U.S. FOOD & DRUG ADMINISTRATION

Complex Generics 2022 Update

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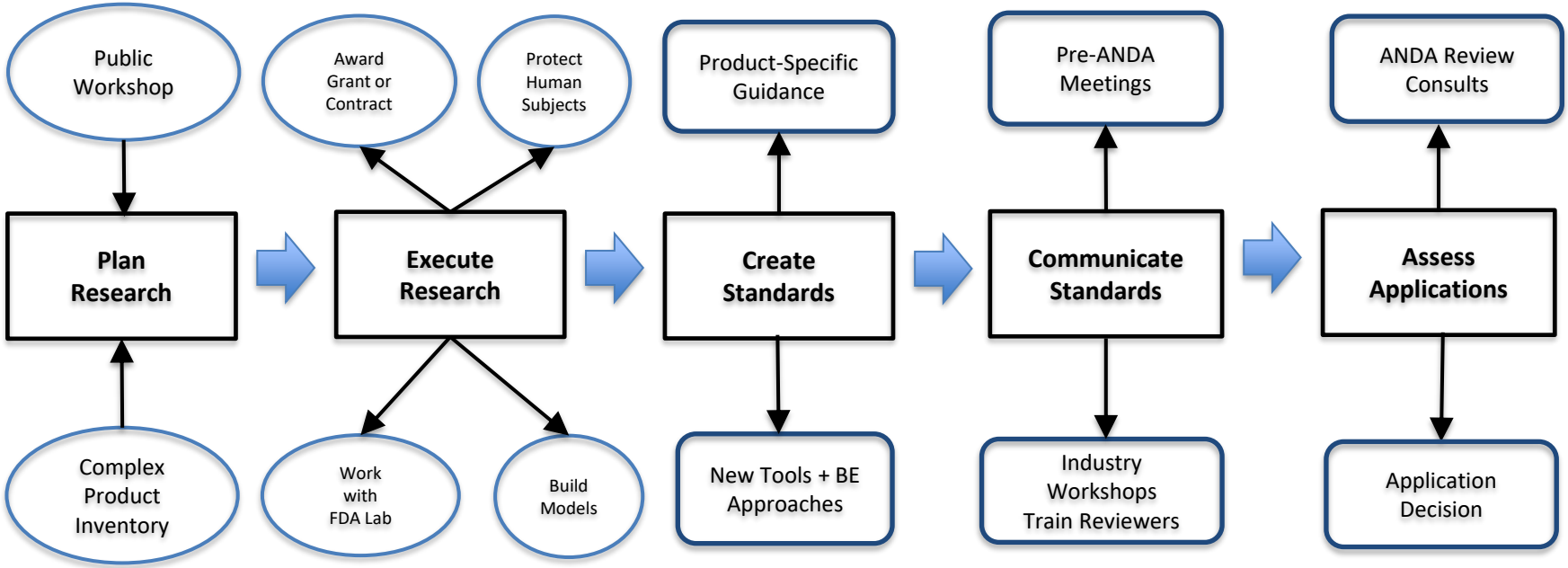
Integrated Pre-ANDA System Operational Model



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ANDA: abbreviated new drug application

Scale of Research

- Stable investment supports internal and external research activities
  - >100 active projects
  - ~20 new grants or contracts/per year to leverage external expertise
- Input from industry via public meeting and FDA-Industry meetings helps direct focus of the research program

- Publications

FY	Publication (peer reviewed / presentation)
2018	67/157
2019	79/136
2020	74/110
2021	72/169
2022	76/122

- Workshops

FY	Workshops
2018	8
2019	5
2020	5
2021	8
2022	8

GDUFA Science and Research Report

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

Unique Features of GDUFA Research

- Tight integration between research and scientific advice to generic applicants
  - Product-Specific Guidance
    - Written by staff doing research
  - Pre-ANDA Meetings
    - Led by staff doing research
- Focus on complex generics

Product-Specific Guidance (PSGs)

