Update on GDUFA Science and Research

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Office of Generic Drugs | CDER | U.S. FDA

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

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The FDA makes sure generic and brand-name drugs are *equivalent*

- Same medicine (active ingredient)
- Same action in the body
- Same quality standards

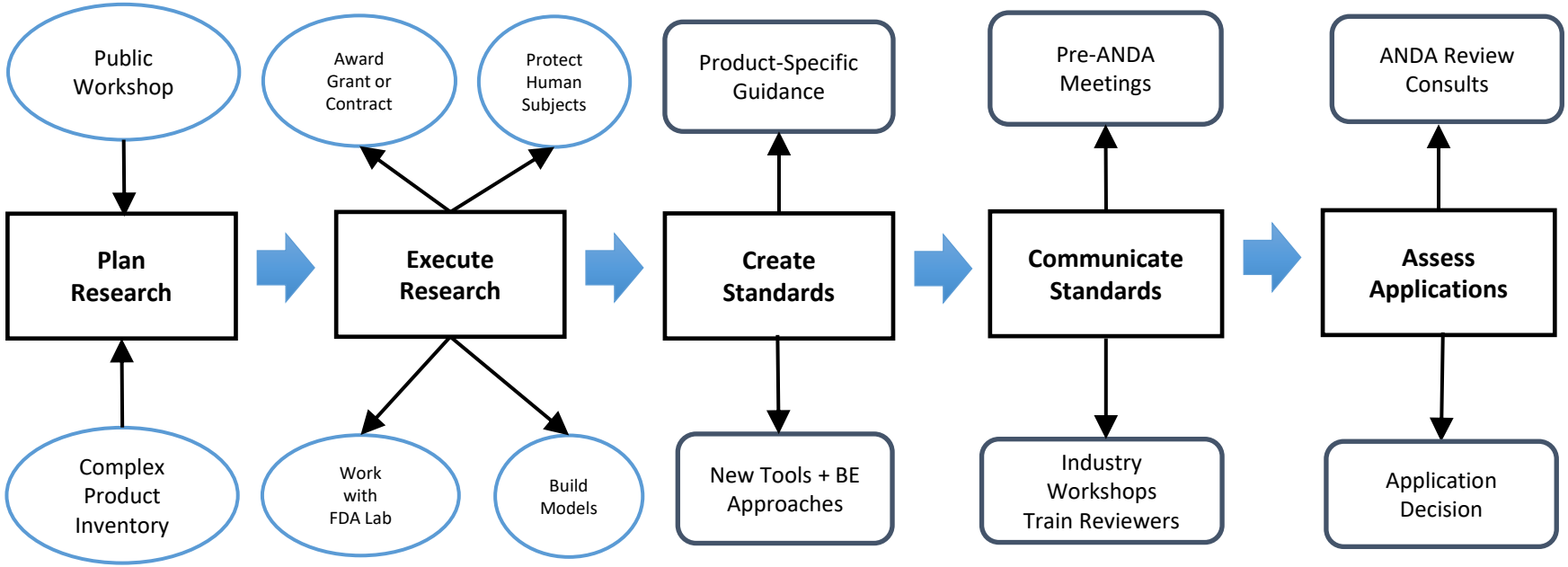
Generic drugs **increase access**

- **More treatment choices**
- **More competition**
- **Lower cost**

Impact of Generic Drug User Fee Amendments (GDUFA) Research

- FDA's research on complex generics helps the development of more generic competition in areas where bioequivalence (BE) evaluation is scientifically challenging
- FDA's research helps to make generic drug development and review more efficient

Integrated Pre-ANDA System Operational Model



The Office of Research and Standards (ORS) is a multidisciplinary **Office** that plans and conducts **Research** and translates the results into generic drug **Standards**

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)
2017	46/98
2018	65/152
2019	74/128

- Workshops
  - 12 GDUFA II Workshops
- Research supports product-specific guidance (PSG) development for complex products

Scale of Product-Specific Guidances (PSGs)

- ~1,900 PSGs are available
- Stable reliable quarterly postings because of GDUFA goals for non-complex new chemical entities (NCEs)
- FY 2019
  - 252 PSGs: 107 New, 145 Revised
    - 24 new PSGs and 117 revised PSGs for complex products
- FY 2020
  - 258 PSGs: 108 New, 150 Revised
    - 30 new PSGs and 94 revised PSGs for complex products

