U.S. FOOD & DRUG ADMINISTRATION

Role of Regulatory Science in Generic Drug Development and Application Assessment

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GDUFA III Stakeholder Meeting
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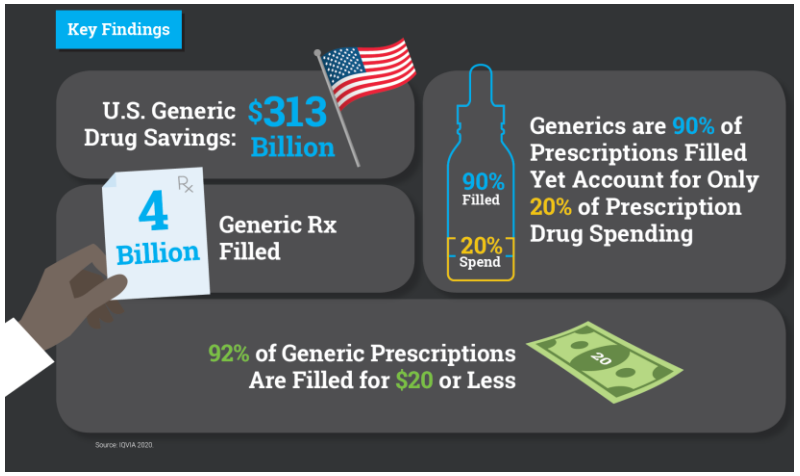
Generic Drugs in the United States

Generic Drugs:

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

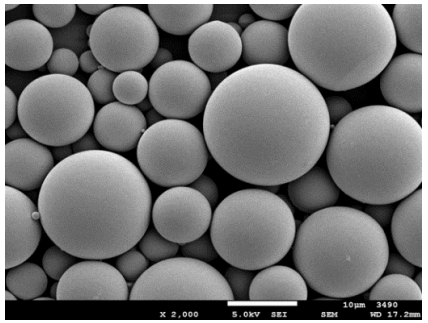
Overall Drug Products



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

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

Topical drug products with generics available < 40%

Ophthalmic products with generics available < 50%

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

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

Our Interest

- To improve access to high quality, affordable generic drugs to the American public
  - Improved access results from:
    - Reduced overall time to approval
    - 1st cycle approvals
    - Reduced number of review cycles to approval
- To meet all GDUFA requirements and commitments
- To work with ICH to develop harmonized standards for global development for generic drugs
  - Reduce financial and regulatory burdens to patient access worldwide
- To be responsive to FDA Commissioner on current landscape related to drug pricing and **Drug Competition Action Plan (DCAP)**

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
GDUFA: Generic Drug User Fee Amendments

Research Strategy for Generic Drugs

Scientific basis to demonstrate "Sameness"/Equivalence

PRE-GDUFA I

GDUFA I (FY2012-2017)

- Robust GDUFA "Regulatory Science Program"
- Modest size ($100M)
- ~100 grants/contracts
- Published ~800 product-specific guidance (PSGs), 40% for complex generic drug products
- Created Foundational Elements for GDUFA II

GDUFA I work provided the foundational elements and infrastructure for GDUFA II Pre-ANDA program

- "Pre-ANDA" meetings
- Timelines for PSGs after NDA approval

GDUFA II (FY2018-FY2022)

- Continue GDUFA Regulatory Science program
- Creates timelines to publish PSGs for non-complex new chemical entities (NCEs)
- Establishes Pre-ANDA program for **complex generic drug products**

GDUFA Regulatory Research

FDA committed to employ regulatory science initiatives for generic drugs based on 2012 GDUFA

FY14 Research Priorities

- Post-market Evaluation of Generic Drugs
- Equivalence of Complex Products
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

