U.S. FOOD & DRUG ADMINISTRATION

Not So Complex? Product-Specific Guidance Updates

Pharmaceutical Quality Symposium: Quality, Supply Chain & Advanced Manufacturing

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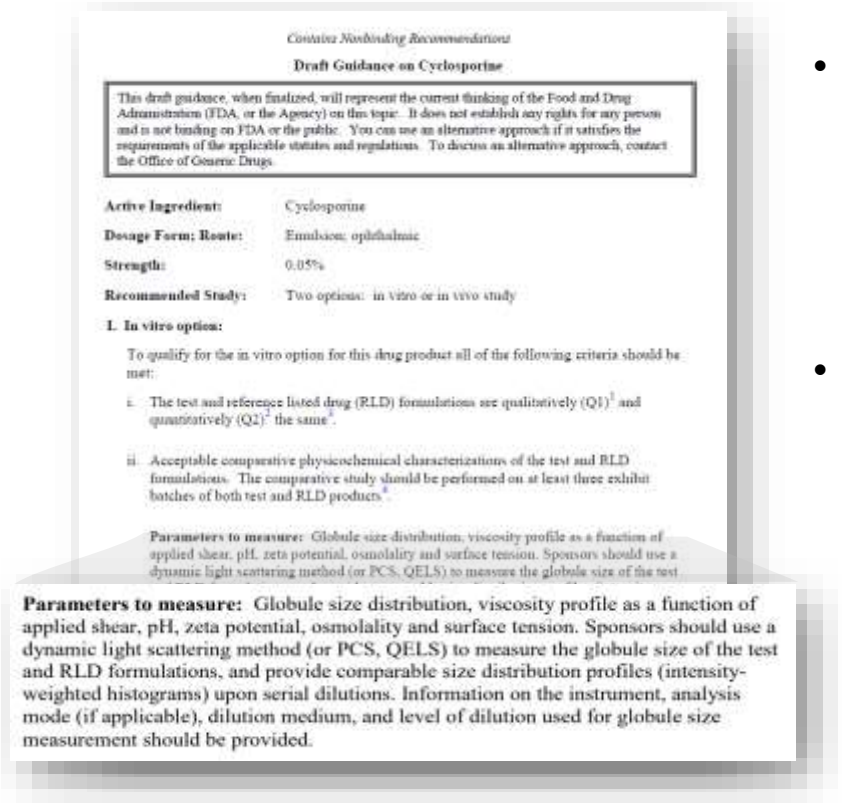
GDUFA Regulatory Science Program

The Generic Drug User Fee Amendments (GDUFA), first enacted in 2012, enables FDA to assess industry user fees to bring greater predictability and timeliness to the review of generic drug applications. To advance generic drug regulatory science and decision-making, GDUFA provides resources that allow FDA to fund research.

- Since FY2013, FDA has awarded over 200 research contracts and grants as well as conducted numerous projects led by FDA staff.
- GDUFA research provides new tools for FDA and industry to evaluate generic drug equivalence. This enables more efficient development and review of generic drugs, including the development of PSG recommendations.
- Results from GDUFA research are presented at scientific and public meetings as well as published in peer-reviewed scientific journals.

Product Specific Guidances (PSGs)



Contains Nonbinding Recommendations

Draft Guidance on Cyclosporine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Cyclosporine

Dosage Form; Route: Emulsion; ophthalmic

Strength: 0.05%

Recommended Study: Two options: in vitro or in vivo study

1. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3].

ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The comparative study should be performed on at least three exhibit batches of both test and RLD products[4].

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test

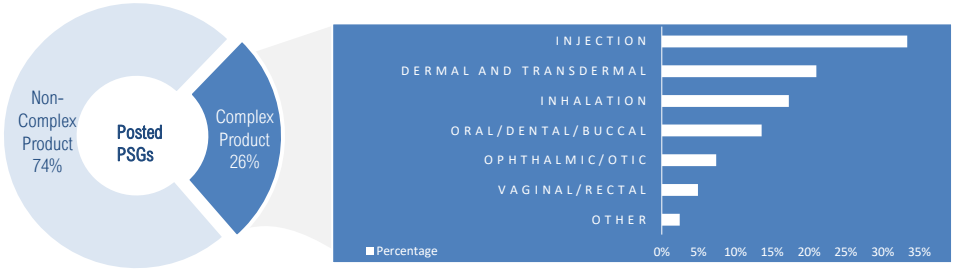
Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided.

