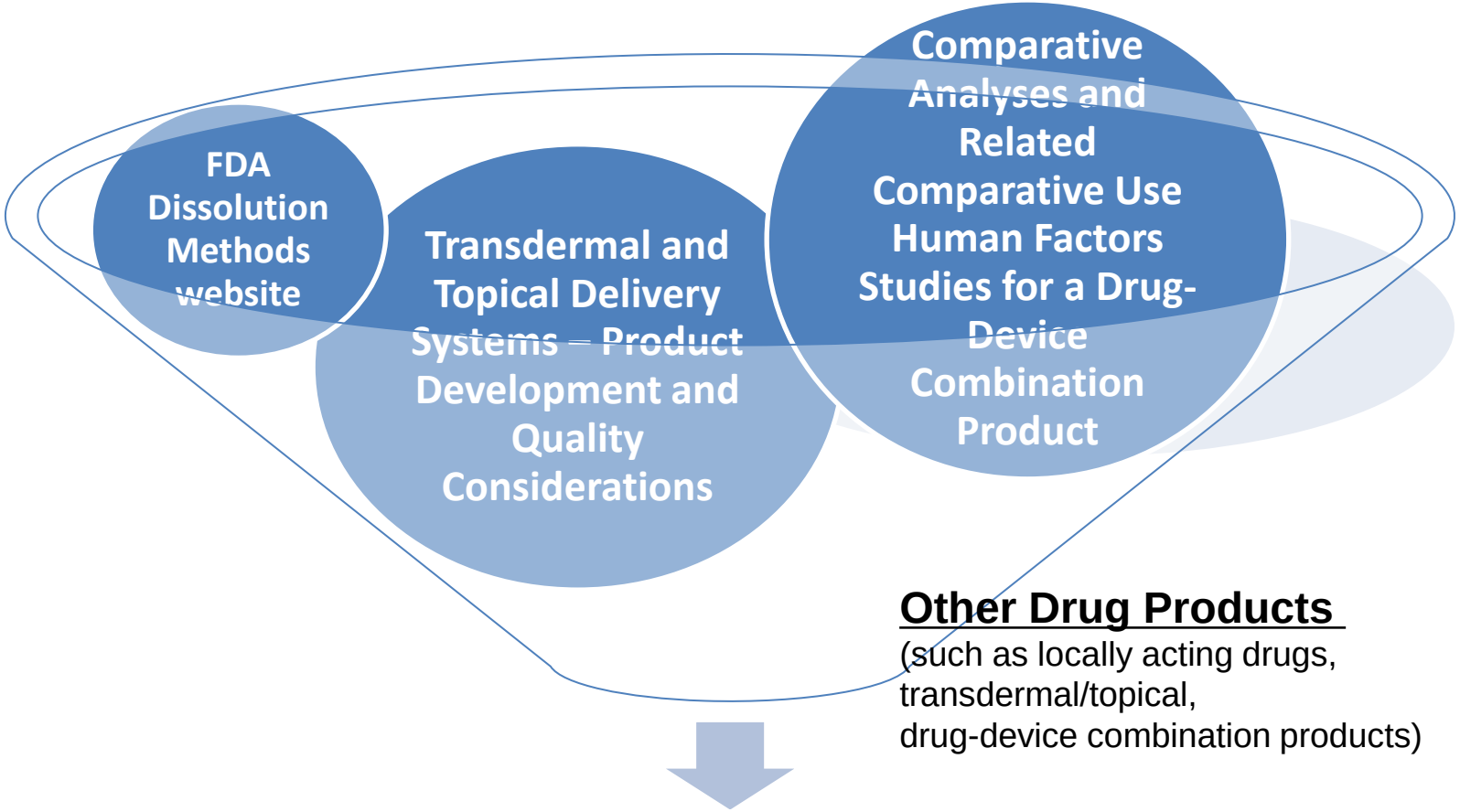
In Vitro Studies; PD Studies; Comparative Clinical Endpoint BE Studies