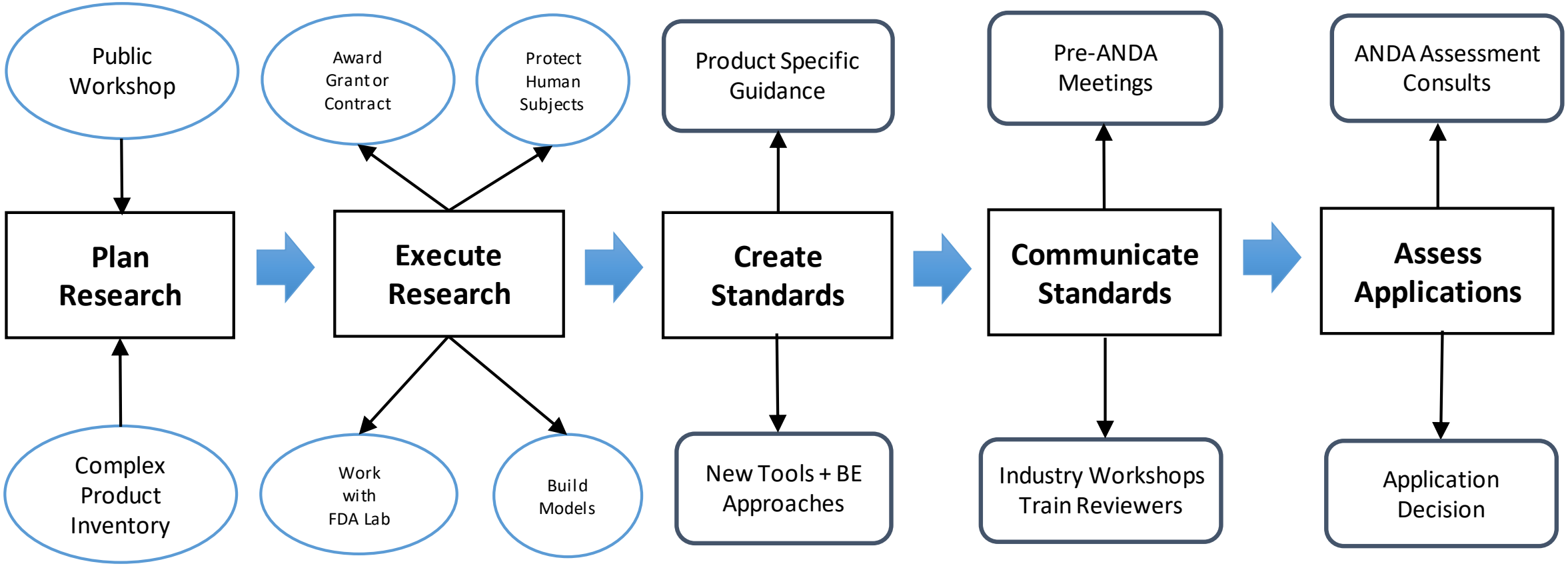
FY20 Research Priorities

- Complex active ingredients, formulations, or dosage forms
- Complex routes of delivery
- Complex drug-device combinations
- Tools and methodologies for bioequivalence and therapeutic equivalence evaluation

Complex Drug Products

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

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

Scale of Research

- >100 active projects
- ~20 new external grants or contracts/per year to leverage external expertise
- Large laboratory research within FDA
  - OPQ and OTS in CDER and other centers including CDRH nanocore and ORA
- Large quantitative methods and modeling program in OGD
- Human Subject Research Oversight in OGD

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

OTS: Office of Translational Sciences
CDRH: Center for Devices and Radiological Health
ORA: Office of Regulatory Affairs

GDUFA Research Areas

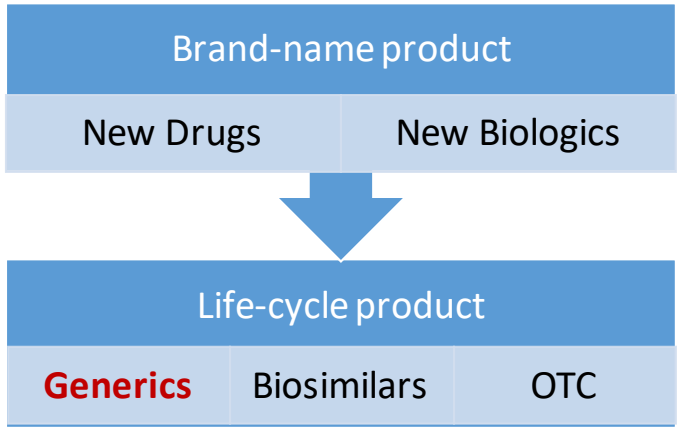
Bioequivalence of Locally Acting Products	Equivalence of Complex Products	Advanced Quantitative Methods	Therapeutic Equivalence
• Ophthalmic • Topical Dermatological • Inhalation and Nasal	• Complex Injectables, Formulations and Nanomaterials • Complex Mixtures and Peptides • Long-Acting Injectables 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

