Complex Drug Products and Potential Challenges to Generic Drug Development

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Generic Drugs in the United States

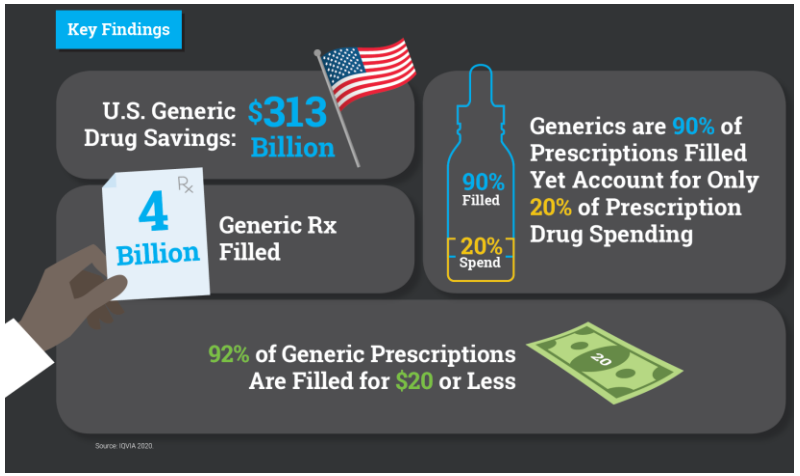
Generic Drugs:

2020:
- **90%** of prescription
- **20%** of prescription drug spending

2021:
- **18.1%** of prescription drug spending

~30% are **Complex Products**
Per GDUFA II Commitment Letter Definition*

Overall Drug Products



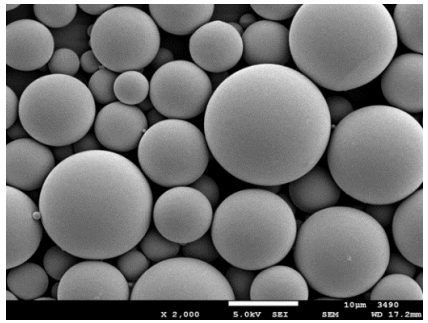
Topical drug products with generics available < 40%

Ophthalmic products with generics available < 50%

Orally inhaled drug products (OIDP)

First Generic for OIDP (approved Jan 30, 2019)

Poly-(lactic-co-glycolic acid) (PLGA) microspheres Long-acting injectable products



No Generics

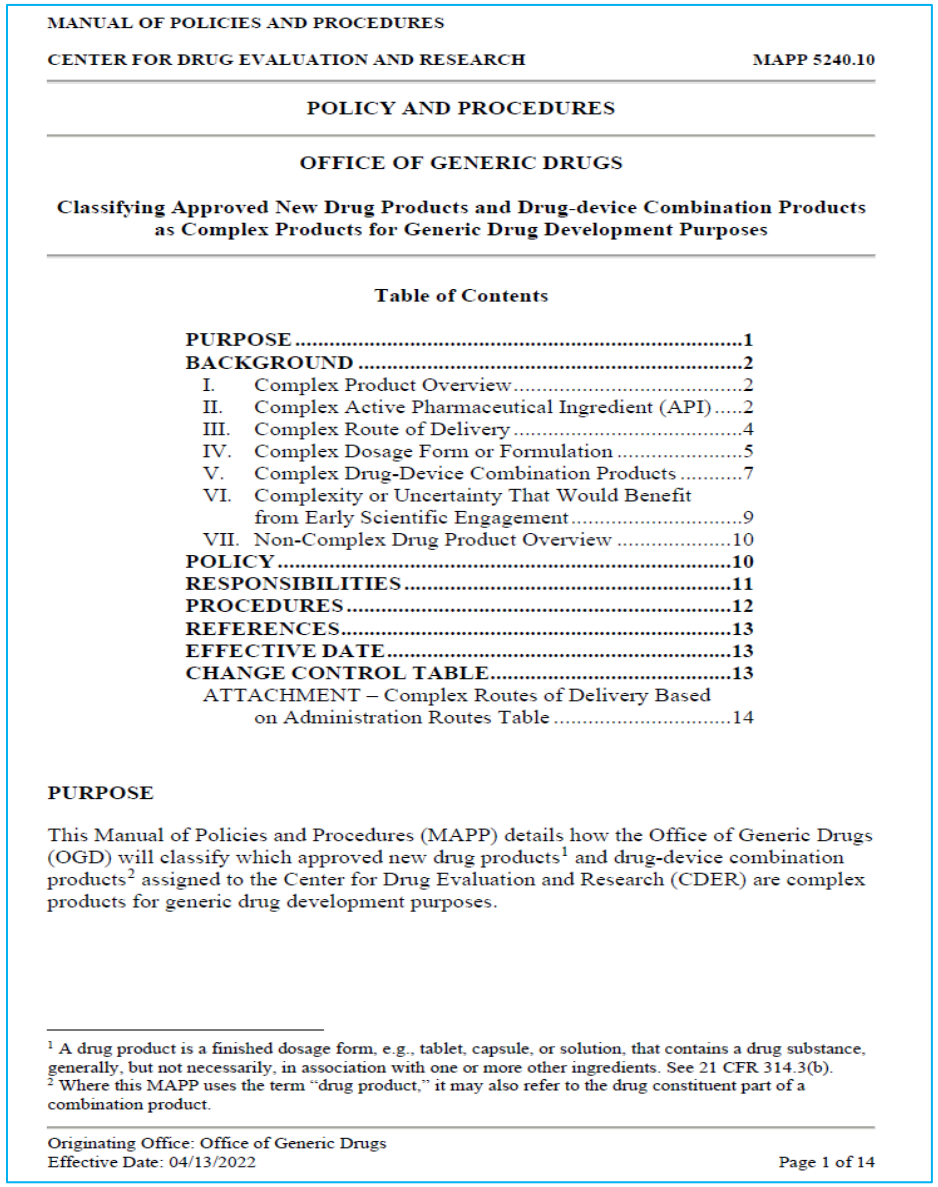
https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pdf
GDUFA: Generic Drug User Fee Amendments
* https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

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

FDA MAPP to Clarify Understanding and Classification about Complex Products



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5240.10

POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes

Table of Contents

PURPOSE

This Manual of Policies and Procedures (MAPP) details how the Office of Generic Drugs (OGD) will classify which approved new drug products[1] and drug-device combination products[2] assigned to the Center for Drug Evaluation and Research (CDER) are complex products for generic drug development purposes.