- PSGs outline FDA's current thinking on the studies and information that are recommended to demonstrate a proposed generic drug product is therapeutically equivalent to a specific Reference Listed Drug (RLD).
- GDUFA III commitment includes goal dates for posting of PSGs for NDAs approved after Oct 1, 2022, that are **complex products**:
  - 50% within 2 years of NDA approval
  - 75% within 3 years.

Challenges and Opportunities

Depending on complexity of a newly approved New Drug Application (NDA), the timeline to develop the PSG may need/benefit from:

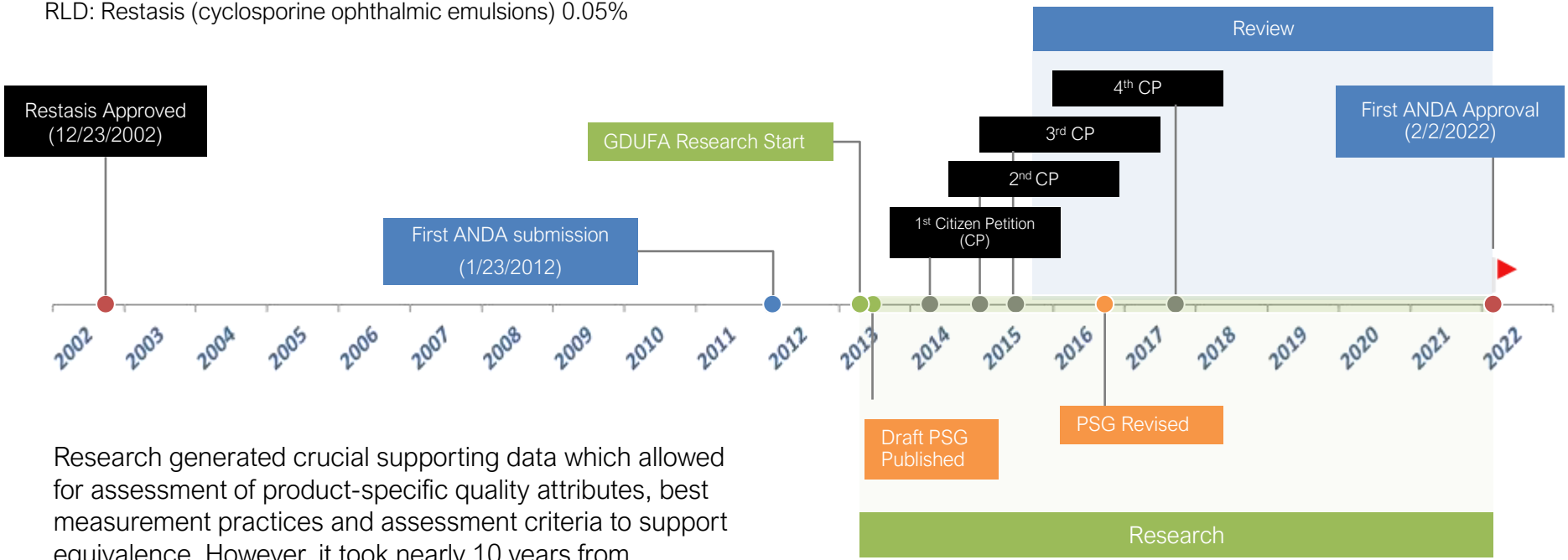
- Knowledge transfer from the NDA review team and other SMEs
- Additional information from research



Challenges	Opportunities
Complexities vary (e.g., formulation, dosage form, route of delivery, complex API)	Collaboration
Scientific knowledge gap (e.g., new material, technology, complex process, critical quality attributes)	Research and innovation
Need for reliable/new analytical methods	Research and innovation
Time constraints (especially if involving additional research to generate evidence)	Early engagement
Life-cycle of the product (NDA to ANDA, supplement)	Communication and collaboration