FY2019 GDUFA Research Report

https://www.fda.gov/drugs/generic-drugs/fy2019-gdufa-science-and-research-report

Overview of OPQ Research Programs

Supports:



1. Manufacturing Science and Innovation
2. Drug Quality Standards and Linkage to Clinical Performance
3. Advanced Characterization of Complex Molecules
4. Physicochemical Characterization of Complex Formulations and Dosage Forms
5. Post-Market Product Quality and Public Health Issues

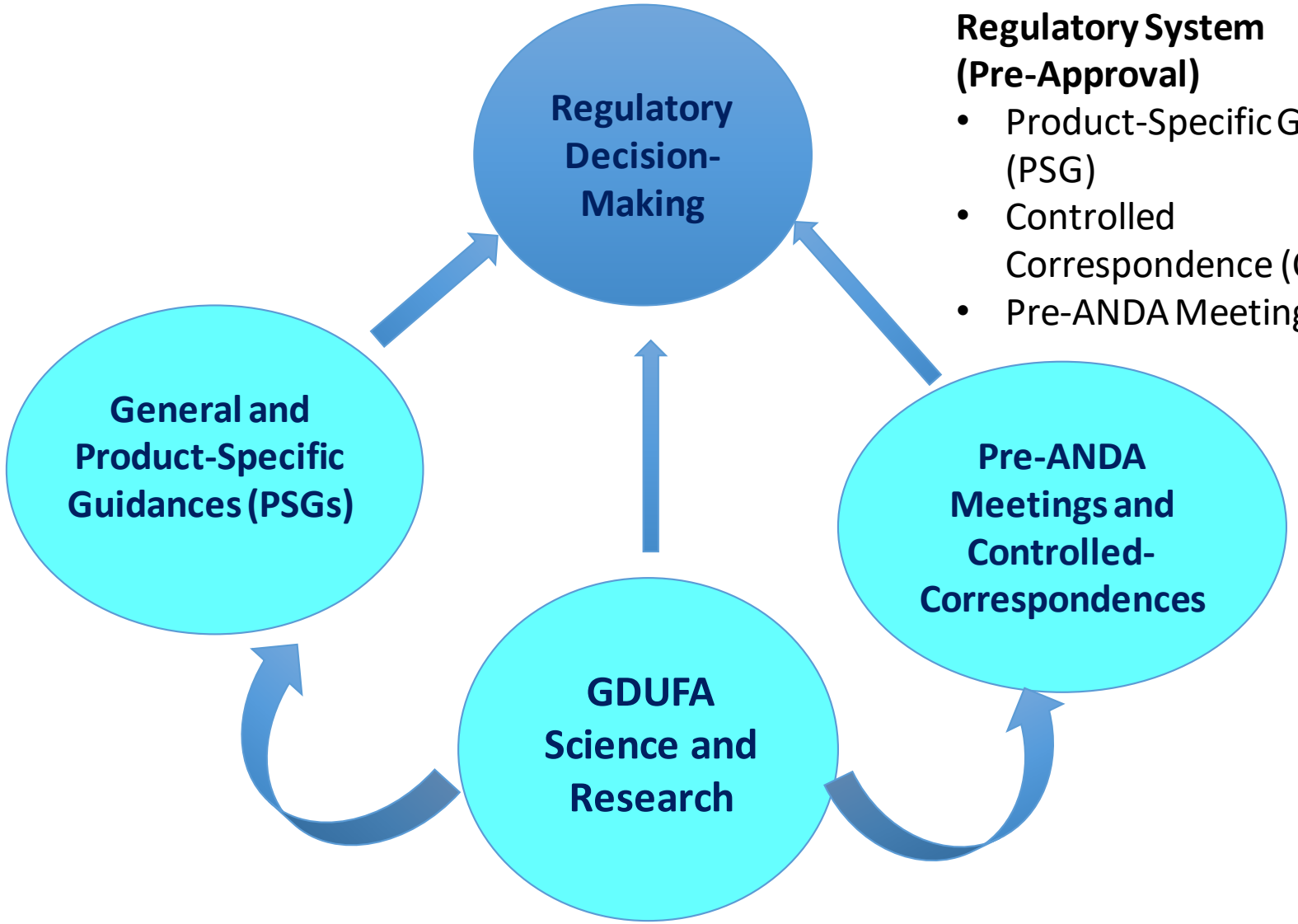
Role of Science and Research: Pre-Approval