[1] A drug product is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. See 21 CFR 314.3(b).
[2] Where this MAPP uses the term "drug product," it may also refer to the drug constituent part of a combination product.

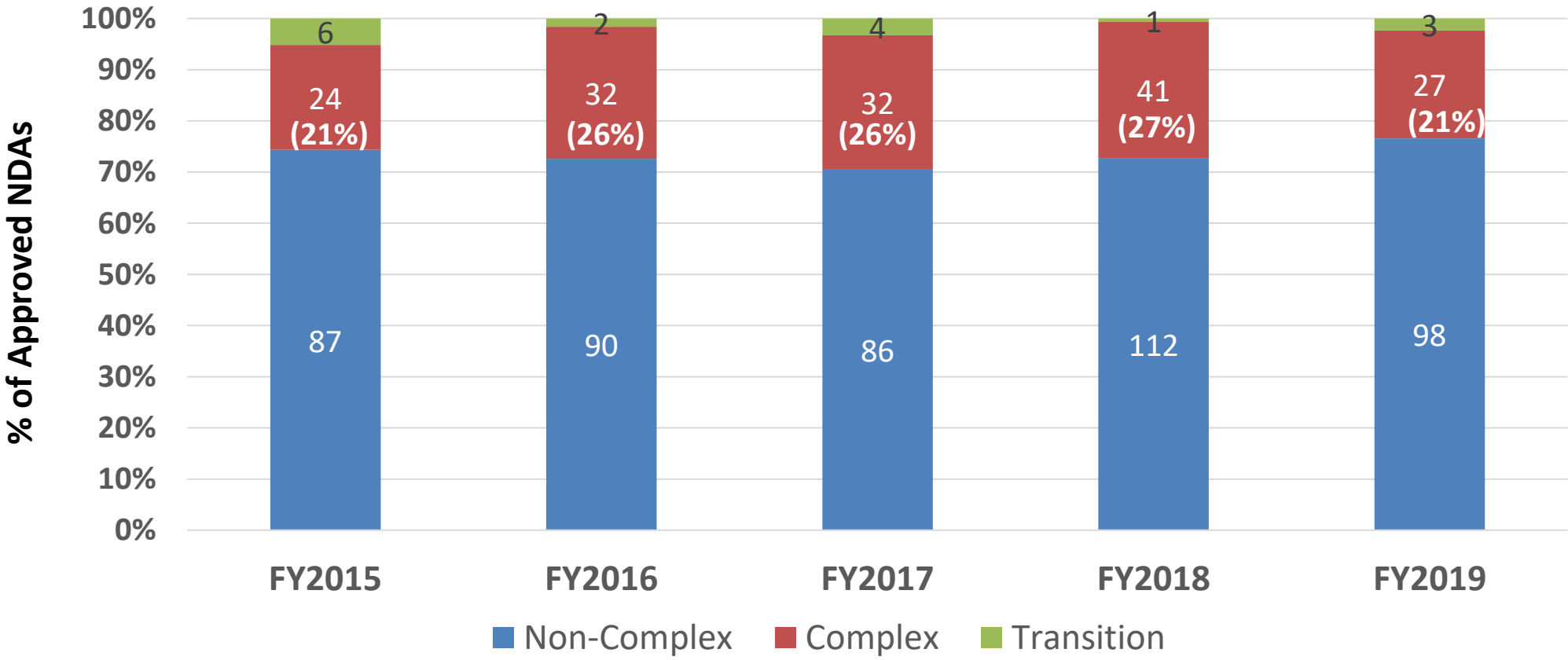
Originating Office: Office of Generic Drugs
Effective Date: 04/13/2022 Page 1 of 14

Manual of Policies and Procedures (MAPP) Published on 04/13/2022

Provides definitions and examples of complex drugs and drug-device combination products, as well as the responsibilities and procedures for complex drug classification and database maintenance.

https://www.fda.gov/media/157675/download

Complex Drug Products in Newly Approved NDAs FY2015-2019 (20-30% are Complex)

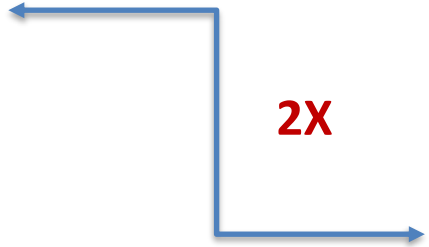


FY: Fiscal year
(Oct 1-Sept 30)

*Numbers noted on the bar graph are the number of approved NDAs, and the height of the graph is normalized