- Key Trends
  - GDUFA II steady increase in PSG activity for complex products
  - FY2019 saw ~30 new or revised PSG that provided a more efficient BE approach
  - FY2020 saw ~32 new or revised PSG that provided a more efficient BE approach
  - Maintenance costs
  - No GDUFA goals related to complex PSG issuance

Scale of Controlled Correspondences (CC)

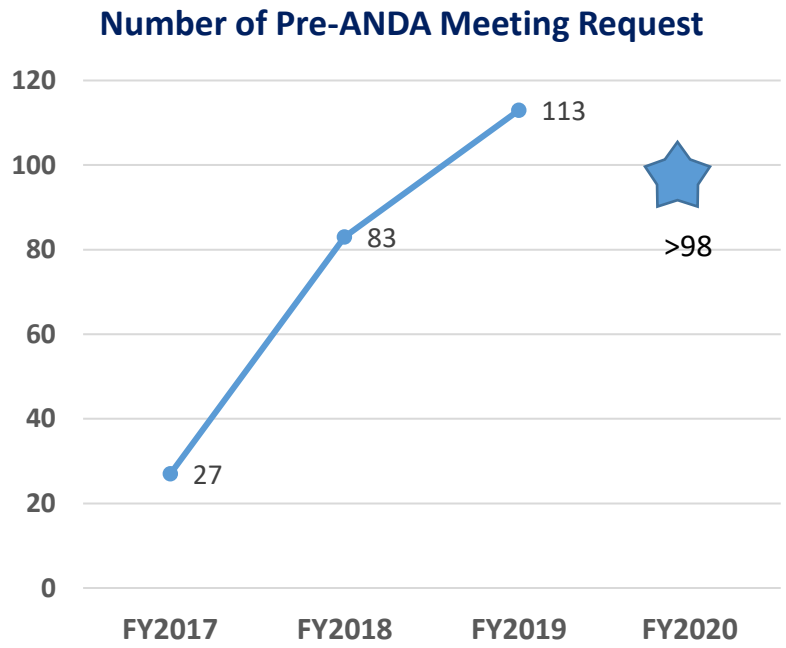
- CC continue to increase
  - FY2020: >3,476 est. 3,600
  - FY2019: 3,206
  - FY2018: 2,936
  - FY2017: 2,668
  - FY2016: 1,884
  - FY2015: 1,677
- Analysis
  - ~40% of controls are about complex products
  - ~7% of controls are “complex controls” with 120 day goal date

Scale of Pre-ANDA Meetings

- FY2020: >106 pre-ANDA meeting requests
- FY2019: 113 pre-ANDA meeting requests
- FY2018: 83 pre-ANDA meeting requests
- FY2017: 27 pre-ANDA meeting requests