Provide access to generic versions of complex products

- Bioequivalence, sameness and analytical challenges

Accelerate the development of generic products

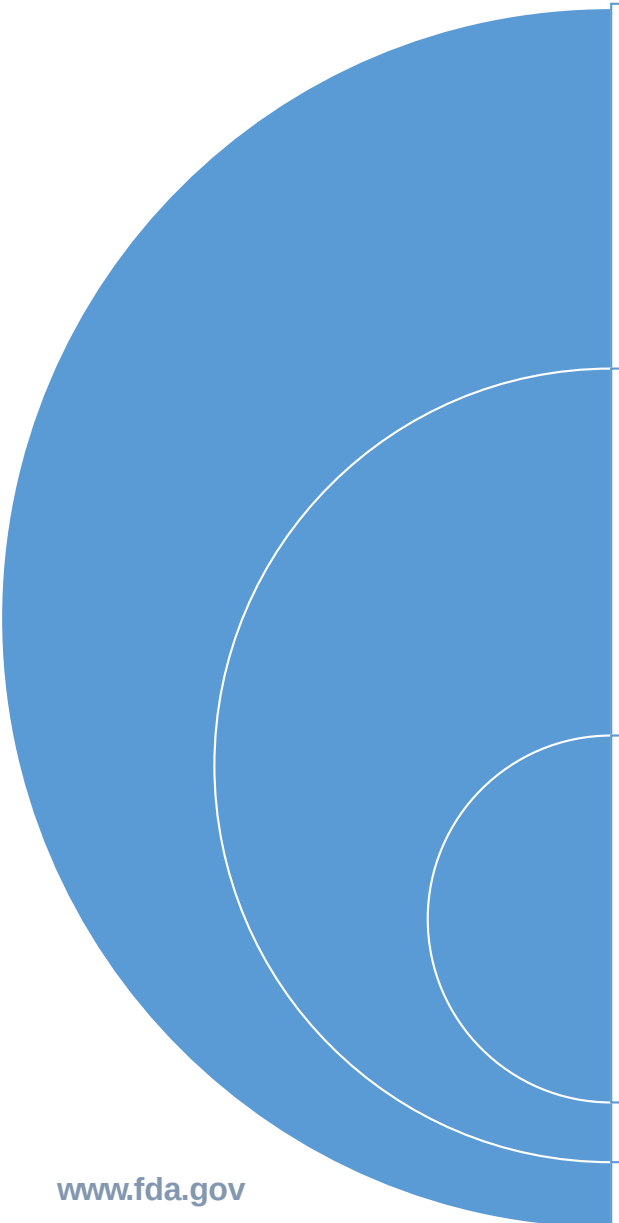
- More efficient ways to demonstrate equivalence



Regulatory System (Pre-Approval)

- Product-Specific Guidance (PSG)
- Controlled Correspondence (CC)
- Pre-ANDA Meetings

Role of Science and Research: Pre-Approval



Product-Specific Guidances (PSGs) Describing the Agency's current thinking and expectations on how to develop generic drug products	• ~1,900 are available • Stable reliable quarterly postings • 258 PSGs issued in FY2020 (104 are for complex products)
Controlled Correspondences (CCs) Inquires from prospective generic drug applicants during drug development	• Continue to increase • ~3600 in FY2020 • 40% are for complex products • 7% for "complex controls" (new in GDUFA II with 120 day goal date)
Pre-ANDA Meetings Meetings for FDA to provide guidance to prospective applicants for product development and other questions; mainly for complex products with no PSGs or with alternative bioequivalence (BE) approach than what's in PSGs	• New in GDUFA II • Use of the pre-ANDA meeting program continues to grow • >100 meeting requests in FY2020 • Pre-ANDA meetings support innovation in BE approaches