Cyclosporine Ophthalmic Emulsions: A Case Study

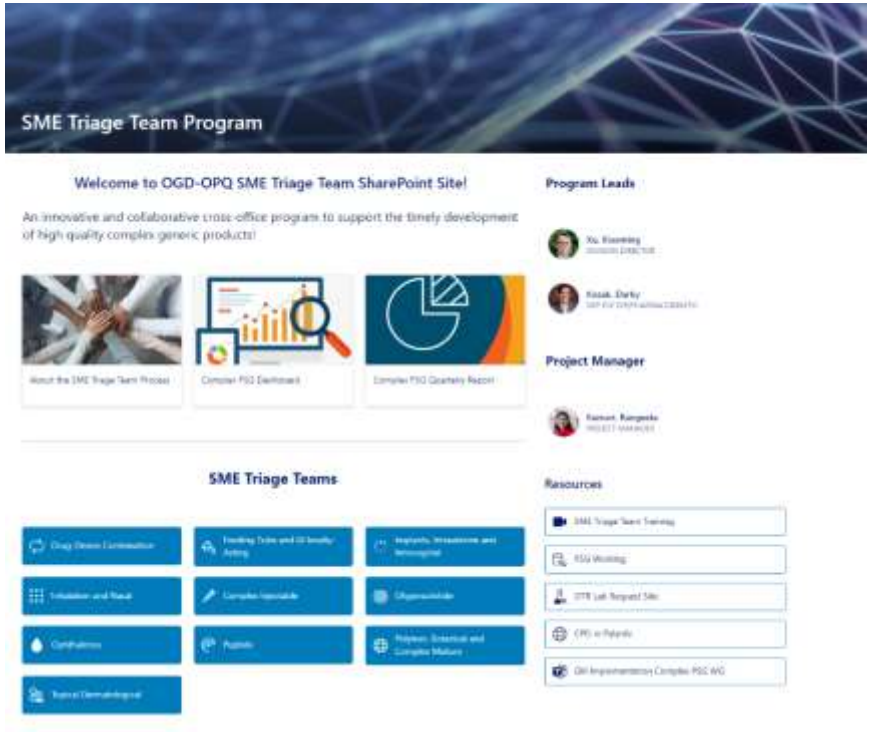
RLD: Restasis (cyclosporine ophthalmic emulsions) 0.05%



Research generated crucial supporting data which allowed for assessment of product-specific quality attributes, best measurement practices and assessment criteria to support equivalence. However, it took nearly 10 years from approval to develop scientific recommendations and another 9 years to translate to approval.

- Z. Rahman et al. ***Mol Pharm*** (2014), 11, 3.
- H. Qu, et al. ***Int J Pharm*** (2018), 538, p.215-222
- P. Petrochenko, et al. ***Int J Pharm*** (2019), 550, p229-239
- Y. Dong et al. ***J Pharm Sci*** (2019) 108, 2002-2011
- Y. Dong et al. ***J Control Release*** (2019), 313, 96-105
- Y. Dong et al. ***J Control Release*** (2020), 327, 360-370
- D. Patel et al. ***J Control Release*** (2021), 333, 65-75.
- R. Bellantone, et al. ***Int J Pharm*** (2022), 121521.

