Overview of the GDUFA Science and Research Program

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2025 Generic Drug Science and Research Initiatives Public Workshop

Science and Research for Generic Drugs

- New drug programs have the gold standard in clinical trials
- In the generic program, we use pharmaceutical science and clinical pharmacology to identify what needs to be the same
  - so, we do not have to repeat clinical trials to provide access to competition.

Generic Industry Three Pillars

Oral Dosage Forms	Solutions (Topical/Injectable)	Complex Generics
56% of FY24 approvals **50% of FY24 submissions**	**31% of FY24 approvals** **31% of FY24 submissions**	**13% of FY24 approvals** **19% of FY24 submissions** 13% non-topical/transdermal
70% of FY04 submission	**20% of FY04 submissions**	**10% of FY04 submissions** 3% non-topical/transdermal

10 Years
10 Impacts on Complex Generics

- Generic DPI
- Q3 BE for Topicals
- PLG-based Generic LAI
- Generics of Recombinant Peptides
- PBPK Models for Locally Acting Products
- CFD models for Lung and Nasal Deposition
- User Interface Evaluation for Combination Products
- Complex Product Database
- 800 Pre-ANDA Meeting Requests since GDUFA II
- 300 Product Specific Guidance with Efficient Methods

GDUFA Science has been essential to establishing Complex Generics

Future Value of Research: To Consumers

Ten Complex Products without Generic Competition

TRELEGY ELLIPTA	FLUTICASONE FUROATE;UMECLIDINIUM BROMIDE;VILANTEROL TRIFENATATE	POWDER	INHALATION
WEGOVY	SEMAGLUTIDE	SOLUTION	SUBCUTANEOUS
BREZTRI AEROSPHERE	BUDESONIDE;FORMOTEROL FUMARATE;GLYCOPYRROLATE	AEROSOL, METERED	INHALATION
BREO ELLIPTA	FLUTICASONE FUROATE;VILANTEROL TRIFENATATE	POWDER	INHALATION
ANORO ELLIPTA	UMECLIDINIUM BROMIDE;VILANTEROL TRIFENATATE	POWDER	INHALATION
VENTOLIN HFA	ALBUTEROL SULFATE	AEROSOL, METERED	INHALATION
SAXENDA	LIRAGLUTIDE	SOLUTION	SUBCUTANEOUS
RYBELSUS	SEMAGLUTIDE	TABLET	ORAL
COMBIVENT RESPIMAT	ALBUTEROL SULFATE;IPRATROPIUM BROMIDE	SPRAY, METERED	INHALATION
MIRENA	LEVONORGESTREL	SYSTEM	INTRAUTERINE

- Total Estimated FY24 sales
  - $20 Billion/year
- All these products have complex scientific issues
- Total investment in GDUFA regulatory science
  - $25 Million/year

Future Value of Research: To Product Developers

- There will be no generic products that are not economically viable
  - Efficient regulatory systems leads to investment
    - Clarity on what studies are needed
    - Identifying the most efficient set of studies
    - PSG and pre-ANDA meetings
    - The predictability of the ANDA review process
  - Research has enabled a constant effort to reduce the regulatory burden by developing more efficient BE approaches

A Portfolio View

- Higher level than project view used to organize reporting
- FDA's FY2024 GUDFA research priorities
  - Available at https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects
- FY 2024 GDUFA Science and Research Report
  - Available at https://www.fda.gov/drugs/generic-drugs/fy-2024-gdufa-science-and-research-report

GDUFA Research Portfolio

- Impurities
- Complex Active Ingredients
- BE for Complex Routes of Delivery
- BE for Complex Dosage Forms and Formulations
- BE for Oral and Parenteral Generics
- Drug-Device Combination Products
- Quantitative Medicine
- Artificial Intelligence (AI) and Machine Learning (ML)

BE - bioequivalence

Today

- The portfolio is large and stable
- Each year we want to have a focused review of some subsections of the portfolio

Today

- Last Year sessions on
  - Impurities
  - Predictive Tools (Quantitative Medicine)
  - Drug-Device Combination Products
- This Year sessions on
  - Complex Active Ingredients
  - In Vitro Methods for Complex Generics
  - Efficiencies for IR and MR generic tablets and capsules

Today

- We are also listening for input on which product-specific guidances (PSGs) are the highest industry priorities
  - We have a forecast list for PSGs expected in the next year
    - https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development
  - We are most interested in input on PSGs that are not on the forecast list

Today

- I will give an overview of the entire portfolio and how it is essential to efforts on drug pricing and competition
- I hope this will stimulate discussion
- Project level details are in the FY2024 research report