Role of Science and Research: Application Assessment

Leverage the Scientific Preparation to Use New Approaches in ANDA Assessment

For Example,

- Abuse-deterrent formulation (ADF) assessment for opioid products
- In vitro release test and in vitro permeation test assessment

Accelerate the Development of Generic Products

For Example,

- More efficient ways to demonstrate equivalence

Integration of Data Analytics and Quantitative Methods in ANDA Assessment

For Example,

- QSAR for pharm-tox screening
- Meta-analysis of BE study data
- Model-based BE

ANDA: Abbreviated New Drug Application

QSAR: Quantitative structure–activity relationship
BE: bioequivalence

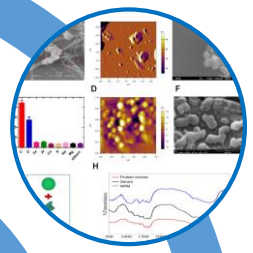
Examples of Key ANDA Approvals

- **Enoxaparin (generic Lovenox approval in July 2010)**
  - An anticoagulant that helps prevent the formation of blood clots
- **Glatiramer Acetate (generic Copaxone approval in Oct 2017)**
  - An immunomodulator medication currently used to treat multiple sclerosis
- **Fluticasone Propionate (FP)/Salmeterol Xinafoate (SX) Dry Powder Inhaler (generic Advair Diskus arppoval in Jan 2019)**
  - A drug-device combination product used to prevent asthma attacks. It is also used to prevent flare-ups or worsening of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis and/or emphysema
- **Albuterol Sulfate Metered Dose Inhaler (MDI) (generic Proventil HFA approval in Apr 2020)**
  - A drug-device combination product for the treatment or prevention of bronchospasm

FDA Research Enabled the Approval of Albuterol Sulfate MDI

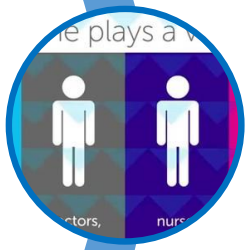
- The inhalers are widely used by people with asthma, but it's become more difficult to get them because they're being used to treat patients with COVID-19
- The U.S. FDA approved the first generic albuterol inhaler in April 2020 in response to inhaler shortages and increased demand caused by the coronavirus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

Role of Science and Research: Post-Approval

Maintaining confidence in generic drug substitution

- Clinical studies to demonstrate substitutability
- Substitution issues with device constituent parts

Responding to emerging issues

- Analytical methods for nitrosamines

Transition to advanced manufacturing for existing products

Robust and adaptive supply chain

Real-world Evidence from a Narrow Therapeutic Index Product (Levothyroxine) Reflects the Therapeutic Equivalence of Generic Drug Products

JAMA Network Open

JAMA Netw Open. 2020 Sep 30;3(9):e2017645. doi:10.1001/jamanetworkopen.2020.17645.

Original Investigation | Diabetes and Endocrinology

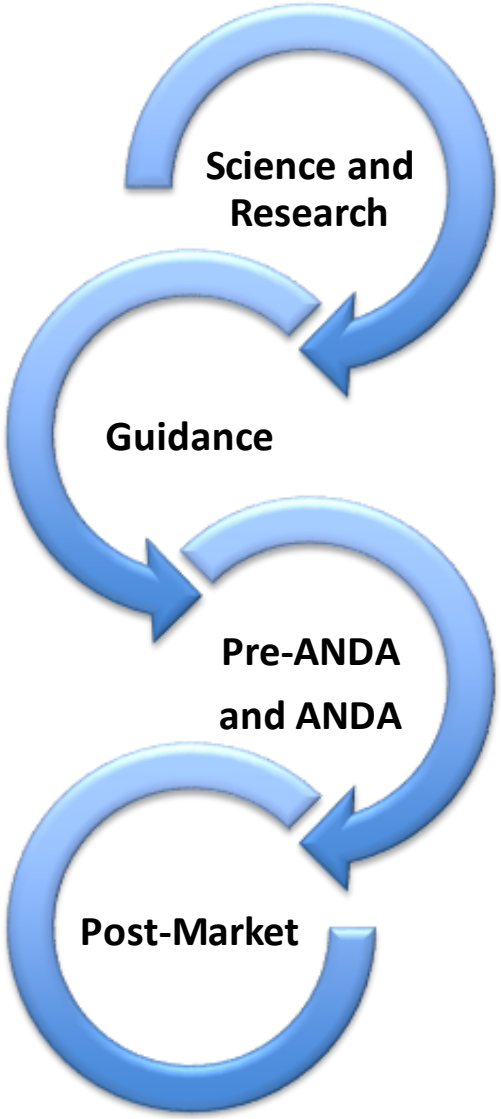
Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels

Juan P. Brito, MD, MSc; Joseph S. Ross, MD, MHS; Lindsey Sangaralingham, MPH; Sarah K. Dutcher, PhD; David J. Graham, MD, MPH; Zhong Wang, PhD; Yute Wu, PhD; Xiaoxi Yao, PhD; Robert C. Smallridge, MD; Victor Bernet, MD; Nilay D. Shah, PhD; Kasia J. Lipska, MD, MHS

Findings In a cohort study of 17,598 patients from a national administrative claims database, a similar proportion of generic vs brand-name levothyroxine users achieved target thyrotropin levels.

Meaning These findings suggest that initiation of generic or brand levothyroxine for mild thyroid dysfunction is associated with similar rates of achieving target laboratory outcomes.

GDUFA Science and Research Outcomes



- Website launched Oct 1, 2019; yearly update
  - GDUFA research supporting the development of generic drug products
  - GDUFA research supporting the generation of evidence needed to support efficient review and timely approval of ANDAs
  - GDUFA research supporting the evaluation of generic drug equivalence

FY2018 and FY2019 Research Outcome Supporting the Evaluation of Generic Drug Equivalence

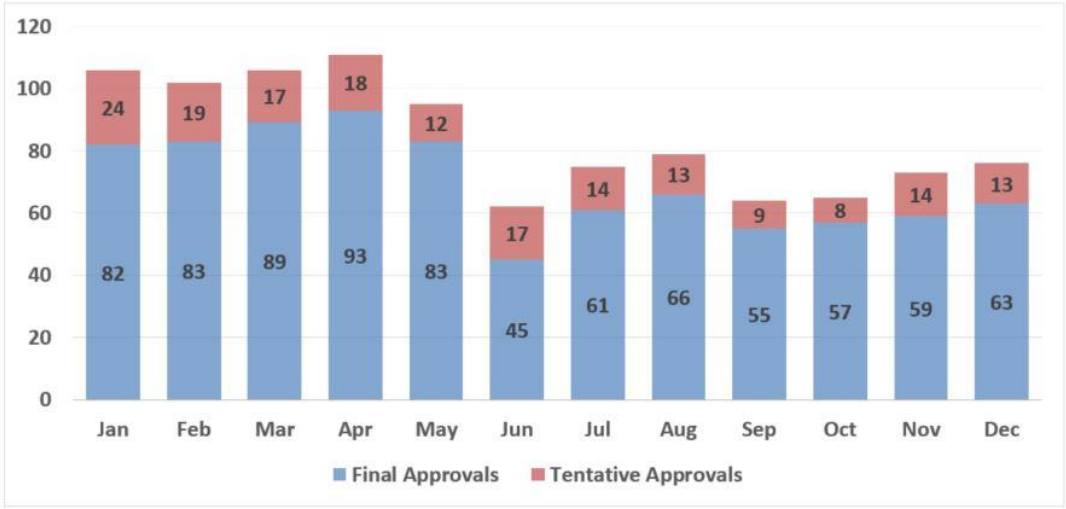
Outcome type	Number FY2018	Number FY2019
Number of pre-ANDA meetings impacted by research	32	52
Number of PSGs that provided new approaches to equivalence	36	27
Number of publications, presentations, and external posters that are relevant to this category	37	36

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports

Summary

- Complex products are important class of drugs that currently lack generic competition
- Moving complex products to ANDA approval is the current challenge
- 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

2019 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.

2019:

- Approval or tentative approval of 1,014 generic drugs
- 11% first generics (107)
- 11% of all generics approvals were for complex generic drugs (110)

https://www.fda.gov/drugs/generic-drugs/2019-office-generic-drugs-annual-report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