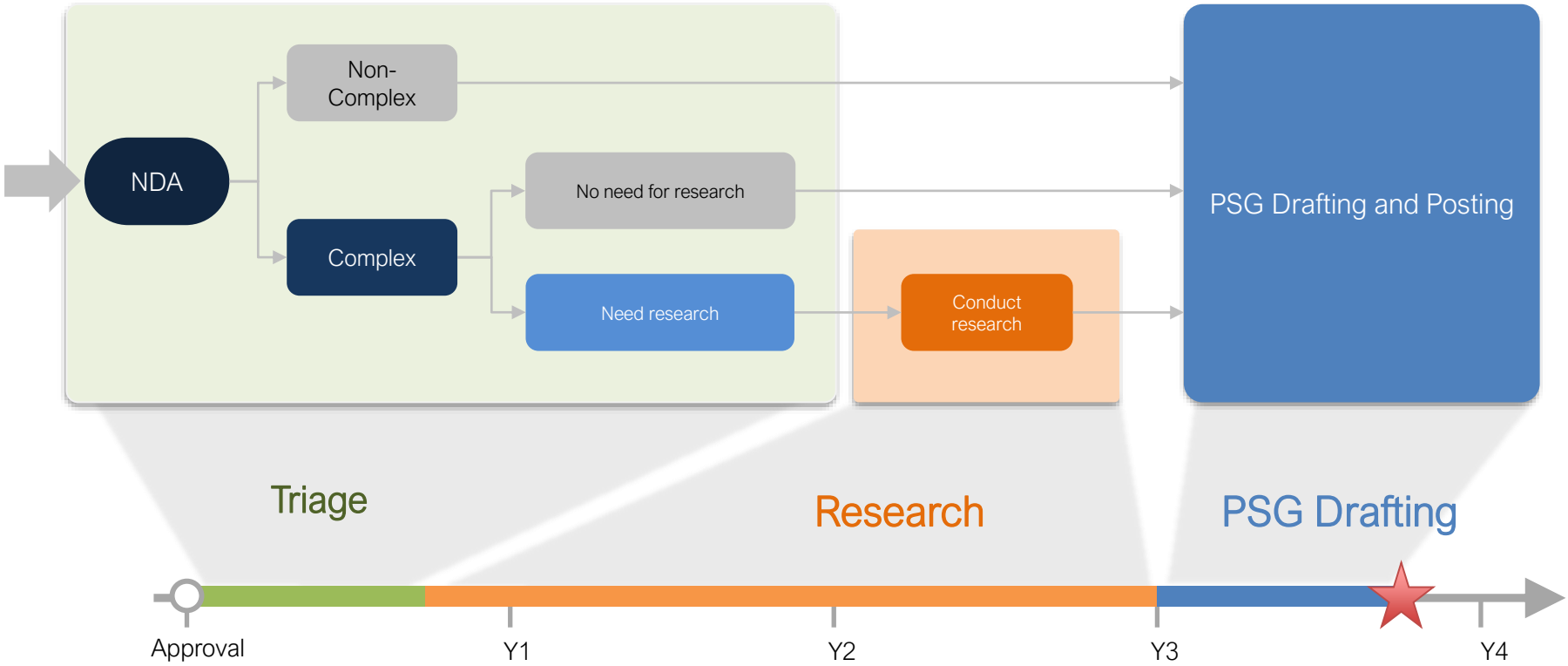
- An internal program to identify and direct research to support PSG development of complex generics
- 10 complex areas
- SMEs across 9 CDER offices
- Over the last two years, conducted 59 SME triage team meetings of newly approved NDAs, with 8 identified research projects



SME Triage Team Program:

- Established a cross-office program (SME Triage Team, STT), to support complex PSG development
- STT program clarified relevant CDER offices of roles and responsibilities in the development process of complex product PSGs.
- STT program successfully connected research and review assessment with PSG development, achieving early identification of knowledge gaps and timely addressing technical challenges.
- Identify product based on complexity area, e.g., ophthalmic, inhalation, dermatological.
- Each complex area has its own SME team, with membership comprises of experts from research, review, and policy.
- SME team make key decisions like: Identify area of complexity; Determine if the complexity needs new research; Decide the research objectives.
- STT program enabled cross-disciplinary collaboration for effective knowledge management to maximize efficient use of Center resources.
- STT program started as a pilot in 2021 and became fully operational in Oct 2022.