Impurities

- Goal
  - Tools to efficiently evaluate and mitigate the risk of potential harmful impurities
- Areas of Focus
  - Nitrosamine-related compounds
- Key Accomplishment
  - Anti-oxidants can reduce certain impurities
  - Scientific foundation for minimizing BE studies for reformulations that add anti-oxidants to reduce potentially genotoxic impurities
    - In September 2024, the FDA issued revision 2 of their Guidance for Industry on the “Control of Nitrosamine Impurities in Human Drugs”
    - Less BE data needed for BCS 1 2 3 drug products based on research
    - BCS 4 current frontier

Complex Active Ingredients

- Goal
  - Methods to characterize complex active ingredients and their immunogenicity risk
- Areas of Focus
  - Peptides
    - ~10% of products have generic competition
    - Surge in ANDA submissions
  - Oligonucleotides
    - No generics
- Key Accomplishment
  - FY25: First generic approval for liraglutide
  - FY24: October 2024, CRCG workshop on Immunogenicity

Complex Dosage Forms and Formulations

- Goal
  - Efficient characterization-based (in vitro) BE approaches for **systemically acting** complex dosage forms
- Areas of Focus
  - Long-acting injectables and implants
    - Only 4 of 39 active reference products have generic competition
  - Liposomes and iron colloids
- Key Accomplishment
  - Multiple generics for PLGA based products
  - In vitro BE for drug substance suspensions

Complex Routes of Delivery

- Goal
  - Efficient characterization-based (in vitro) BE approaches for **locally acting** complex dosage forms
- Areas of Focus
  - Inhalation
    - Few MDI and DPI ANDAs => Support alternatives to FEV1 clinical study
    - Transition to new propellants
  - Topical
    - non-Q1Q2 formulation BE methods
    - Implementation of IVPT/IVRT
  - Ophthalmic and Otic
    - Studies to support Q2 changes and Q1Q2 waiver requests
    - Long-acting ophthalmic implants (no generics)
  - Nasal
  - GI-acting
- Key Accomplishment
  - PSG for all inhalation products have alternative to clinical endpoint BE studies
  - FY24, 20 topical product ANDAs approved via Q3 methods

Drug-Device Combination Products

- Goal
  - Methods to evaluate the impact of differences in the device constituent part compared to the reference listed drug
- Areas of Focus
  - Role of Human Factors studies in ANDA evaluation
    - Alternatives to evaluate user interface differences
  - Transdermal Systems
- Key Accomplishment
  - Complete first human factors study under IDIQ (Barrel Extension)
  - Updates to sensitization studies for transdermal systems

BE for Oral and Parenteral Generics

- Goal
  - More efficient BE evaluations via waiver expansions and global harmonization
- Areas of Focus
  - M13 Implementation
  - Strength “waivers” for modified-release (MR) products
- Key Accomplishment
  - M13 finalization and implementation in 2024
  - 814 updated PSG
  - Estimated 200 fed BE studies/year are now not recommended

Quantitative Medicine

- Goal
  - Predictive models to support more efficient BE evaluations across product categories
- Areas of Focus
  - PBPK for local routes of delivery
  - Model-integrated evidence (MIE) for long-acting injectables
  - Oral Absorption models for waiver evaluations
- Key Accomplishment
  - MIE meeting pilot has been used
  - Model Master File (MMF) process exists

AI/ML

- Goal
  - Develop AI/ML methods which FDA can use to improve the efficiency and consistency of scientific assessments and advice
- Areas of Focus
  - AI driven model development and validation for QM
  - Agent based work-flows for high reliability
  - Retrieval methods for whole application reliability
- Key Accomplishment
  - Automation of maximum daily dose determinations

What about the Next 10 Years?

- Complex Generics
  - Bigger percentage of OGD work
  - Bigger value for industry
  - More meetings/interactions
  - Implementing novel methods with Center for Complex Generics
  - Drug Device Combinations
- Quantitative Medicine
  - More efficient studies (MIE pilot)
  - Model Master Files
  - PK data warehouse
  - Use Quantitative Medicine to reduce unneeded studies or making in vitro BE limits clinically relevant for complex generics
  - Prediction for pediatric populations not used in BE studies

What about the Next 10 Years?

- Non-complex Generics
  - More biowaivers
  - Non Q1-Q2 injectables
  - Global harmonization
  - Confidence in commodity products
  - Robustness to shortages
- Artificial Intelligence
  - Review transformation
  - Faster model building
  - Data foundation and open environments

Summary

- Without a scientific foundation, there would not be generic competition

- We look forward to your input as we refine and focus our research portfolio to accelerate access to safe and effective generic products!


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