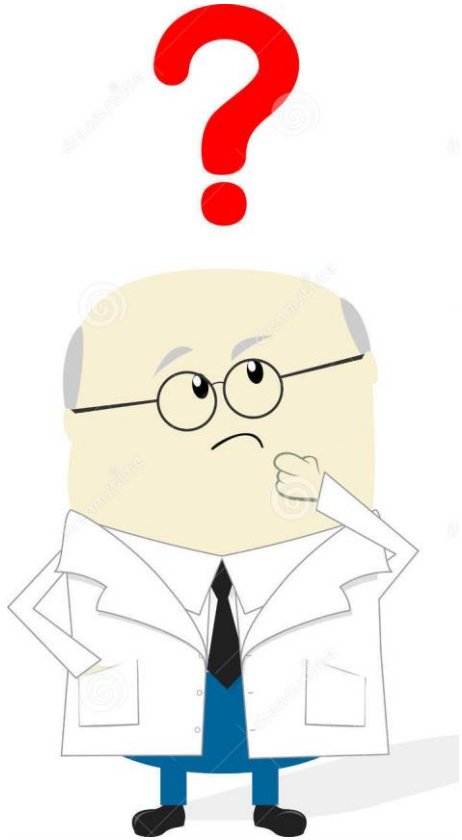
Complex ANDA Approvals

- ~20-30% of reference products (new drugs) are complex



- Percent of Full ANDA approvals that are complex products
- FY2021: 13.2%
- FY2020: 13.0%
- FY2019: 12.7%
- FY2018: 12.5%
- FY2017: 12.0%

Equivalence Determination
"Simple" vs "Complex"



GENERIC DRUG (ANDA) Requires Demonstration of *"SAMENESS" or EQUIVALENCE*

- Identify a Single RLD
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength

Pharmaceutical Equivalence (PE)

- Same Labeling
- **Bioequivalence (BE)**
- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls (CMC) Information
- cGMPs (facilities)

PE + BE → TE (Therapeutic Equivalence)

Challenges for Complex Generic Drug Products

- Pharmaceutical Equivalence (PE)
  - How to demonstrate active ingredient “sameness”, e.g., mixture of APIs
  - How to characterize complex formulation
  - How to compare inactive ingredients if needed*
  - How to compare impurities if needed

- Bioequivalence (BE)
  - Locally acting → Straightforward BE (systemic PK) approach frequently not applicable
    - Comparative clinical endpoint bioequivalence (BE) studies not ideal
      - Insensitive indicator for equivalence
      - Large, expensive studies
      - Frequently poorly conducted

- Therapeutic Equivalence (TE)
  - What kinds of comparative analyses are needed to support substitution?
  - How to demonstrate that certain inactive ingredients, impurities and other allowable differences in a proposed generic drug product do not affect its safety or efficacy as compared to reference listed drugs?

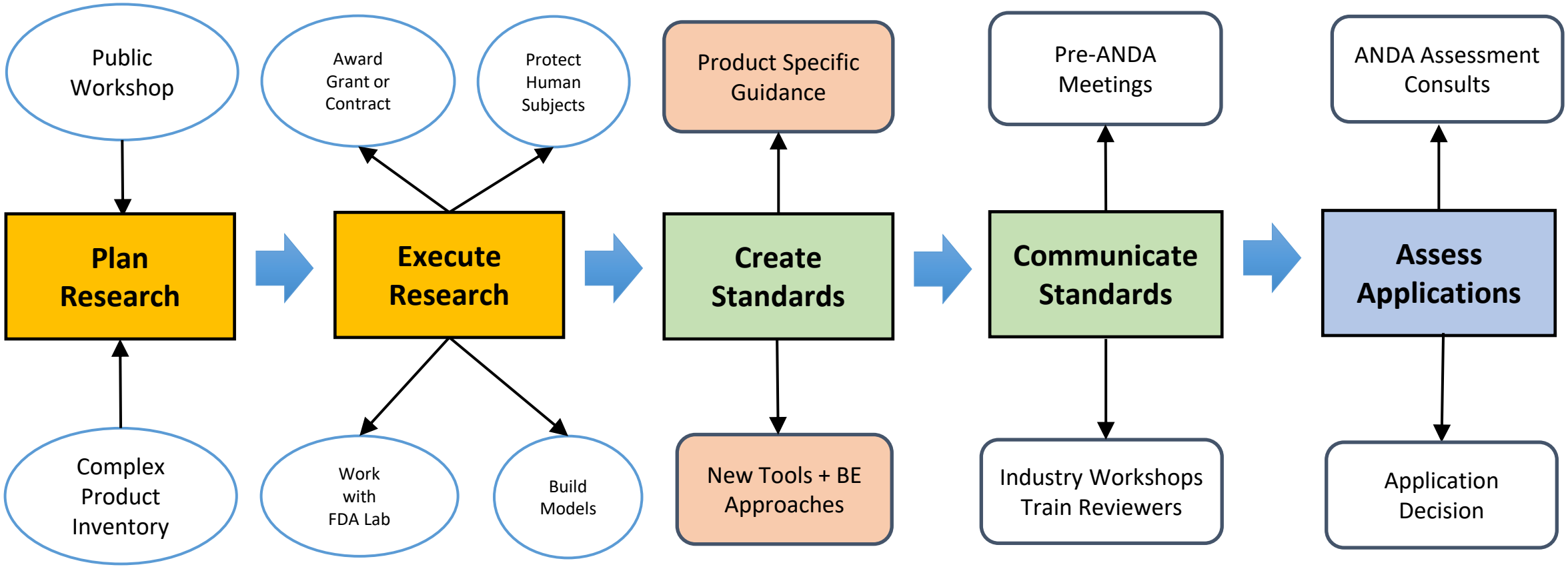
* If required under 21 CFR 314.94(a)(9) or recommended by a product-specific guidance

Bioequivalence Approaches

- In vivo BE with pharmacokinetic endpoints
- In vivo BE with pharmacodynamic endpoints
- In vivo BE with clinical endpoints
- **In vitro BE studies**
- Other

21 CFR 320.24(b)

Integration of Science and Research into Guidance Development and Application Assessment