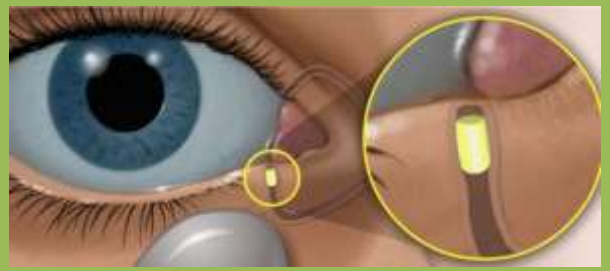
Timeline to Support Complex Product PSG



Today

VERKAZIA, cyclosporine emulsion
(NDA 214965)
Approval: 6/23/2021
PSG Published: 8/2/2022

14 months to publish PSG

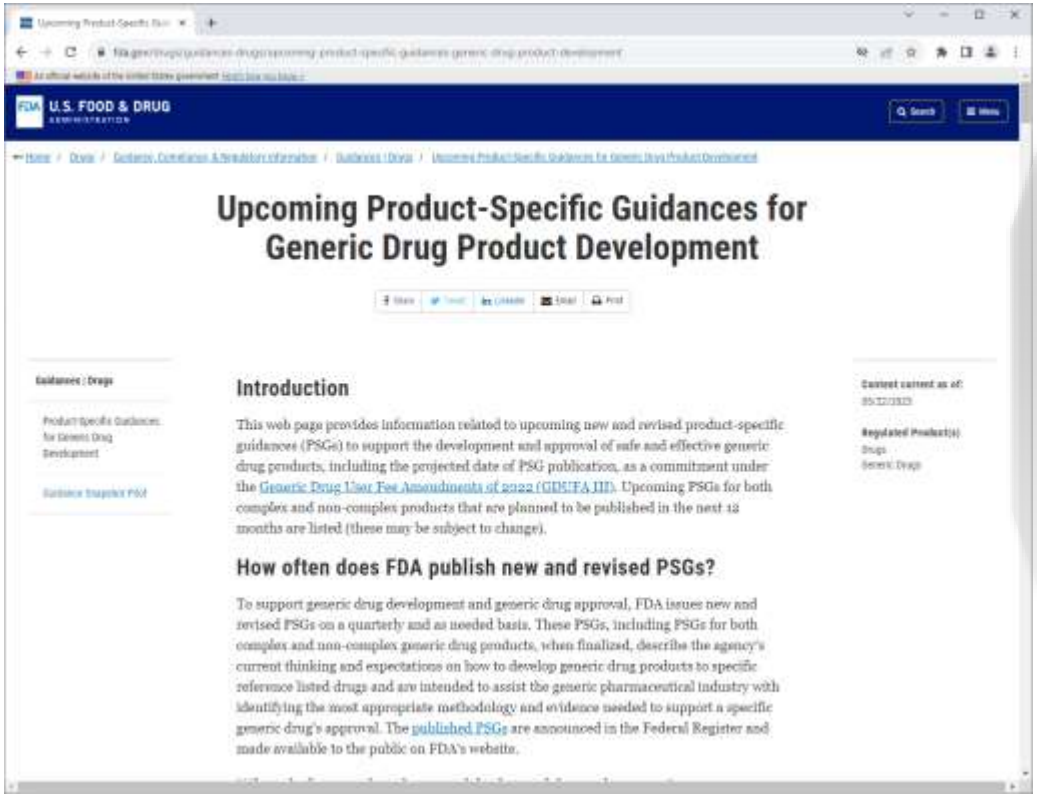


DEXTENZA (dexamethasone ophthalmic insert, NDA 208742)
Approval: 11/30/2018

Research is ongoing to address knowledge gaps in material characterization and Q3 attributes*.

H Nejad, et al. Impact of Material and Manufacturing Process on Performance of an Ophthalmic Implant. Invest. Ophthalmol. Vis. Sci. 2023;64(8):735.