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

Scale of Pre-ANDA Meetings



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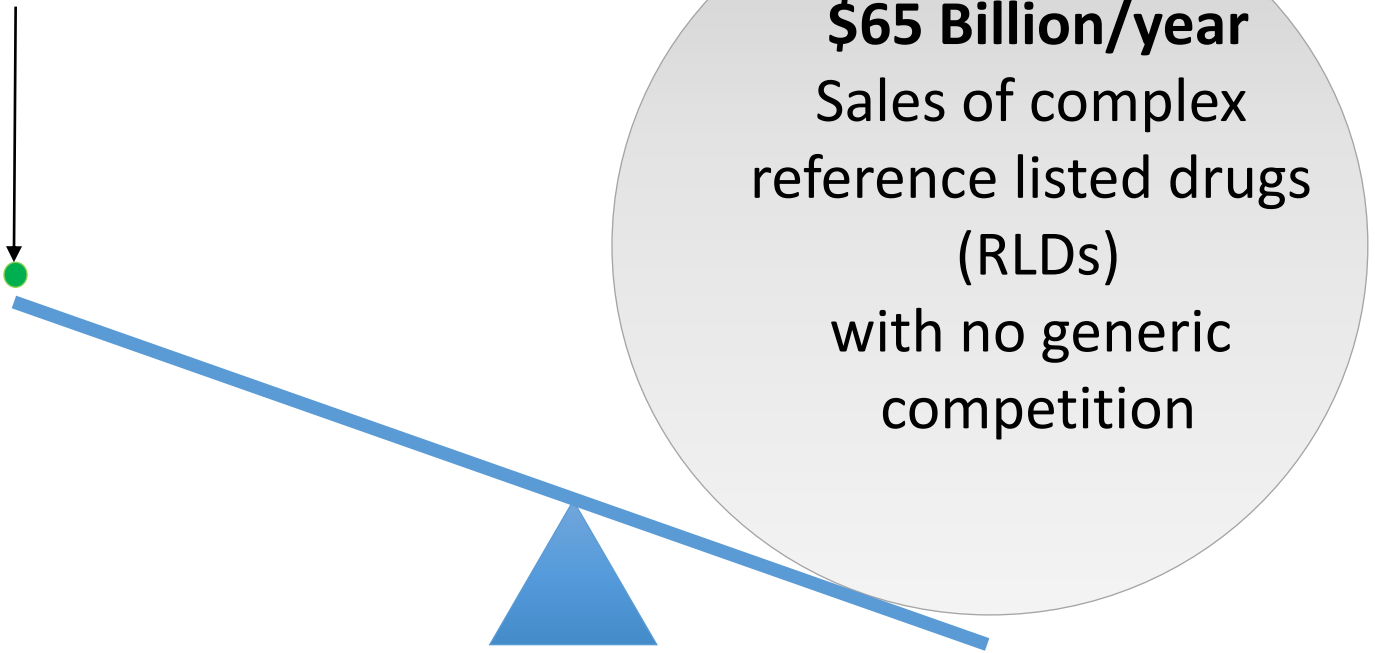
Return on Pre-ANDA Research Investments

Pre-ANDA program
(~$25 Million for research)



$65 Billion/year
Sales of complex reference listed drugs (RLDs) with no generic competition

Example: Public Priorities for Complex Routes of Delivery

- Expand characterization-based BE methods across all topical dermatological products
- Expand characterization-based BE methods across all non-solution ophthalmic products
- Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) comparative clinical endpoint BE studies for inhaled corticosteroids
- Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products that are more predictive of and sensitive to differences in local delivery

Found at https://www.fda.gov/media/132370/download

Success!: Complex Routes of Delivery

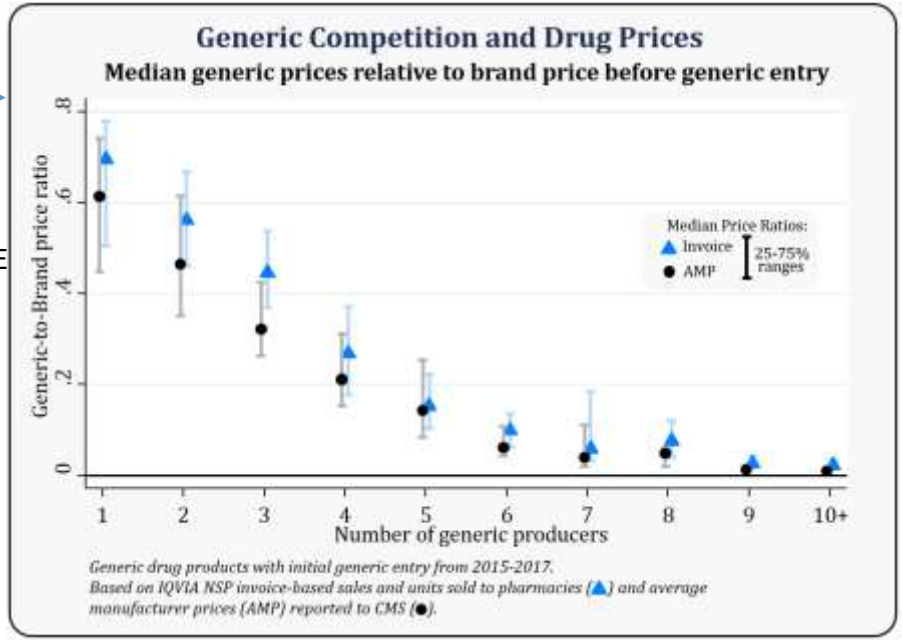
- For all of these areas our research investments have been successful!
  - There are scientifically sound alternatives to comparative clinical endpoint BE studies that are generally applicable for all of these areas
  - Alternatives are appearing in our product-specific guidances, general guidance and being discussed in pre-ANDA meetings