BE: bioequivalence

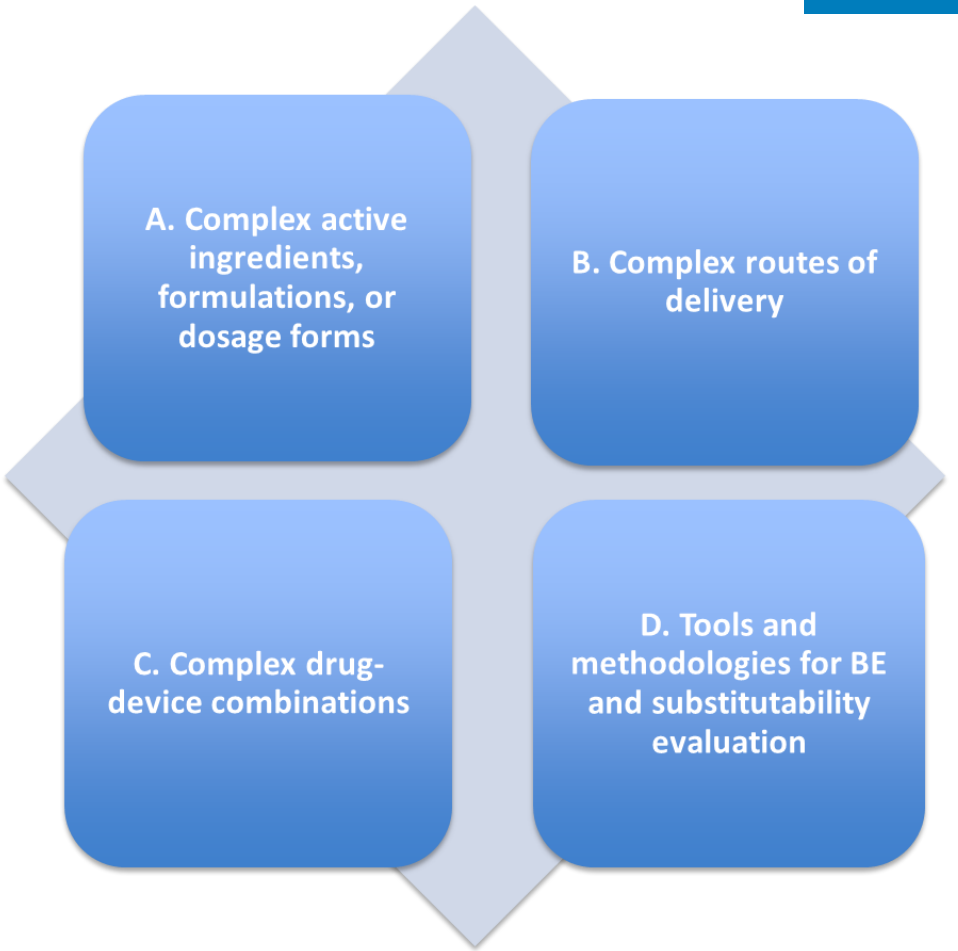
Modified from: Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, Clinical Pharmacology & Therapeutics (CPT), 2019, Vol.105(4), p.878-885

GDUFA Regulatory Science

- 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 2013, FDA has awarded 188 research contracts and grants as well as numerous projects conducted by FDA staff.
  - This 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.

GDUFA Regulatory Science

- GDUFA research priorities are set annually based on public feedback[1]
  - FY 2022 *GDUFA Regulatory Science Initiatives Public Workshop* was held as a virtual event on **May 9-10, 2022**[2]
  - Currently 90+ on-going collaborative projects in four key areas[3]
- Research projects are conducted by FDA laboratories as well as via contracts or grants with academia, industry, or other government agencies.[4]



1. https://www.fda.gov/drugs/generic-drugs/science-research
2. https://www.fda.gov/drugs/news-events-human-drugs/fy-2022-generic-drug-science-and-research-initiatives-public-workshop
3. https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects
4. https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Kozak and Xu, SBIA, April 27, 2022

GDUFA Science and Research Report

- The FY2021 GDUFA Science and Research Report is available at: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports
- It highlights the scope and impact of **all** GDUFA-supported research across FDA
- High transparency to the generic industry on what we use GDUFA resources for

FY2021 GDUFA Research Report
https://www.fda.gov/drugs/generic-drugs/fy-2021-gdufa-science-and-research-report