PSGs

Different Dosage Forms

Dissolution Methods; Tablet Scoring; Enteral Feeding Tube

PK: pharmacokinetics: PD: pharmacodynamic

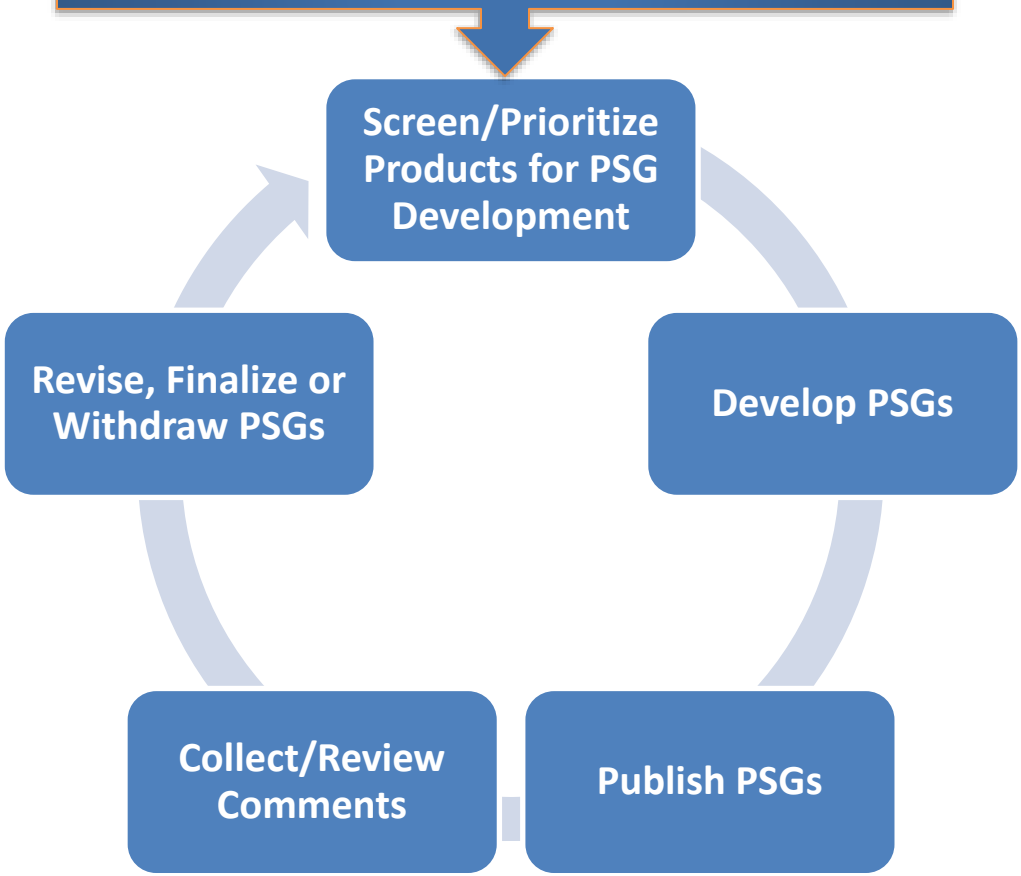


Other Drug Products
(such as locally acting drugs, transdermal/topical, drug-device combination products)

PSGs

https://www.fda.gov/media/132674/download; https://www.fda.gov/media/102349/download; http://www.accessdata.fda.gov/scripts/cder/dissolution/

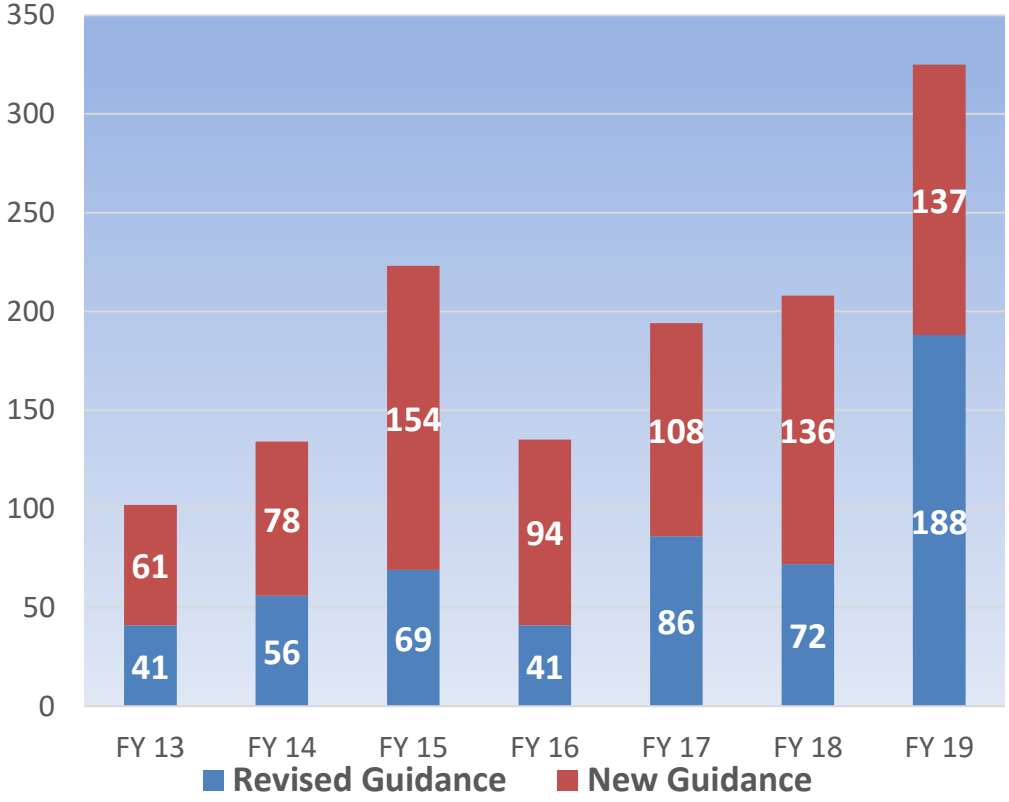
Approval of New Drugs/ Changes to Approved New Drugs