- ~2029 PSGs are available
- FY 2022
  - 177 PSGs: 110 New, 67 Revised
    - 39 new PSGs and 20 revised PSGs for complex products
- FY 2021
  - 131 PSGs: 72 New, 59 Revised
    - 26 new PSGs and 26 revised PSGs for complex products
- FY 2020
  - 258 PSGs: 108 New, 150 Revised
    - 30 new PSGs and 94 revised PSGs for complex products
- FY 2019
  - 252 PSGs: 107 New, 145 Revised
    - 24 new PSGs and 117 revised PSGs for complex products
- FY 2018
  - 208 PSGs: 136 New, 71 Revised
    - 55 new PSGs and 19 revised PSGs for complex products

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- Key Trends
  - Stable reliable quarterly postings because of GDUFA goals for non-complex new chemical entities (NCEs)
  - GDUFA II steady production of new PSGs for complex products
  - FY2022 saw ~20 new or revised PSGs that provided a more efficient BE approach
  - FY2023 topical batch added 80 PSGs separate from quarterly posting

Product-Specific Guidance (PSGs)

FY	Innovation Index
2022	20
2021	20
2020	32
2019	28
2018	34

- Innovation Index
  - New or revised PSGs that provided a more efficient bioequivalence (BE) approach
  - Topical Batch was posted in FY2023
    - 28 innovative PSGs for FY23 already

Controlled Correspondences (CC)

- CC Submissions Stabilize
  - FY2022: 4,014
  - FY2021: 4,025
  - FY2020: 3,641
  - FY2019: 3,206
  - FY2018: 2,936
  - FY2017: 2,668
  - FY2016: 1,884
  - FY2015: 1,677
- Analysis
  - ~40% of controls are about complex products
  - ~7% of controls are “complex controls” with 120-day goal date
  - ~100 controls/year provided feedback on comparative analysis for combination products

Pre-ANDA Meetings

FY	Pre-ANDA Meeting Requests
2022	134
2021	124
2020	103
2019	112
2018	83

- Use of the pre-ANDA meeting program continues to grow
  - GDUFA I: 27 in the last year
- FDA has exceeded all GDUFA II goals related to pre-ANDA meetings
- Pre-ANDA meetings support innovation in BE approaches

Complex ANDA Approvals

- Percent of Full ANDA approvals that are complex products
- FY2022: 13%
- FY2021: 13%
- FY2020: 13%
- FY2019: 13%
- FY2018: 13%
- FY2017: 12%

- ~25% of reference listed drug products are complex
- At parity, complex generic activity will be double what it is now

Complex ANDA Submissions

- Percent of ANDA submissions that are complex products
- FY2022: 16%
  - 13% had Pre-ANDA meeting
- FY2021: 17%
  - 14% had Pre-ANDA meeting
- FY2020: 15%
  - 16% had Pre-ANDA meeting
- FY2019: 14%
  - 9 % had Pre-ANDA meeting
- FY2018: 14%
  - 3% had Pre-ANDA meeting
- FY2017: 14%
  - 4% had Pre-ANDA meeting

- Submissions are ahead of approvals
- ~25% of reference listed drug products are complex
- At parity, complex generic activity will be double what it is now
- ANDAs that used the pre-ANDA meeting process have quadrupled in GDUFA II

Access Index

- Definition
  - % of active NDAs (listed in the active section of the Orange Book) with an equivalent product approved
- All non-complex
  - 50% have generics
    - Other
      - No interest
      - Pending application
      - Patent or exclusivity
- All complex products
  - 35% have generics
- Non-topical complex products
  - 27% have generics

Topical Dermatological Products

- Four type of BE approaches (non-solutions)
  - Older products (AT rated in Orange Book)
    - No BE studies but some characterization focus on pharmaceutical equivalence
  - Vasoconstrictor Pharmacodynamic BE studies
    - Only for Corticosteroids
  - Comparative Clinical Endpoint BE studies
    - In patients
  - Q3 or in vitro BE studies
    - Include comparative characterization, IVRT and IVPT depending on the product