GDUFA Research Areas

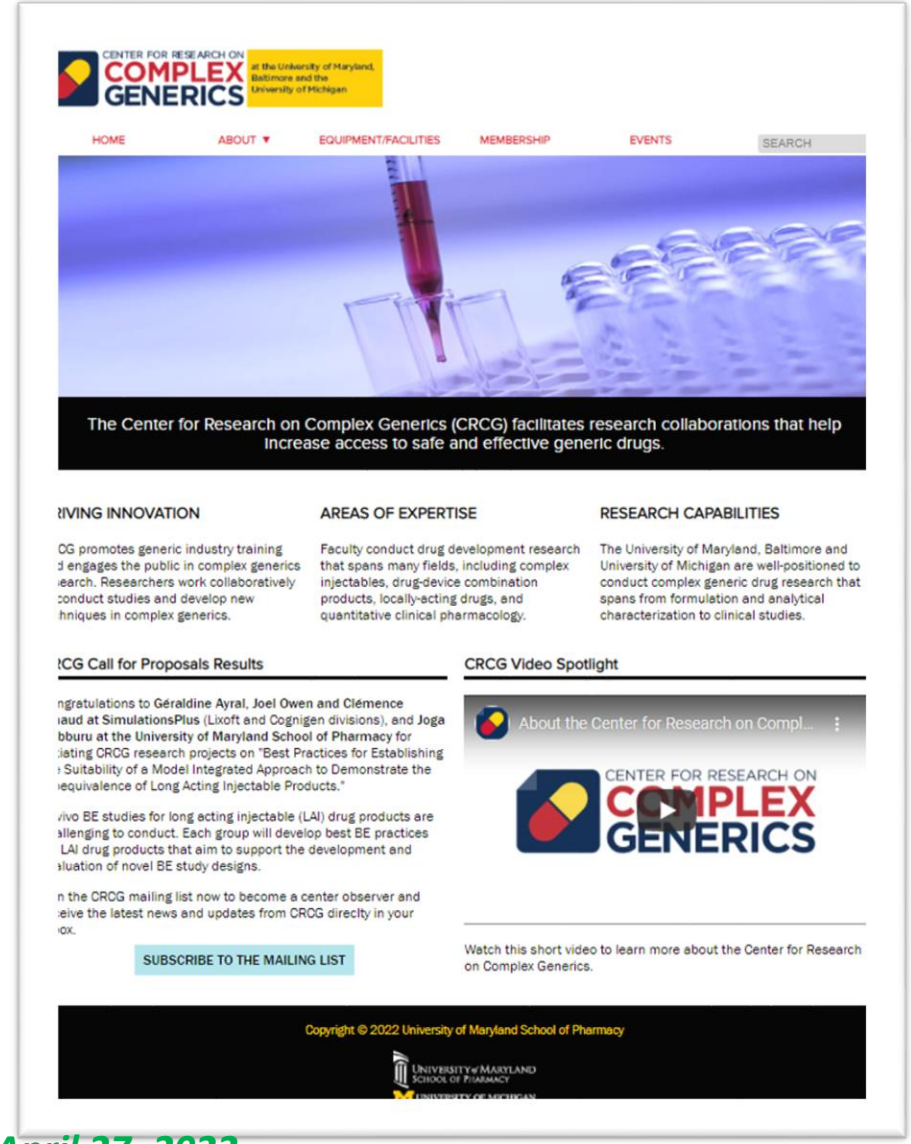
Bioequivalence of Locally Acting Products	Equivalence of Complex Products	Advanced Quantitative Methods	Therapeutic Equivalence
• Ophthalmic • Topical Dermatological • Inhalation and Nasal	• Complex Injectables, Formulations and Nanomaterials • Complex Mixtures and Peptides • Long-Acting Injectables and Implants	• Locally-Acting Physiologically-Based Pharmacokinetic Modeling • Oral Absorption Models • Quantitative Clinical Pharmacology • Data Analytics	• Patient Substitution Studies • Abuse-deterrent Opioid Drug Products • Drug-Device Combination Products

FY2021 GDUFA Research Report

https://www.fda.gov/drugs/generic-drugs/fy-2021-gdufa-science-and-research-report

Center for Research on Complex Generics

- Started in 2020 via a GDUFA grant, the **Center for Research on Complex Generics (CRCG)**[1] is a partnership between FDA, the University of Maryland, and the University of Michigan to facilitate research collaborations that help increase access to safe, effective and high-quality generic drugs. The CRCG:
  - Supports FDA's efforts to enhance research collaborations with the generic industry.
  - Hosts educational events and workshops:
    - June 29, 2022; *In Vitro Release Test and In Vitro/In Vivo Correlation of Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products*
    - Oct. 27 - 28, 2022; *Model Integrated Bioequivalence Approaches in Complex Generic Product Development*
    - Nov. 3, 2022; *Evaluation of Cutaneous Pharmacokinetics to Facilitate Complex Generic Topical Product Development*
    - Dec 6, 2022: *FDA-CRCG Training on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned*
  - Promotes generic industry training and engaging the public in complex generics research.
  - Conducts collaborative research that facilitate complex generics.