Today (cont.): PSG Forecast List



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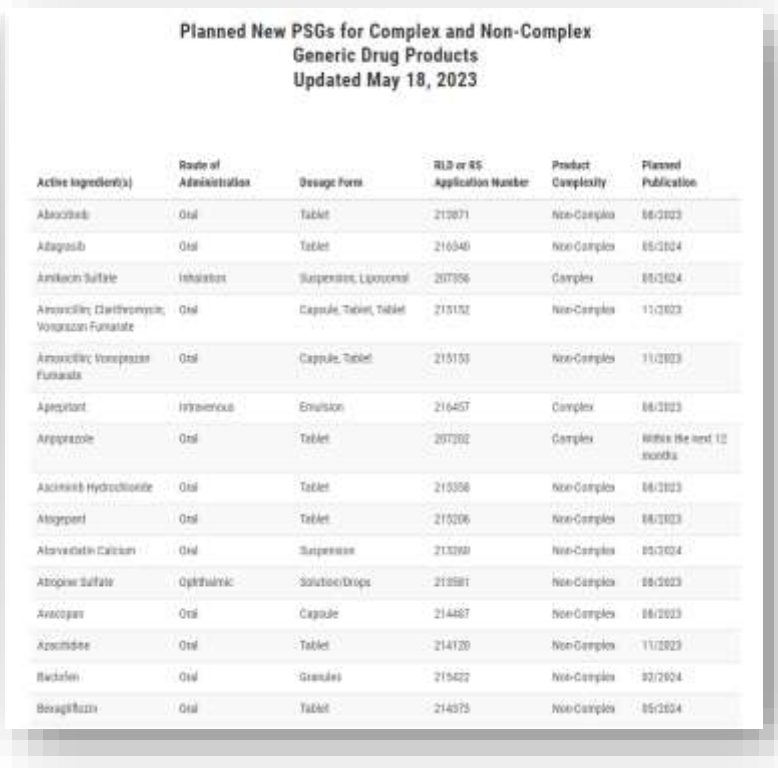
Upcoming Product-Specific Guidances for Generic Drug Product Development

Introduction

This web page provides information related to upcoming new and revised product-specific guidances (PSGs) to support the development and approval of safe and effective generic drug products, including the projected date of PSG publication, as a commitment under the Generic Drug User Fee Amendments of 2022 (GDUFA III). Upcoming PSGs for both complex and non-complex products that are planned to be published in the next 12 months are listed (these may be subject to change).

How often does FDA publish new and revised PSGs?

To support generic drug development and generic drug approval, FDA issues new and revised PSGs on a quarterly and as needed basis. These PSGs, including PSGs for both complex and non-complex generic drug products, when finalized, describe the agency's current thinking and expectations on how to develop generic drug products to specific reference listed drugs and are intended to assist the generic pharmaceutical industry with identifying the most appropriate methodology and evidence needed to support a specific generic drug's approval. The published PSGs are announced in the Federal Register and made available to the public on FDA's website.



Planned New PSGs for Complex and Non-Complex Generic Drug Products
Updated May 18, 2023

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Product Complexity	Planned Publication
Abrocitinib	Oral	Tablet	213871	Non-Complex	06/2023
Adagrasib	Oral	Tablet	216340	Non-Complex	05/2024
Amikacin Sulfate	Inhalation	Suspension, Liposomal	207356	Complex	05/2024
Amoxicillin; Clarithromycin; Vonoprazan 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	06/2023
Aripiprazole	Oral	Tablet	207202	Complex	Within the next 12 months
Asciminib Hydrochloride	Oral	Tablet	215358	Non-Complex	06/2023
Atogepant	Oral	Tablet	215206	Non-Complex	06/2023
Atorvastatin Calcium	Oral	Suspension	213269	Non-Complex	05/2024
Atropine Sulfate	Ophthalmic	Solution/Drops	213581	Non-Complex	06/2023
Avacopan	Oral	Capsule	214487	Non-Complex	06/2023
Azacitidine	Oral	Tablet	214120	Non-Complex	11/2023
Baclofen	Oral	Granules	215422	Non-Complex	02/2024
Bexagliflozin	Oral	Tablet	214375	Non-Complex	05/2024

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

Summary

- FDA's product-specific guidance program provides FDA's current thinking on the type of studies and information to support the development and approval of safe, effective, and high-quality generic drug products.
- GDUFA research offers opportunity for targeted generation of evidence and knowledge in areas of high complexity and challenge.
- Lifecyle approach towards knowledge generation and information sharing is critical to the timely development of PSG.

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