Topical Dermatological Products

ANDA Approvals

Study	FY18	FY19	FY20	FY21	FY22
VASO	22	20	18	4	3
AT	18	15	11	8	3
Clinical BE	13	26	7	9	13
Q3 based	3	12	4	9	9

ANDA Submissions

Study	FY18	FY19	FY20	FY21	FY22
VASO	25	12	7	4	0
AT	10	11	10	4	1
Clinical BE	11	10	11	5	1
Q3 based	7	11	25	33	17

GDUFA Science and Research Creating Competition and Growth

Pre-GDUFA

- Vasoconstrictor assays and older AT rated products support most generics
- Most other generic topical products supported by comparative clinical endpoint BE studies (500+ subjects common)
- 2012 six ANDA approvals supported by CEBE

GDUFA I

- Science and research on in vitro BE approaches begins

GDUFA II

- PSG and pre-ANDA meetings on product specific in vitro approaches

Current State

- Oct 2022: Three general guidances on in vitro approaches and 80 PSG updates posted
- Past three years of ANDA submissions
  - 16 Comparative clinical endpoint BE studies
  - 75 Q3 BE submissions
- Science and research investment created new business opportunities and expanded generic competition

GDUFA III

- New mechanisms to accelerate assessments of complex generic submissions

Inhalation: DPI and MDI

	FY18	FY19	FY20	FY21	FY22
Submitted ANDA	3	1	6	2	1
Approved ANDA	0	1	3	2	2

No ANDA approvals in GDUFA I

Access Index: 4/36 (11%) of active MDI/DPI NDAs have approved generics

- 2019: ANDA 208891
  - Fluticasone Propionate; Salmeterol Xinafoate inhalation powder
  - First generic DPI
- Dec 2021: ANDA 213948
  - Fluticasone Propionate; Salmeterol Xinafoate inhalation powder
  - Continue to provide generic inhalation products, third generic
- Dec 2021: ANDA 211699
  - Budesonide; Formoterol Fumarate Dihydrate Aerosol Metered
  - First generic
  - non-Q1Q2 inhalation product

Key Research Priority: Efficient BE approaches

Advice: Discuss combined in vitro, PK and modeling approaches at pre-ANDA meetings

Complex Peptides and Oligonucleotides

	FY18	FY19	FY20	FY21	FY22
Submitted ANDA	2	6	4	16	13
Approved ANDA	3	1	0	2	3

- Dec 2020: ANDA 208086
  - Glucagon injectable
  - first synthetic peptide referencing recombinant

Peptide Access Index: 41 active NDA with generics for 10% of them

Key Scientific Challenge: Methods for peptide immunogenicity

Key Emerging area: New approvals for oligonucleotide-based drugs 0% with generics

Key Scientific Challenge: Characterization of oligonucleotide products

Complex Injectables and Ophthalmics (non-solutions)

	FY18	FY19	FY20	FY21	FY22
Submitted ANDA	14	23	24	29	19
Approved ANDA	12	9	5	11	13

Non-LAI Access Index: 27%
LAI Access Index: 2/56 3.5%

Key Scientific Challenge: Long-acting injectables (LAI) and implants

Use pre-ANDA meetings to discussion material science/characterization, IVIVC and model-based BE study designs

- Feb 2022: ANDA 205894 (Cyclosporine Ophthalmic Emulsion)
  - First generic
  - Novel in vitro approach
- Jan 2021: ANDA 212514 (Amphotericin B)
  - First generic
  - PK in healthy subjects, difference from previous PSG recommendation (patients)

Center for Complex Generics

- FDA awarded a Center for Research on Complex Generics (CRCG)
  - Grant to the University of Maryland and the University of Michigan
  - http://www.complexgenerics.org/
- Enhance research collaborations with the generic industry to further the FDA's mission of increasing access to safe and effective generic medicines
  - Collaborative research, training, and exchange of resources
  - Three workshops in FY2022
  - Aggregated industry input for research prioritization
  - Focus on implementation of new approaches in ANDA submissions