1. https://complexgenerics.org/about/

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

Pre-ANDA Program

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

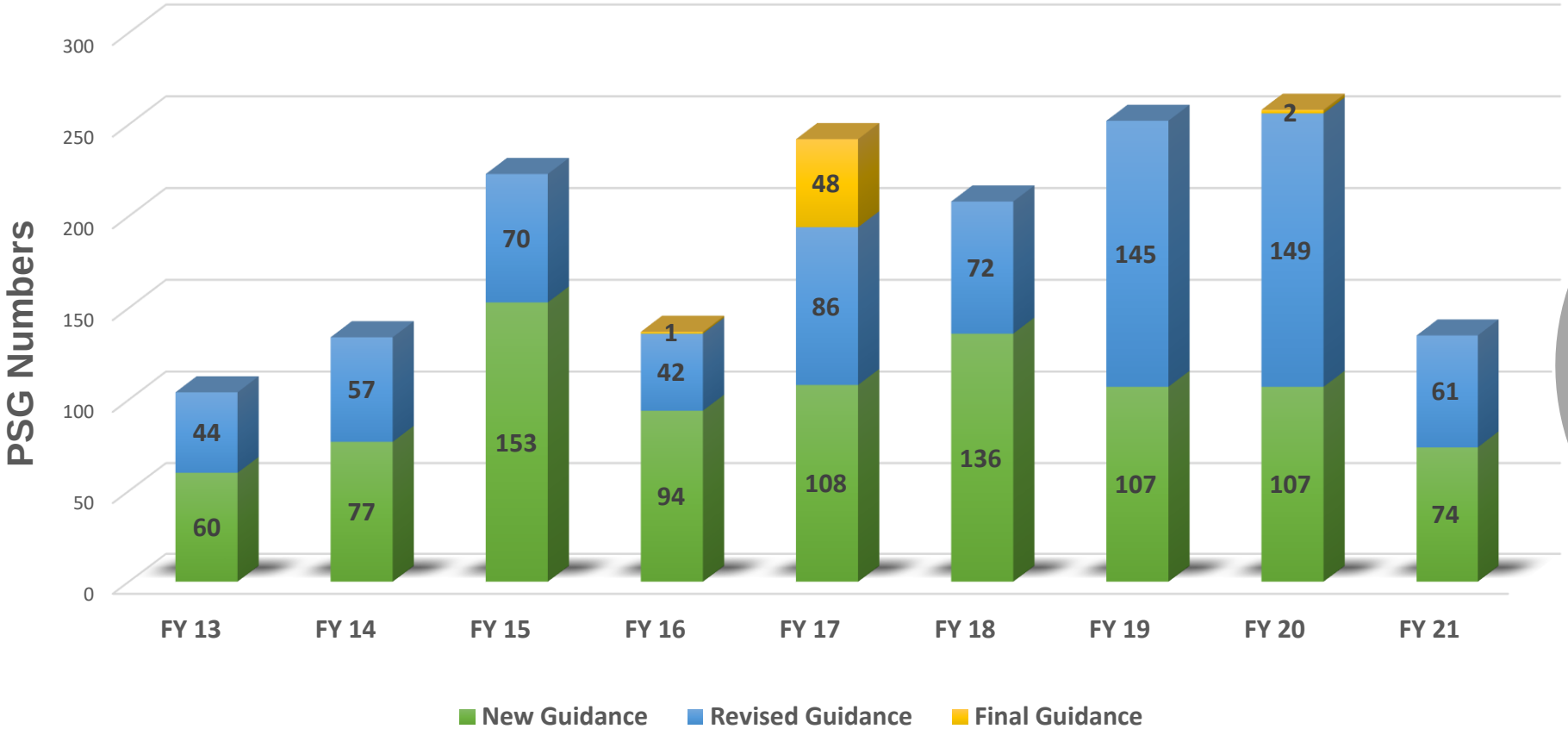
GDUFA: Generic Drug User Fee Amendments

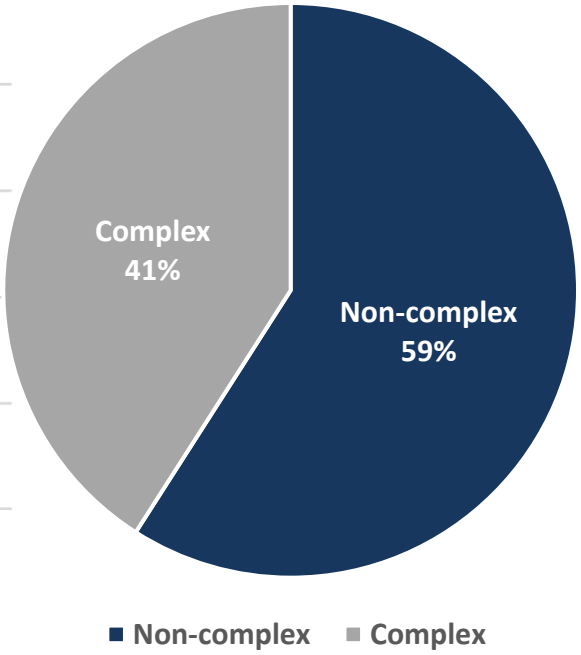
Product-Specific Guidances (PSGs)

- A key outcome of GDUFA research is the development of PSGs.
- Started in 2007, PSGs outline FDA's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs (RLDs).
  - PSGs are posted on a quarterly basis and as of April 2022, there are **1,978 posted PSGs**.
  - **PSG website:** https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development
  - **Upcoming PSGs for complex products**: https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development
- PSG priorities and goal dates.[1]
  - For New Chemical Entity non-complex products, FDA will issue a PSG for 90% at least 2 years prior to the earliest lawful ANDA filing date (e.g., not more than 3 years post New Drug Application (NDA) approval).
  - For newly approved complex products, FDA will strive to issue product-specific guidance as soon as scientific recommendations are available.

[1] GDUFA II Commitment Letter https://www.fda.gov/media/101052/download

PSGs Published (FY 2013-FY 2021)





Examples of New Chemical Entity Complex Products (FY 2018-2019)

APPROVAL DATE	NDA NUMBER	PROPRIETARY NAME	ACTIVE INGREDIENT	ROUTE OF DELIVERY	DOSAGE FORM	SPONSOR	PSG STATUS
12/5/2017	209637	OZEMPIC	SEMAGLUTIDE	SUBCUTANEOUS	SOLUTION	NOVO NORDISK INC	ISSUED 03/2020
12/11/2017	208945	XEPI	OZENOXACIN	TOPICAL	CREAM	FERRER INTERNACIONAL SA	ISSUED 02/2019
1/26/2018	208700	LUTATHERA	LUTETIUM DOTATATE LU-177	INTRAVENOUS	SOLUTION	ADVANCED ACCELERATOR APPLICATIONS USA INC	ISSUED 11/2019
5/18/2018	207078	LOKELMA	SODIUM ZIRCONIUM CYCLOSILICATE	ORAL	FOR SUSPENSION	ASTRAZENECA PHARMACEUTICALS LP	ISSUED 06/2020
7/27/2018	210589	OMEGAVEN	FISH OIL TRIGLYCERIDES	INTRAVENOUS	EMULSION	FRESENIUS KABI USA LLC	ISSUED 06/2020
8/10/2018	209627	ANNOVERA	ETHINYL ESTRADIOL; SEGESTERONE ACETATE	VAGINAL	RING	THERAPEUTICSMD INC	Pending or Active Research; Upcoming
8/10/2018	210922	ONPATTRO	PATISIRAN SODIUM	INTRAVENOUS	SOLUTION	ALNYLAM PHARMACEUTICALS INC	
10/5/2018	211172	TEGSEDI	INOTERSEN SODIUM	SUBCUTANEOUS	SOLUTION	AKCEA THERAPEUTICS INC	
11/16/2018	210910	AEMCOLO	RIFAMYCIN SODIUM	ORAL	TABLET, DELAYED RELEASE	REDHILL BIOPHARMA INC	ISSUED 03/2020
3/5/2019	211243	SPRAVATO	ESKETAMINE HYDROCHLORIDE	NASAL	SPRAY	JANSSEN PHARMACEUTICALS INC	ISSUED 08/2020
6/21/2019	210557	VYLEESI (AUTOINJECTOR)	BREMELANOTIDE ACETATE	SUBCUTANEOUS	SOLUTION	PALATIN TECHNOLOGIES INC	ISSUED 03/2021