Working List of PSGs

- Screen products to develop PSGs
  - Approved NDAs, submitted ANDAs, public requests, FDA internal requests/needs, scientific research
- Use of prioritization strategies to develop or revise PSGs
  - NCE exclusivity, drug shortage status, number of pending ANDAs, number of products available in market, sales and unit price data, orphan product status
- Major or significant deviations from the FDA BE Guidance
- Newly identified safety concerns

Ongoing Efforts on PSGs



- New and revised PSGs published on a quarterly basis
- FDA's ongoing efforts in maintaining these published PSGs
- Update already published PSGs by incorporating the latest current thinking as new information becomes available
  - Fed/fasted BE studies
  - RLDs with additional approval of different strength(s) or indications, new safety findings

RLD: reference listed drug

A Recent Major Effort in PSG Revision: Fed/Fasting BE Studies

- FDA Draft Guidance – BE Studies with PK Endpoints for Drugs Submitted Under an ANDA (2013):
  - Generally recommends a fed BE study for orally administered IR drug products in addition to a fasting BE study
  - No such fed study is recommended if IR drug products are to be taken only in empty stomach
  - Only a fed or fasting BE study is recommended if serious adverse events are anticipated under fasting or fed conditions
- Before the PSG updates, ANDA applicants were asked for a fed study as part of the ANDA review, if determined to be necessary to establish BE
- A number of PSGs of solid oral dosage forms (IR and MR drug products) were recently revised to include a fed or fasted BE study recommendation

https://www.fda.gov/media/87219/download; IR: immediate release; MR: modified release

Additional Sources of Help Besides PSGs

Controlled Correspondences

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

Pre-ANDA Meetings

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

Upcoming PSGs for Complex Generic Drug Product Development Webpage

- Contains information related to upcoming new and revised PSGs for complex generic drug products
- https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development

What is a Complex Product?

- Defined in the GDUFA II Commitment Letter and generally includes:
  - Products with complex active ingredients, formulations, routes of delivery, or dosage forms;
  - Complex drug-device combinations;
  - Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

https://www.fda.gov/media/101052/download; https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-developmentt

Planned Revision Categories

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

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

GDUFA-Funded Research and PSGs

- Supports FDA's regulatory advice and decision-making
- Contributes to the development of PSGs
- Recent examples:
  - Levonorgestrel intrauterine system
  - Beclomethasone dipropionate metered inhaler

https://www.fda.gov/drugs/generic-drugs/science-research ; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021225.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020911.pdf;

Challenge Question 1

PSG recommendations do not address:

A. Active Ingredient(s)

B. Dosage Form, Route

C. Pediatric Study Subjects

D. Analyte(s) to Measure

Challenge Question 2

The typical comment period for a draft PSG is:

A. 30 days

B. 60 days

C. 90 days

D. 120 days

Summary

- PSGs and general BE guidance provide scientific recommendations to efficiently develop generic drug products
- PSGs are developed based on public health priorities, requests from industry, current and anticipated patient / industry needs, and on scientific research
- FDA's ongoing efforts to update PSGs with the latest current thinking as new information becomes available
- Additional sources, such as controlled correspondences, Pre-ANDA meetings, and planned new and revised PSGs for complex generic drug products are available to facilitate generic drug product development

Resources

- CDER Guidance Webpage: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm

- 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

- Draft Guidance for Industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Dec. 2013): https://www.fda.gov/media/87219/download

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