Parallel Scientific Advice (PSA) Pilot

- The pilot established a new PSA process for complex generic drugs (FDA)/hybrid products (EMA)
- Launched September 15, 2021
- First Meetings: Sept 2021 and Sept 2022
- The PSA General Principles document can be accessed via the "Global Generic Drug Affairs" website
  - https://www.fda.gov/drugs/generic-drugs/global-generic-drug-affairs

Summary

- The Pre-ANDA system provides clarity and improves development efficiency
- For complex products, research provides an essential input to the pre-ANDA system
- Pre-ANDA interactions support innovative approaches to BE that can accelerate access to generics

Thanks! For GDUFA II

- To the hundreds of staff across CDER in OGD, OPQ, and OTS/DARS, and other offices that contributed to the research, PSG, and pre-ANDA meetings
- To the enumerable CDER staff who participated in the ANDA reviews of complex generics
- For more details
  - https://www.fda.gov/drugs/generic-drugs/science-research

GDUFA FY2023 Research Priorities

- Develop Methods for Generics to Address Impurities such as Nitrosamines
- Enhance the Efficiency of BE Approaches for Complex Active Ingredients
  - Oligonucleotides and Immunogenicity
- Enhance the Efficiency of BE Approaches for Complex Dosage Forms and Formulations
  - Long Acting Injectables and implants
- Enhance the Efficiency of BE Approaches for Complex Routes of Delivery
  - Inhalation
  - Non Q1Q2 topicals and IVPT
- Enhance the Efficiency of BE Approaches for Complex Drug-Device Combination Products
  - Device comparisons
  - Environmentally friendly propellants
- Improve the Efficiency of BE Approaches for Oral and Parenteral Generic Products
  - Non Q1Q2 parenteral
  - Harmonization of fed BE
  - Expand biowaivers waivers (PBPK)
- Facilitate the Utility of Model-Integrated Evidence (MIE) to Support Demonstrations of BE
  - Long Acting Injectables and inhalation
  - Model Master Files
- Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools
  - Surveillance
  - Operations

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects/

Moving to GDUFA III

- Moving complex generics to approval as an action focus
- This was an important mutual goal for FDA and Industry in the GDUFA III negotiations

Moving to GDUFA III

- Targeted to enhance communications around complex generics before applications have been submitted
  - Product-Specific Guidance for Complex Generics
    - Most will be available within 3 years of NDA approval
    - More clarity on the key ‘sameness factors’

Moving to GDUFA III

- Targeted to enhance communications around complex generics before applications have been submitted
  - Pre-submission Meeting
    - Use this when you do new or unique studies for complex generics (following a product development meeting)
    - Information shared will help FDA form an assessment team early and coordinate between product development meeting and application assessment

Moving to GDUFA III

- Targeted to enhance communications around complex generics after applications have been submitted
  - Post-CR Scientific Meeting
    - After you receive a Complete Response (CR)
    - Use this when you need to do new and different studies for complex generics
    - Get advice before doing them
    - Pre-Oct 1 CR can request this meeting

Moving to GDUFA III

- Targeted to enhance communications around complex generics after applications have been submitted
  - Enhanced Mid-cycle Meeting
    - Use this when you think scientific advice will aid a response to a deficiency in this (extended) cycle
    - ANDAs found acceptable for filing on or after October 1. 2022 can request this meeting

Moving to GDUFA III

- Targeted to enhance communications around generics impacted by PSG changes
  - Product-Specific Guidance Teleconferences
    - Use this when a PSG change impacts in vivo studies
      - Get immediate feedback on the impact to your development program if your in vivo studies have already begun

Moving to GDUFA III

- Targeted to enhance communications around generics impacted by PSG changes
  - Product-Specific Guidance Meeting
    - Use these as a follow up to the PSG teleconference
      - Get scientific advice when you want to do something different from the new PSG

Summary

- Advances in science and research provide opportunities for growth in the generic space
- A growing generic sector is how to increase access to medicines delivered via complex products
- GDUAFA III improvements are intended to help move complex applications through the assessment process more efficiently


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