PSGs for Topical Dermatological Products

Potential ways for establishing BE for complex topicals:

- Comparative clinical endpoint BE studies
  - Clinical endpoint (CE)
  - Pharmacodynamic endpoint (e.g., vasoconstrictor (VC) studies)

- *Efficient* BE approach that includes the following studies as appropriate
  - Formulation assessment and Characterization tests (Q3)
  - In vitro BE studies (IVRT and/or IVPT)
  - In vivo pharmacokinetic (PK) BE studies

Courtesy: P. Ghosh

PSGs for Topical Dermatological Products

A Modular and Scalable Approach to BE Evaluation

- Sameness of inactive ingredient components and quantitative composition, e.g., qualitative **(Q1)** and quantitative **(Q2)** sameness
- **Q3** (Physical & Structural Characterization) as relevant to the nature of the product
- **IVRT** (In Vitro Release Test)
- **IVPT** (In Vitro Permeation Test) or another bio-relevant assay may be appropriate for some products
- In vivo systemic **PK** studies may be appropriate for some products

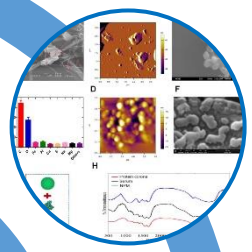
Example: Acyclovir (cream, 5%) PSG:
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf

Courtesy: P. Ghosh

FDA Research Enabled the Approval of Albuterol Sulfate MDI

- The inhalers are widely used by people with asthma, but it's become more difficult to get them because they're being used to treat patients with COVID-19
- The U.S. FDA approved **the first generic albuterol inhalers in 2020** in response to inhaler shortages and increased demand caused by the coronavirus pandemic

FDA research supported every part of the BE evaluation that enabled ANDA approval of albuterol MDI



In Vitro BE

- FDA research helped select the in vitro tests
- Quantitative analysis developed BE methods for the in vitro tests
- FDA labs helped optimize the implementation of the in vitro BE tests

In Vivo BE

The pharmacodynamic (PD) study design has been optimized by advanced pharmacometric modeling

Device Comparison

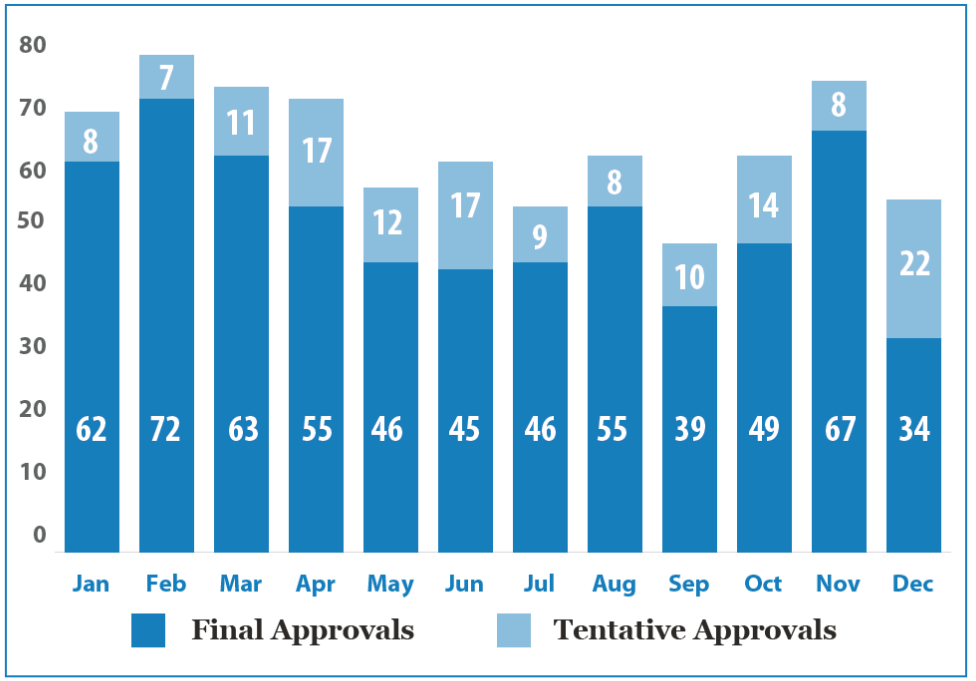
FDA research helped develop the framework by which we compared the Test and Reference devices

https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-commonly-used-albuterol-inhaler-treat-and-prevent-bronchospasm
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020503.pdf

Summary

- Complex products are an important class of drugs that currently lack generic competition
- The current challenge is to efficiently develop and approve complex generic drug products
- Regulatory science and research
  - provides essential input to the standard and policy development, application assessment, and post marketing activities
  - helps FDA be prepared to address future challenges

2021 Generic Drugs Approved and Tentatively* Approved



A tentative approval does not allow the applicant to market the generic drug product and postpones the final approval until all patent/exclusivity issues have been resolved.

2021:

- Approval of 633 generic drugs
- 14.7% first generics
- 14.2% of for complex generic drugs