Future Research for Complex Routes of Delivery

- Still have work to do
  - Some alternatives are limited to very similar formulations
  - Details of implementation
    - Best analytical tools for specific classes of products
    - Appropriate acceptance limits for T to R comparisons (use Physiologically Based Pharmacokinetic (PBPK) models)
  - We continue to research what is needed to efficiently and broadly implement these new approaches to bioequivalence

Return on Research Investment to the Public Depends on Successful ANDAs

Topical dermatological products with clinical endpoint BE ($20M study) often attract zero or one competitor



After 2012,PSG for Acyclovir Ointment with in vitro BE recommendation

13 approved ANDA

Savings to health care system
80% of pre-generic spend

Raney S and Luke M, *J Am Acad Dermatol.* 82 (6), 1570-1571, 2020

Keys to Success for Complex Generics

- Understanding why the RLD is complex
- Monitor and use new science
- Mapping the regulatory landscape and its interaction with science
  - Guidances and Citizen Petitions
  - Recent changes for combination products
- Use the pre-ANDA program
- Monitor changes in the RLD and the regulatory landscape during ANDA review
  - Be mindful of standard “simpler” issues such as Q1Q2 that impact ANDA development

Center for Complex Generics

- FDA recently awarded a Center for Research on Complex Generics (CRCG)
  - Five-year, $5 million 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

COVID-19 Response

- The generic drug program prioritizes and expedites review of generic drugs that are used to treat COVID-19 or its symptoms
  - 3-month approval time for some priority ANDAs
  - Complex products (Albuterol, Propofol) accelerated
  - Expedited review of supplements to address potential shortages of COVID-19 drugs

COVID-19 Response

- COVID-19 has potential impact on all generic development programs
- GDUFA Science and Research has informed our COVID-19 response
- Modeling and Simulation are critical to a generic drug system that can adapt to the interruptions in product development

Example Questions about Interruptions

- My study was halted in the middle and my clinical trial materials expire before I can restart so I want …..
- My dropout rate is going to be much higher and I want to switch to an adaptive design in the middle of my study
- Some subjects missed PK sampling points and I still want to use the data from those subjects
- I want to alter my study design to minimize subject visits

COVID-19 Study Interruptions Regulatory Processes

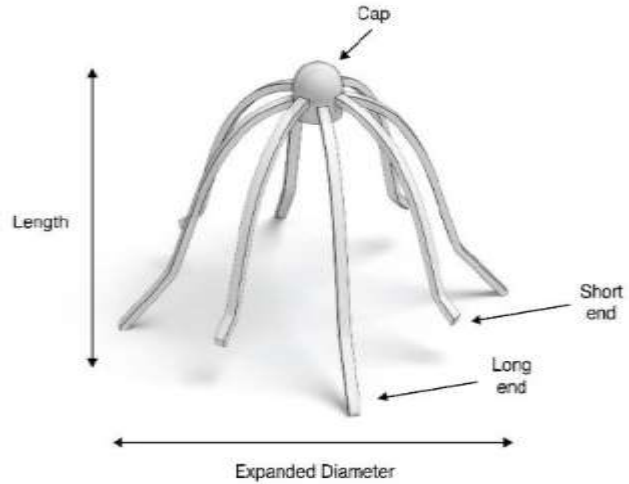
- Use the Controlled Correspondence process
- FDA is expediting responses
- FDA is open to novel approaches to maintain the product development pipeline and maintain access to the full spectrum of generic products
- Modeling and Simulation is a key to support that the alternative approaches are appropriate

Future Environment

- ~30% of potential RLD are for complex products
  - ~12% of approved ANDAs are for complex products
- Key is moving complex applications through the system

Future Environment

Research and PSG development should keep pace
with new RLD product developments that add complexity



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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