https://www.fda.gov/drugs/generic-drugs/office-generic-drugs-2021-annual-report


FDA
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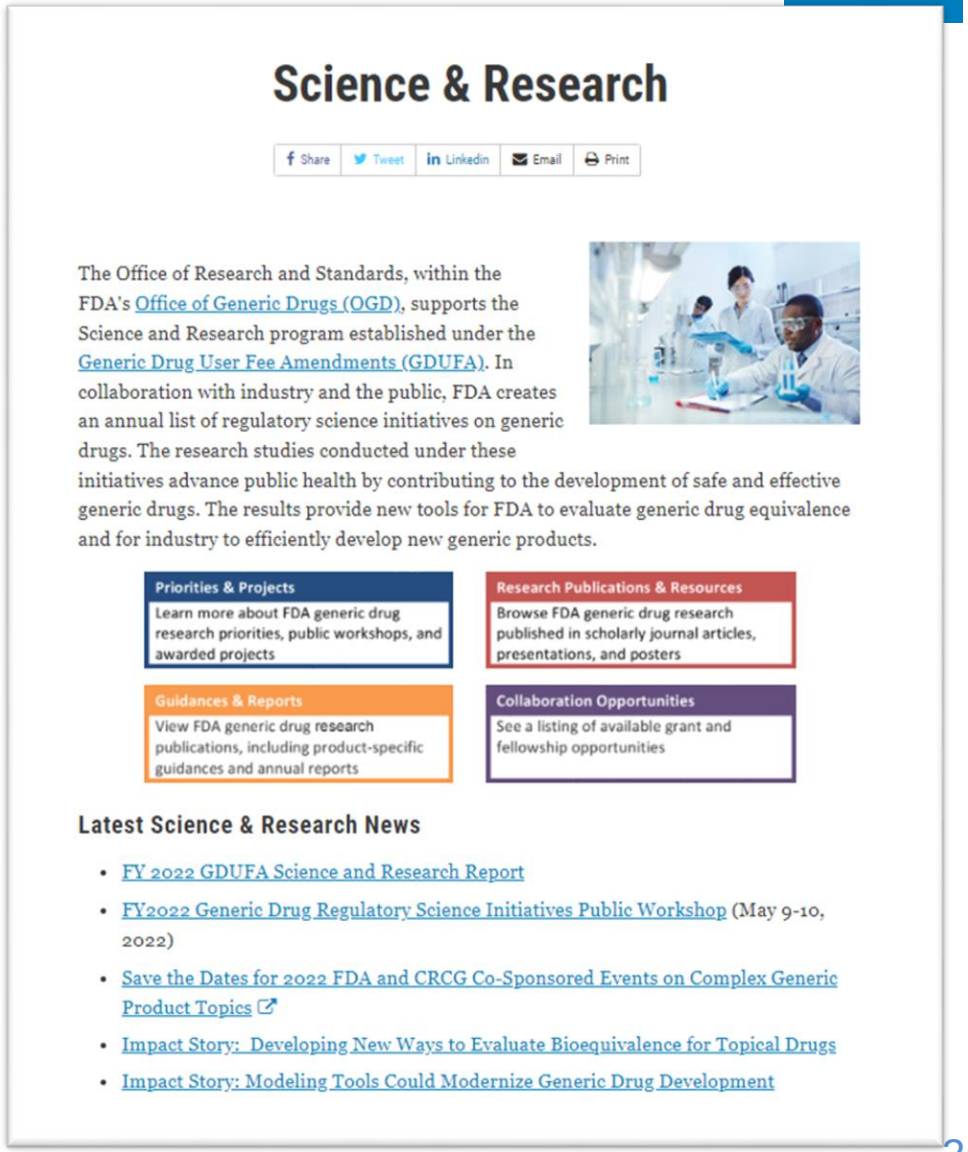
ADMINISTRATION

GDUFA Regulatory Science

- FDA's GDUFA Science & Research website is a valuable resource.
  - GDUFA Science and Research Reports that describe the annual research activities, progress, and outcomes
  - Links to OGD's past and upcoming Scientific Workshops & Meetings, Webinars, and Research News
  - Links to past GDUFA research contract and grant awards as well as open research funding opportunities and needs
  - List of FDA co-authored GDUFA-funded articles, presentations, and posters



Science & Research

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The Office of Research and Standards, within the FDA's Office of Generic Drugs (OGD), supports the Science and Research program established under the Generic Drug User Fee Amendments (GDUFA). In collaboration with industry and the public, FDA creates an annual list of regulatory science initiatives on generic drugs. The research studies conducted under these initiatives advance public health by contributing to the development of safe and effective generic drugs. The results provide new tools for FDA to evaluate generic drug equivalence and for industry to efficiently develop new generic products.

Priorities & Projects
Learn more about FDA generic drug research priorities, public workshops, and awarded projects

Research Publications & Resources
Browse FDA generic drug research published in scholarly journal articles, presentations, and posters

Guidances & Reports
View FDA generic drug research publications, including product-specific guidances and annual reports

Collaboration Opportunities
See a listing of available grant and fellowship opportunities

Latest Science & Research News

- FY 2022 GDUFA Science and Research Report
- FY2022 Generic Drug Regulatory Science Initiatives Public Workshop (May 9-10, 2022)
- Save the Dates for 2022 FDA and CRCG Co-Sponsored Events on Complex Generic Product Topics
- Impact Story: Developing New Ways to Evaluate Bioequivalence for Topical Drugs
- Impact Story: Modeling Tools Could Modernize Generic Drug Development

https://www.fda.gov/drugs/generic-drugs/science-research

Adapted from Kozak and Xu, SBIA, April 27, 2022

The Concepts of Q1, Q2, Q3

- Q1: Components in a product
  - Q1 characterization of a reference product provides a profile of the qualitative components (ingredients) in that reference product
- Q2: Composition of a product
  - Q2 characterization of a reference product provides a profile of the quantitative formulation composition of that reference product
- Q3: Arrangement of matter in a product
  - Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product

Q3 Characterization

1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
5. Characterization of rheological behavior
6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

Acyclovir (Cream, 5%) PSG

RLD: NDA 021478

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

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

I. In vitro option:

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

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf

Acyclovir (Cream, 5%) PSG

C. IVRT Comparison

1. The IVRT pivotal study comparing the acyclovir release rates between the test and RLD products should be performed in a manner compatible with the general procedures and statistical analysis method specified in the United States Pharmacopeia (USP) General Chapter <1724>, Semisolid Drug Products – Performance Tests. The cumulative amount of acyclovir released at each sampling time point should be reported for each diffusion cell, as well as relevant summary statistics for the IVRT study. Detailed study protocols and reports should be submitted in module 5.3.1 of the electronic Common Technical Document

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf