Complex Generic Drug Products -Challenges in Development

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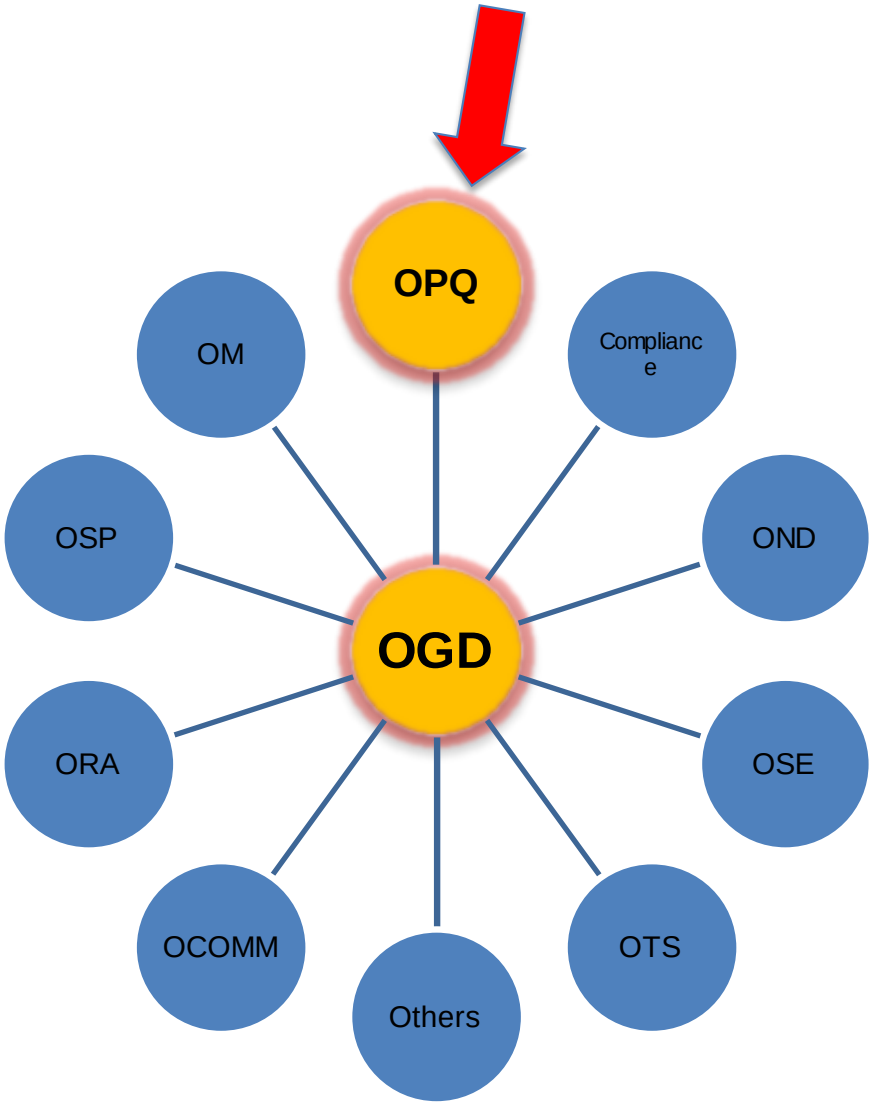
These slides are prepared to have an informal discussion with EMA colleagues during my fellowship visit from October 16-26, 2018.

FDA Generic Drug Program

- **The Office of Generic Drug (OGD)** at CDER, FDA is the interface for abbreviated new drug application (ANDA) applicants to interact with for the Generic Drug Program, similar to the Office of New Drugs (OND) for NDAs

- **The Office of Product Quality (OPQ) and OGD** collaborate to evaluate Pharmaceutical Quality, Bioequivalence, and Labeling

- Other FDA units also involve:
  - Office of Regulatory Affairs
  - Office of the Commissioner, Office of Chief Council
  - CDRH, CBER

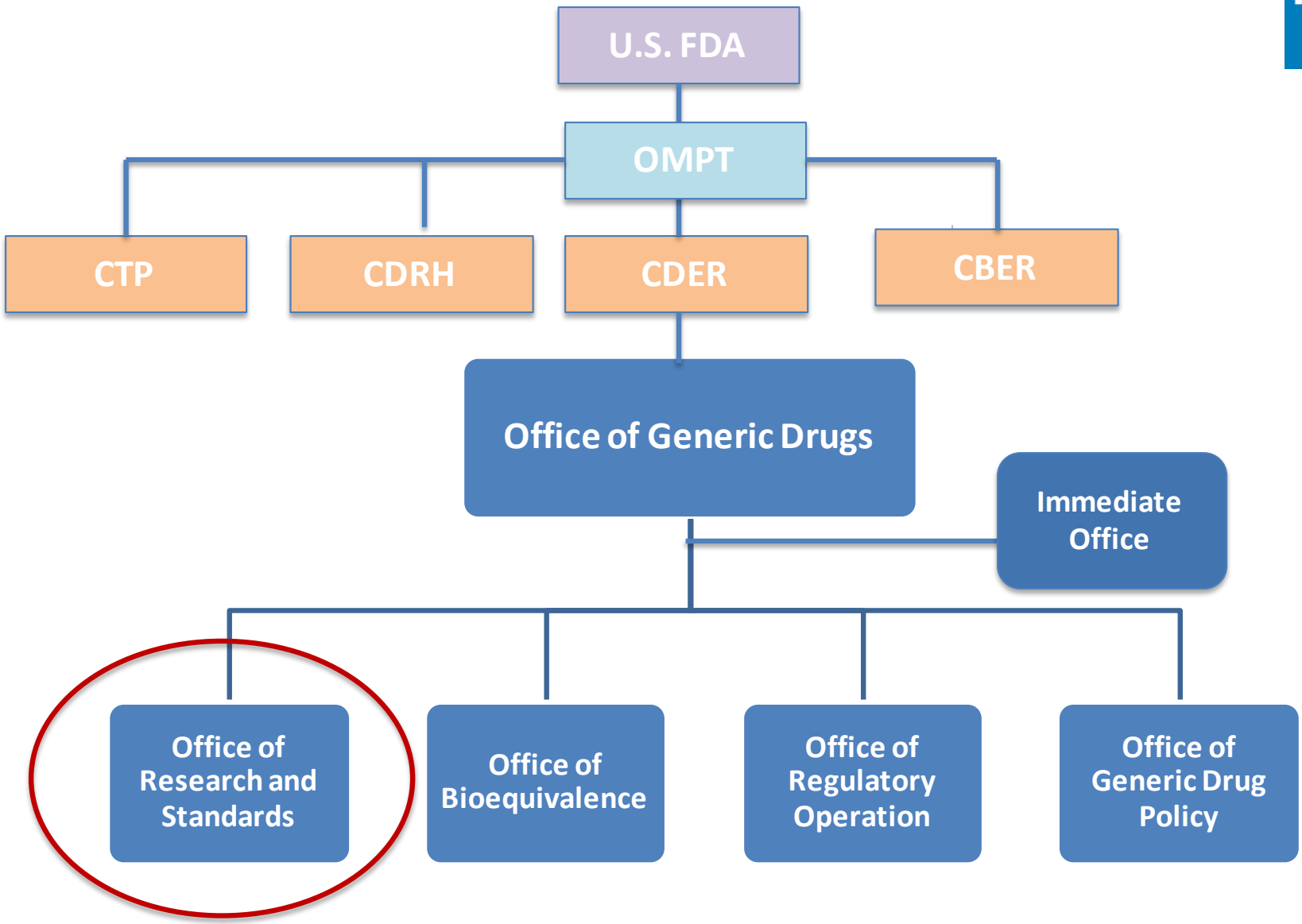


Our Interest

- To improve access to high quality, affordable generic drugs to the American public
  - More applications to FDA does not mean more access
- Improved access results from:
  - Reduced overall time to approval
  - 1st cycle approvals
  - Reduced number of review cycles to approval
- To meet all GDUFA requirements/commitments
- To work with ICH to develop harmonized standards for global development for generic drugs to 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)

GDUFA: Generic Drug User Fee Amendment

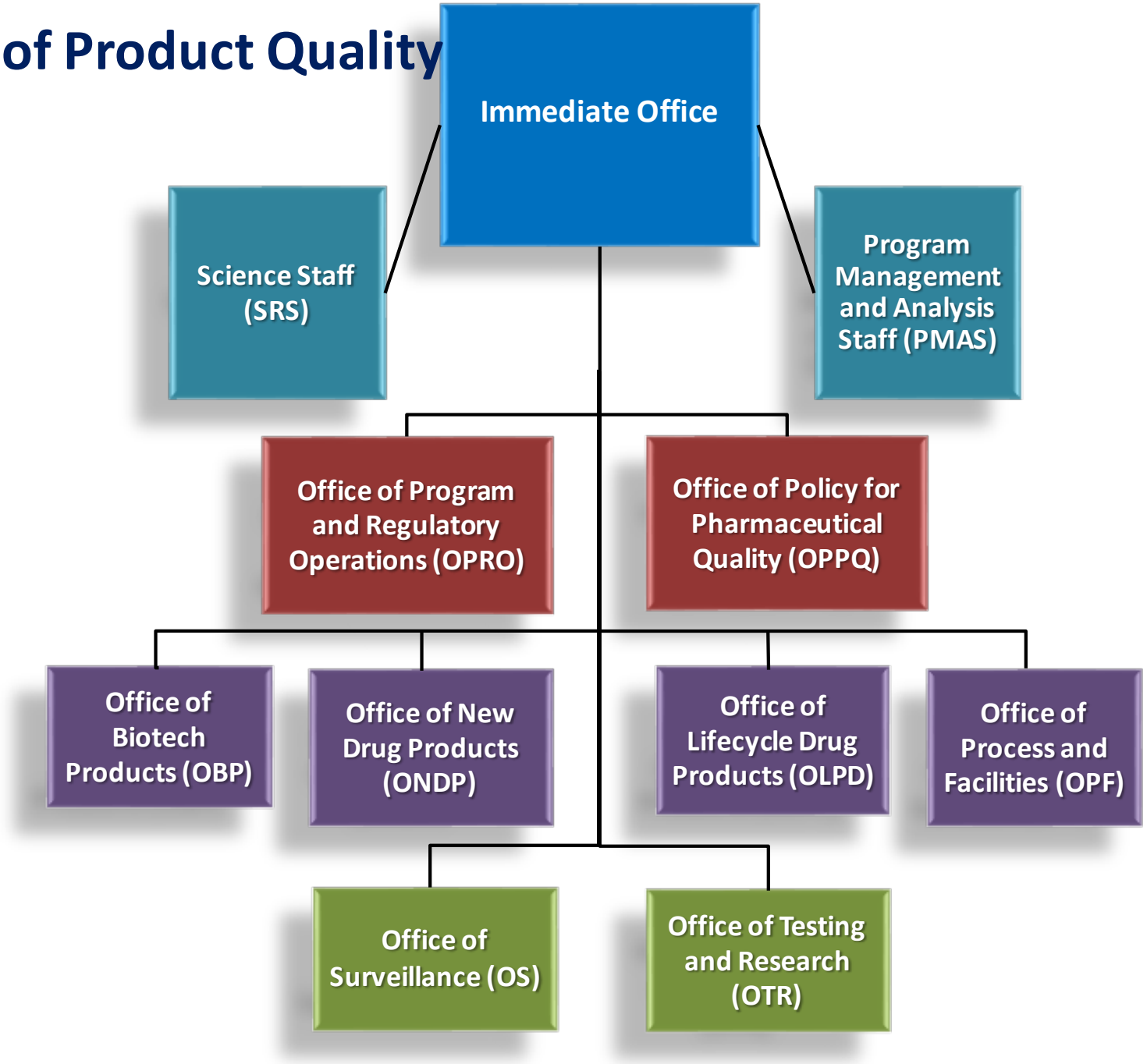
Office of Generic Drugs



FDA: Food and Drug Administration
OMPT: Office of Medical Products and Tobacco
CDER: Center for Drug Evaluation and Research

CBER: Center for Biologics Evaluation and Research
CDRH: Center for Devices and Radiological Health
CTP: Center for Tobacco Products

Office of Product Quality
CDER



Drug Price Competition and Patent Restoration Act of 1984 (Hatch-Waxman Amendments)

- Created the generic drug industry
- Increased availability of generics in US
- Grand bargain for Brand and Generic Industries
  - Brand Industry Gains:
    - 5-year New Chemical Entity (NCE) Exclusivity
    - 3-year New Clinical Studies Exclusivity
    - Patent Term Extension to account for time patented product is under review by FDA
  - Generic Industry Gains:
    - Abbreviated New Drug Application (ANDA) pathway
    - Challenge brand patents in court prior to marketing
    - 180-day Generic Drug Exclusivity

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Approval Pathways

Four different routes for the two broad categories of drug applications under the FD&C Act	
1.	Stand-alone new drug application (NDA) submitted under **505(b)(1)** and approved under 505(c)
2.	**505(b)(2)** NDA submitted under 505(b)(2) and approved under 505(c)
3.	Abbreviated new drug application (ANDA) submitted and approved under **(505(j))**
4.	**Petitioned ANDA** submitted under 505(j)(2)(C) and approved under 505(j)

Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf

Abbreviated Approval Pathways

- **ANDA (505(j))**
  - Application for a duplicate of a previously approved drug product (the reference listed drug (RLD)) that relies on FDA's finding that the RLD is safe and effective
  - Demonstrates sameness to the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and labeling (with certain exceptions)
  - Includes sufficient information to demonstrate bioequivalence to the RLD
  - May contain certain differences from an RLD as long as investigations are not necessary to establish safety and effectiveness

Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf

Abbreviated Approval Pathways

- **505(b)(2) NDA**
  - Contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference
  - May rely on FDA's finding of safety and/or effectiveness to the extent that the proposed drug product shares characteristics with the listed drug
  - Includes a "bridge" between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate such reliance is scientifically justified

Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
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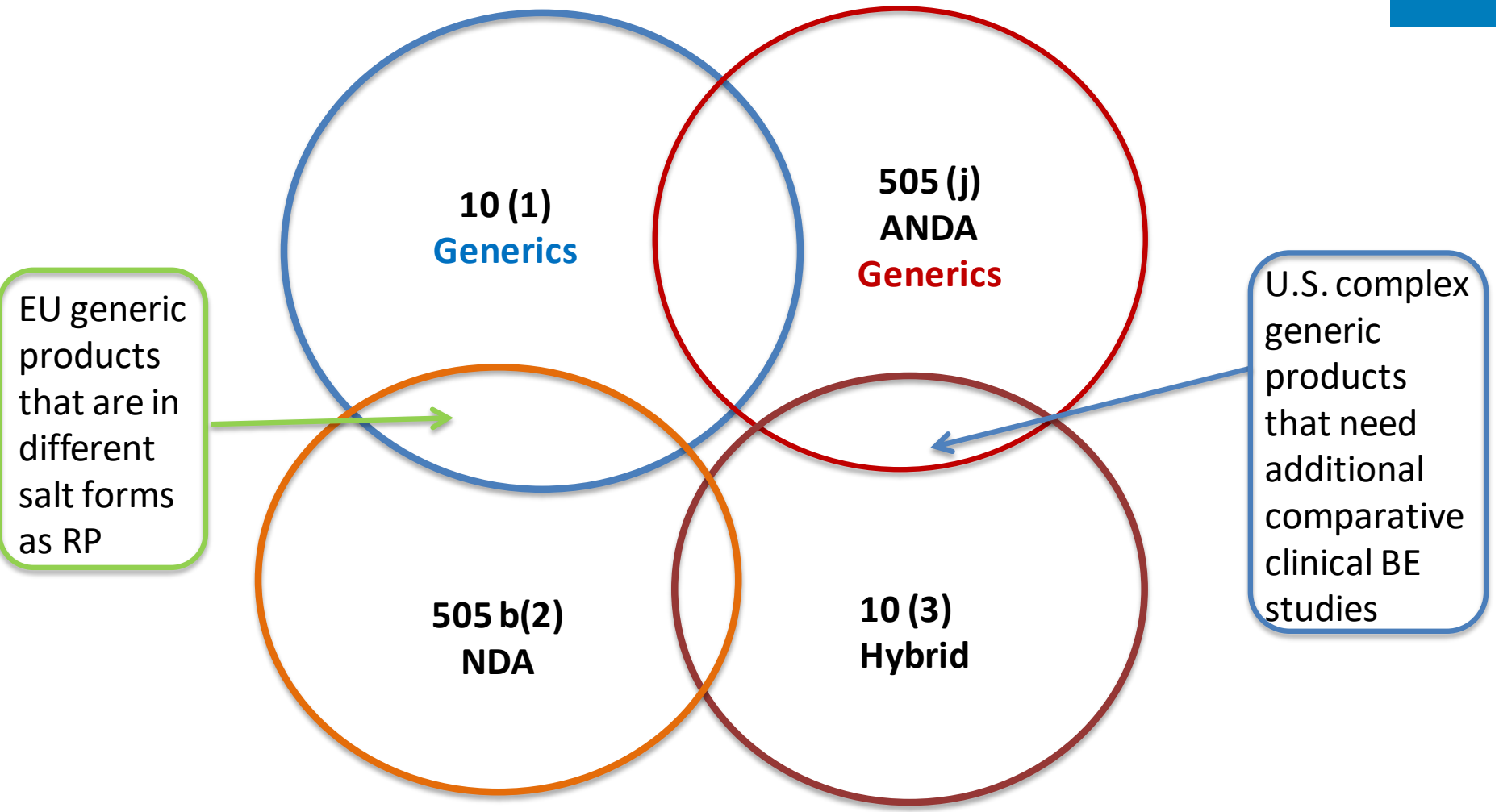
EMA vs. FDA

-Abridges or Abbreviated Pathways for small molecule drugs



In the US, biologics and biosimilar are regulated by different law. It is under Public Health Service (PHS) Act: 351 a and 351 k. At the FDA, biosimilar (351 k) is reviewed by a different group under OND (will be a new office in CDER) that is a separate office from the OGD.

Basic Generic Drug Requirements

No Significant Differences from the Reference Listed Drug (RLD)

- **PHARMACEUTICAL EQUIVALENCE:** the foundation of equivalence
  - Same active ingredient(s)
  - Same strength
  - Same dosage form
  - Same route of administration
- **Bioequivalence:** supports true pharmaceutical equivalence
  - absence of a significant difference in the **rate** and **extent** of absorption after administration
  - **available at the site of drug action** when administrated at the same molar dose under similar conditions

Limited confirmatory clinical studies may be acceptable in an ANDA if the purpose is not to establish safety and effectiveness.

Allowed Difference in Generics

A generic product cannot have *significant differences.* These would include differences that would impact the safety or efficacy profile of the branded drug product (RLD). Generics may vary in the following, depending on the drug product:

- Shape
- Scoring configuration
- Release mechanism
- Packaging
- Excipients
- Buffers, Preservatives, Thickening Agents, Tonicity Adjusters (for Ophthalmic Products)
- Expiration dating
- Minor labeling differences
- Storage requirements

Reference Listed Drug (RLD)

- For every ANDA, there must be a corresponding reference product (RLD); this is typically the brand drug, the NDA
- When the NDA is submitted for approval, all relevant patents must be submitted with the application
- Upon approval, these patents are listed in the Orange Book
- Patents can place external limitations on generic development (e.g. formulation, drug release mechanism)
- FDA does not evaluate patents

Orange Book

- Full name: Approved Drug Products with Therapeutic Equivalence Evaluations

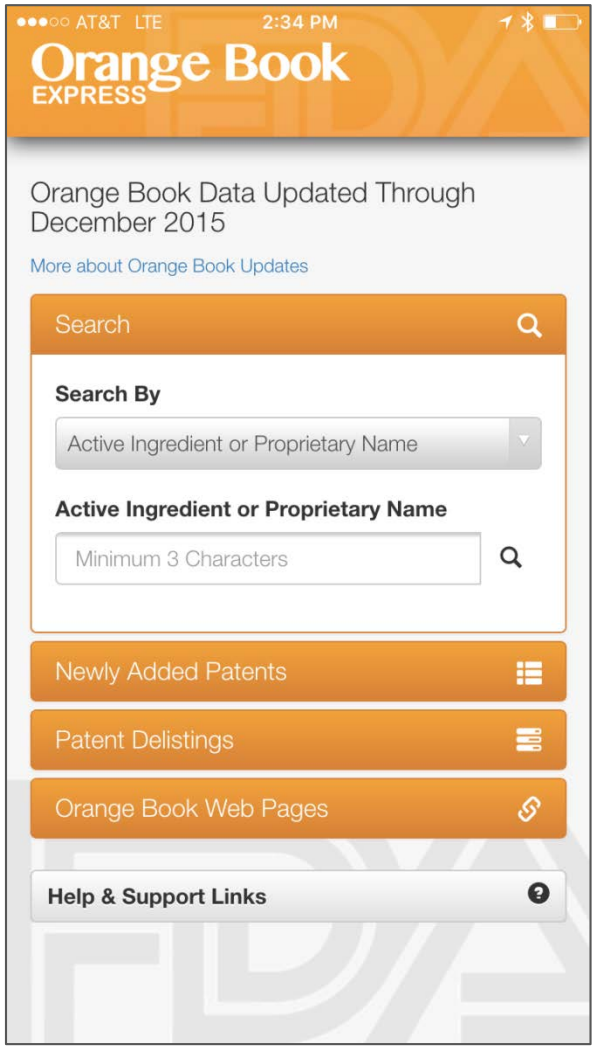
- The first print publication occurred October 1980, and the color orange was selected since it was almost Halloween.

- All FDA approved drugs products listed
  - NDA's, ANDA's and non-monograph Over-the-Counter (OTC) products
- Therapeutic equivalence codes
  - "A" = substitutable
  - "B" = Inequivalent, NOT substitutable
- Expiration dates: patent and exclusivity.
- Reference Listed Drugs noted
  - Brand drugs identified by FDA for generic companies to compare their proposed products with

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

Orange Book Express Mobile App

- Search the public Orange Book Database for Approved Drugs and Patent and Exclusivity Information
- Search all marketing statuses (Rx, OTC, Discontinued) with one search
- Identify RLDs and determine if a drug product is considered to be a therapeutic equivalent
- Browse Patent Delistings and Newly Added Patents
- Launched 11/9/2015
- Available for Android and iOS devices



Download on the App Store

ANDROID APP ON Google play

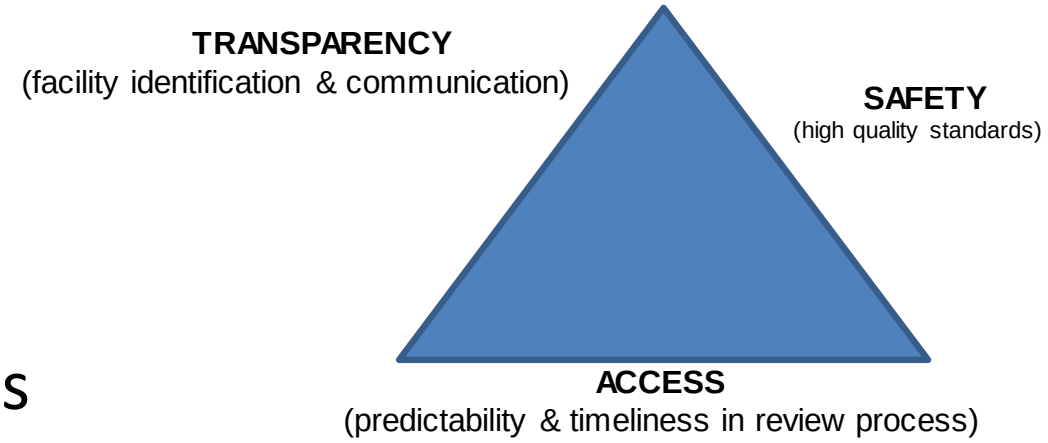
Generic Drug User Fee Amendments (GDUFA)

- First started in Oct 2012 (GDUFA I)
- Signed July 9, 2012
- 5 year program
  - Oct 1, 2012-Sept 30, 2017
- Timely reviews of generic applications
  - Progressive metrics that ramp up to a 10 month GDUFA review goal for all original ANDA applications
  - Other metrics for controls, amendments and supplements
  - Inspectional parity for domestic and foreign sites

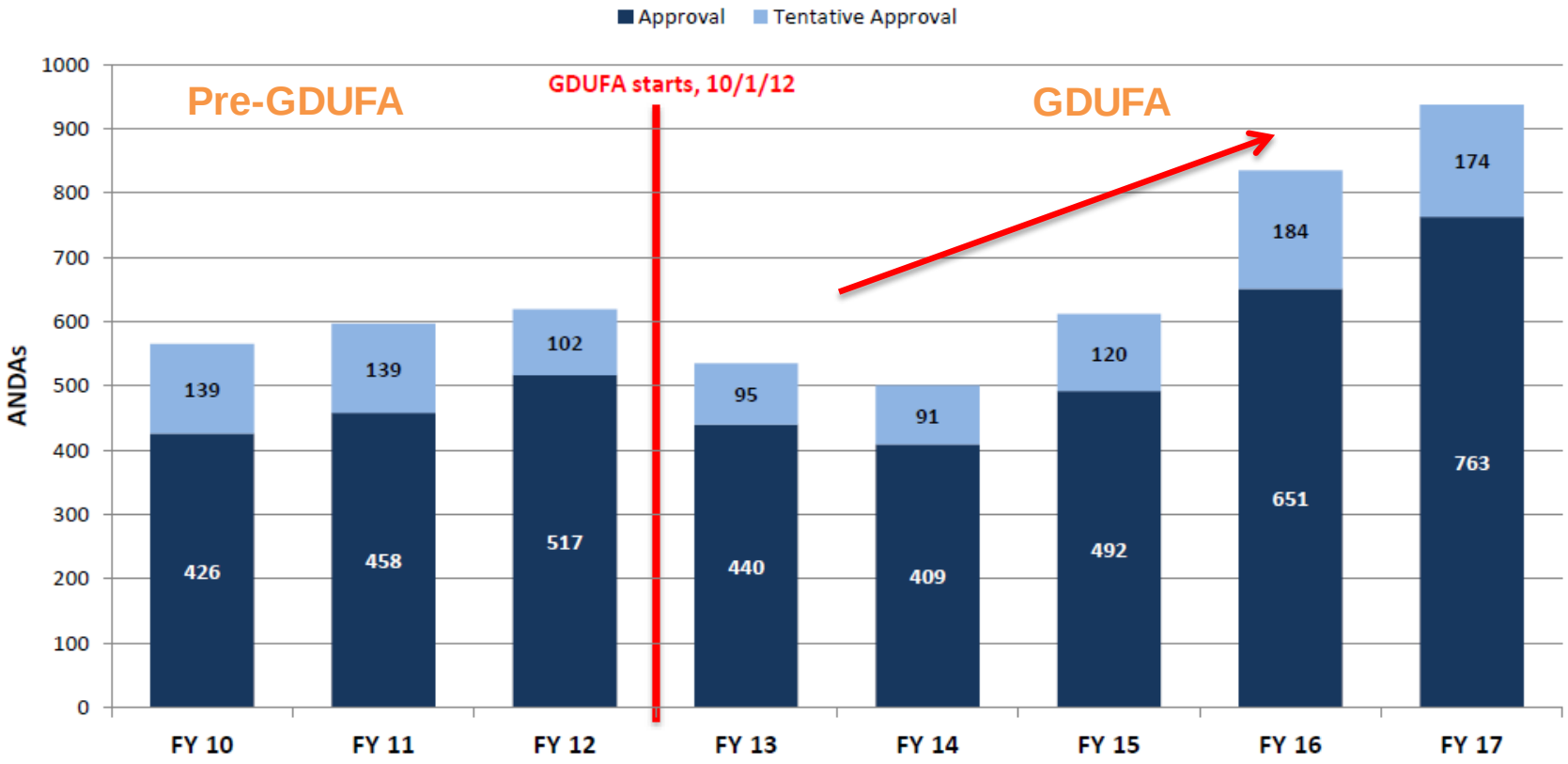
GDUFA I
MAJOR PROGRAM GOALS

(5 year plan)

1. Metrics
   - Applications
   - GDUFA Backlog
   - cGMP Inspections
2. Efficiency enhancements
3. **Regulatory science**



GDUFA Process Improvements Bring Increased Approvals and Tentative Approvals (Tas)



*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

GDUFA I Research Outcomes

- Awarded >100 research grants and contracts
- Published 788 of PSGs
  - 495 new and 293 revisions
- Held 65+ pre-ANDA meetings
- Approved first generic ANDAs linked to GDUFA research projects
  - Sevelamer carbonate powder for suspension (6/2017)
  - Sevelamer carbonate tablets (7/2017)
  - Glatiramer acetate for injection, 20 & 40 mg/mL (10/2017)
  - Colesevelam HCl tablets (5/2018)
  - Colesevelam HCl powder for suspension (7/2018)

GDUFA II

- Second “cycle”
- Covers: October 1, 2017 through September 30, 2022
- Program performance goals
- New and enhanced pathways
  - Complex generics definition and associated enhanced regulatory assistance
  - Pre-ANDA meetings
  - Product-specific guidance goal dates

Resources: https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm580458.htm
Commitment letter:
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Drug Competition Action Plan (DCAP)- To Improve Drug Access

- Announced by FDA's Commissioner, Dr. Scott Gottlieb, in June 2017
- Goal is to bring more competition to drug market as a way to improve drug access
- This plan has three main components:
  - **Reducing gaming by branded companies** that can delay generic drug entry;
  - **Resolving scientific and regulatory obstacles** that can make it difficult to win approval of generic versions of certain complex drugs;
  - **Improving efficiency and predictability of FDA's generic review process** to reduce the time it takes to get a new generic drug approved and lessen the number of review cycles undergone by generic applications before they can be approved

https://blogs.fda.gov/fdavoice/index.php/2017/06/fda-working-to-lift-barriers-to-generic-drug-competition/

Drug Competition Action Plan & GDUFA II

- DCAP aligns with generic drug user fee program (GDUFA II)
- GDUFA II agreement critical to facilitating access, consistent with two major objectives:
  - reducing the number of review cycles to approval
  - increasing approvals of safe, high-quality, and lower-cost generic drugs
- The goals and commitments include:
  - program to better facilitate development and review of abbreviated new drug applications (ANDAs) for complex generic products
  - new review goals for priority ANDA applications
  - greater accountability and reporting, and a modified user fee structure and relief for small business

Complex Generic Products -Cornerstone of GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals
- Complex drug-device combinations
  - Nasal sprays, metered dose inhalers, dry powder inhalers
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement
  - Opioids with abuse deterrent formulations

GDUFA: Generic Drug User Fee Amendments; API: Active Pharmaceutical Ingredient

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Products

A defined term in the GDUFA II Commitment Letter

COMPLEX…	Example	Example Products
Active ingredients	Peptides, complex mixtures, natural source products	Glatiramer acetate
Formulations	Liposomes, emulsions	Liposomal formulation
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	PLGA microspheres
Drug-Device Combinations	Dry powder inhalers, nasal sprays, transdermal systems	Mometasone Nasal Spray
Other products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

Generic Drug User Fee Amendment (GDUFA) II Commitment Letter: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Why?

- Complex drug products are critical to the care of many serious medical conditions such as multiple sclerosis, schizophrenia, metastatic breast cancer, osteoporosis, COPD, diabetes mellitus

- Some of these drugs are costly, thus limiting patient access

- Some markets for brand name drugs are BILLION dollar markets
  - Advair sales: $4.6 billion (2013); $69 billion (1992-2017[1])
  - Peptide products: ~100 global peptide products, $15-20 billion annual sales[2]
  - Restasis: $1.41 billion (2017[1])
  - Victoza: $1.8 billion (Q1&2 2017[3])
  - And More: Symbicort, Spiriva

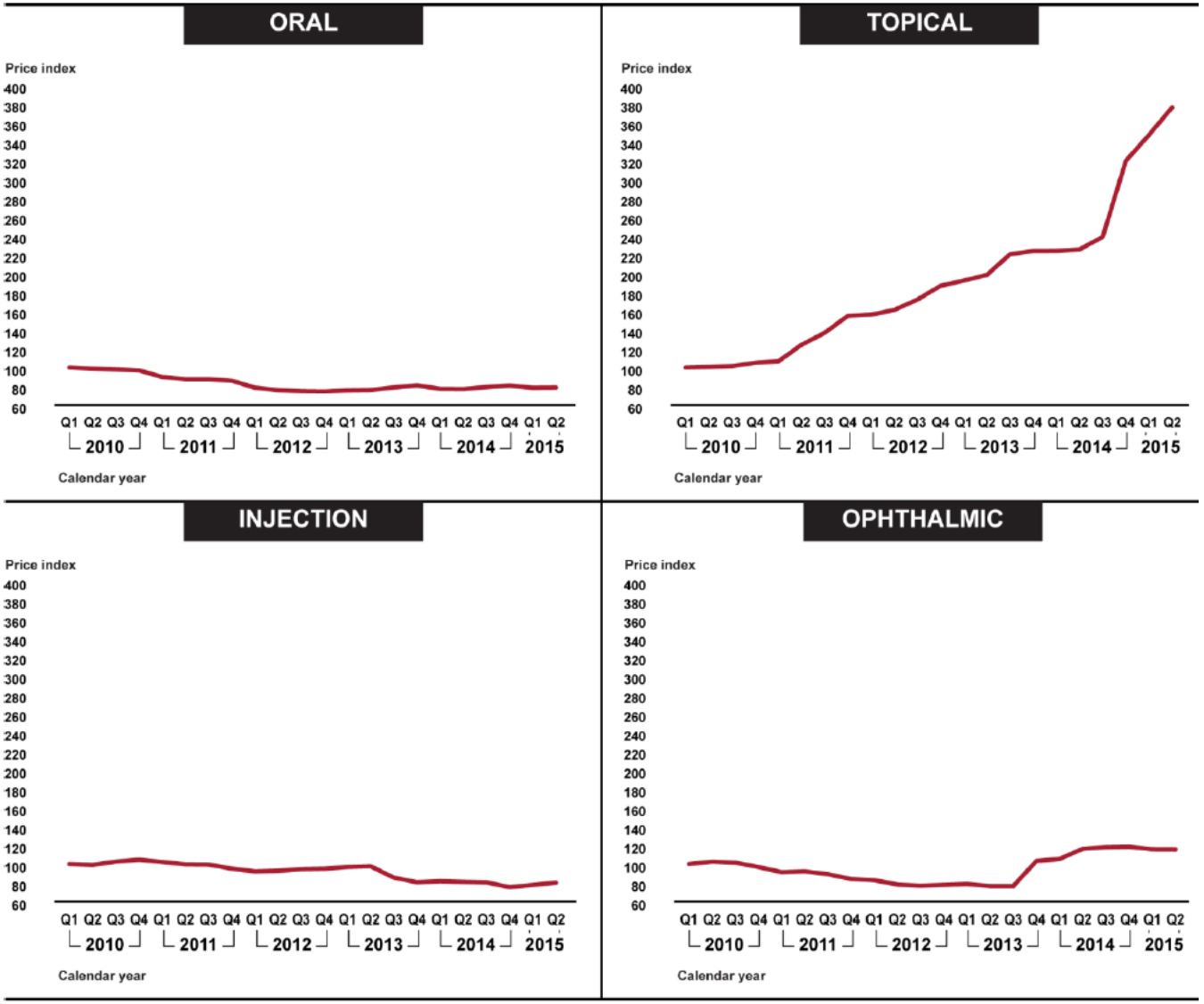
- Yet many complex drug products have relatively small market capitalization and are less enticing for generic drug developers
  - Lack of generic drug product development and ANDA submission
  - Results in little to no generic drug competition and limited patient access

- Challenging **scientific**, regulatory and legal considerations

1. www.fiercepharma.com
2. https://www.fda.gov/Drugs/ScienceResearch/ucm578111.htm
3. www.biopharmadive.com

GAO Report (GAO-16-706)

Price Increases for Brand and Generic Topical drugs



Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

COMPLEX GENERIC DRUG PRODUCTS

- For some brand name drugs (or RLDs), FDA has not even received any generic drug applications (ANDAs)
  - FDA cannot approve generics if industry does not develop the drug and submit an ANDA
  - FDA publishes and updates List of Off-patent, off-exclusivity drugs without an approved generic (Part of Drug Competition Action Plan (DCAP))

    https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM564441.pdf

- Some uncertainly for industry on how to develop these generic drug products and gain approval

- Because of the complexity of developing complex generic drug products and demonstrating "sameness"/equivalence, closer FDA-industry communications are needed (Pre-ANDA program under GDUFA II)

CONTENTS OF GENERIC DRUG APPLICATION (ANDA)

- Identify Single Reference Listed Drug (RLD)
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength
- Same Labeling
- Bioequivalence (BE)
- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls (CMC) Information
- cGMPs (facilities)

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

- Identify Single RLD
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength
- Same Labeling
- **Bioequivalence (BE)**

Pharmaceutical Equivalence (PE)

- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls (CMC) Information
- cGMPs (facilities)

THERAPEUTIC EQUIVALENCE

Generic drug has the same clinical efficacy and safety profiles **(e.g., same therapeutic effect)** as brand name drug (RLD) when administered to patients under conditions specified in the labeling

- The generic drug product has no significant differences from the RLD
- Can be substituted for each other without any adjustment in dose or other additional monitoring or training
- Substitution occurs at the pharmacy level

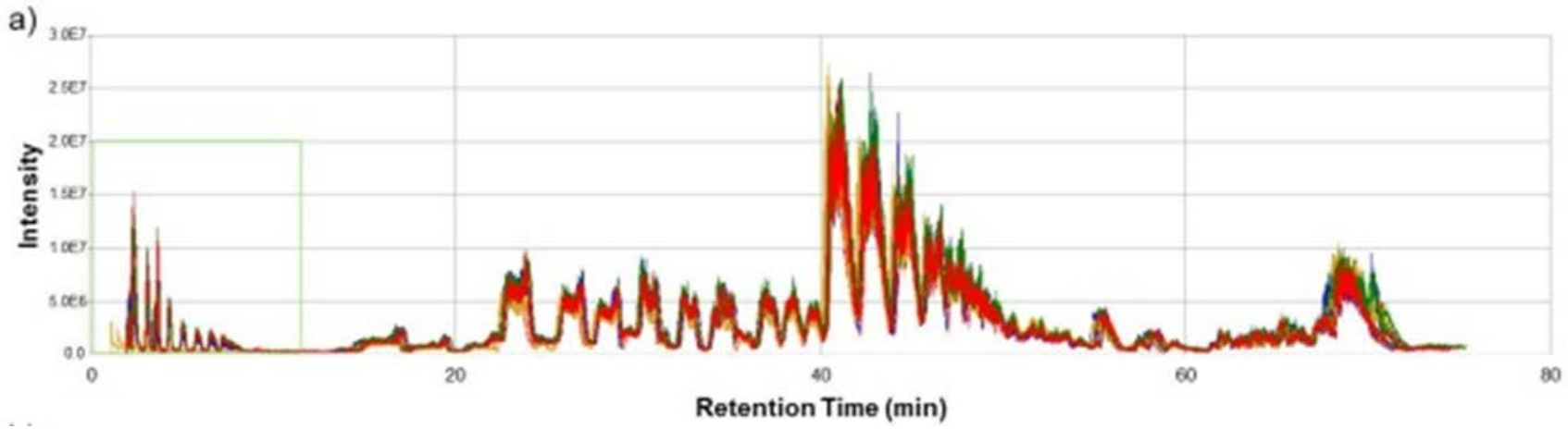
CHALLENGES FOR COMPLEX GENERIC DRUG PRODUCTS

- Pharmaceutical Equivalence
  - How to demonstrate active ingredient "sameness"
- Bioequivalence
  - 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
  - What kinds of comparative analyses are needed to support substitution?
  - Are the inactive ingredients, if different from RLD, allowable?
- Historically (pre-GDUFA), lack of FDA guidance (Product Specific Guidances/PSGs) on how to demonstrate "sameness" or equivalence (PE, BE, TE)

Characterization of Complex Drug Substances

Develop “fingerprint-like” characterization to assess chemical structure of complex molecules

- Assess chemical equivalence amongst complex molecules that are heterogeneous (e.g., heparin, enoxaparin and glatiramer acetate).
- Develop chemometric methods for comparing multivariate analytical data of complex drug products (e.g., enoxaparin and glatiramer acetate).



LC-MS chromatographic alignment of glatiramer acetate (GA) samples. These data supported the regulatory review and informed the decision to approve the first generic GA product (from Sandoz) in 2015

RESEARCH STRATEGY FOR GENERICS

Scientific basis to demonstrate "sameness"/Equivalence

GDUFA I (FY2012-2017)

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

PRE-GDUFA I

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 NMEs
- Establishes Pre-ANDA program for complex generic drug products

GDUFA REGULATORY SCIENCE PROGRAM

- Huge Success Story
- Spectacular return on investment for industry particularly related to the development, regulation and review of complex generic drugs
- Evidence-, research- and science-based standards setting program
- Develops and validates methodologies used to demonstrate "sameness"/Equivalence

OUTCOMES:

1. Provides information for industry on HOW to develop
2. Assists FDA assessors/reviewers and scientists when evaluating ANDA
3. Results in ANDA approvals

APPLY FOUNDATIONAL SCIENCE TO OVERCOME CHALLENGES

We can resolve these "sameness" or equivalence challenges by using foundational and state of the art science and scientific methodologies to:

- Characterize complex active ingredients
  - Complexity of API, e.g., peptides, oligonucleotides, mixtures
- To understand and measure the critical quality attributes of drug product formulations
  - Characterize microstructure and physicochemical properties
  - Minimize risk of drug product formulation failures
  - Enable in vitro approaches to BE
- To understand patient use
  - Complexity of drug-device combinations

SAMPLING OF ANDAS APPROVED

2017-2018

Complex API (all first approved generic)

- Sevelamer carbonate powder for suspension (6/2017)
- Sevelamer carbonate tablets (7/2017)
- Glatiramer acetate for injection, 20 & 40 mg/mL (10/2017)
- Colesevelam HCl tablets (5/2018)
- Colesevelam HCl powder for suspension (7/2018)

Complex Formulation

- Doxorubicin liposomal injection (05/2017)-2nd approved generic

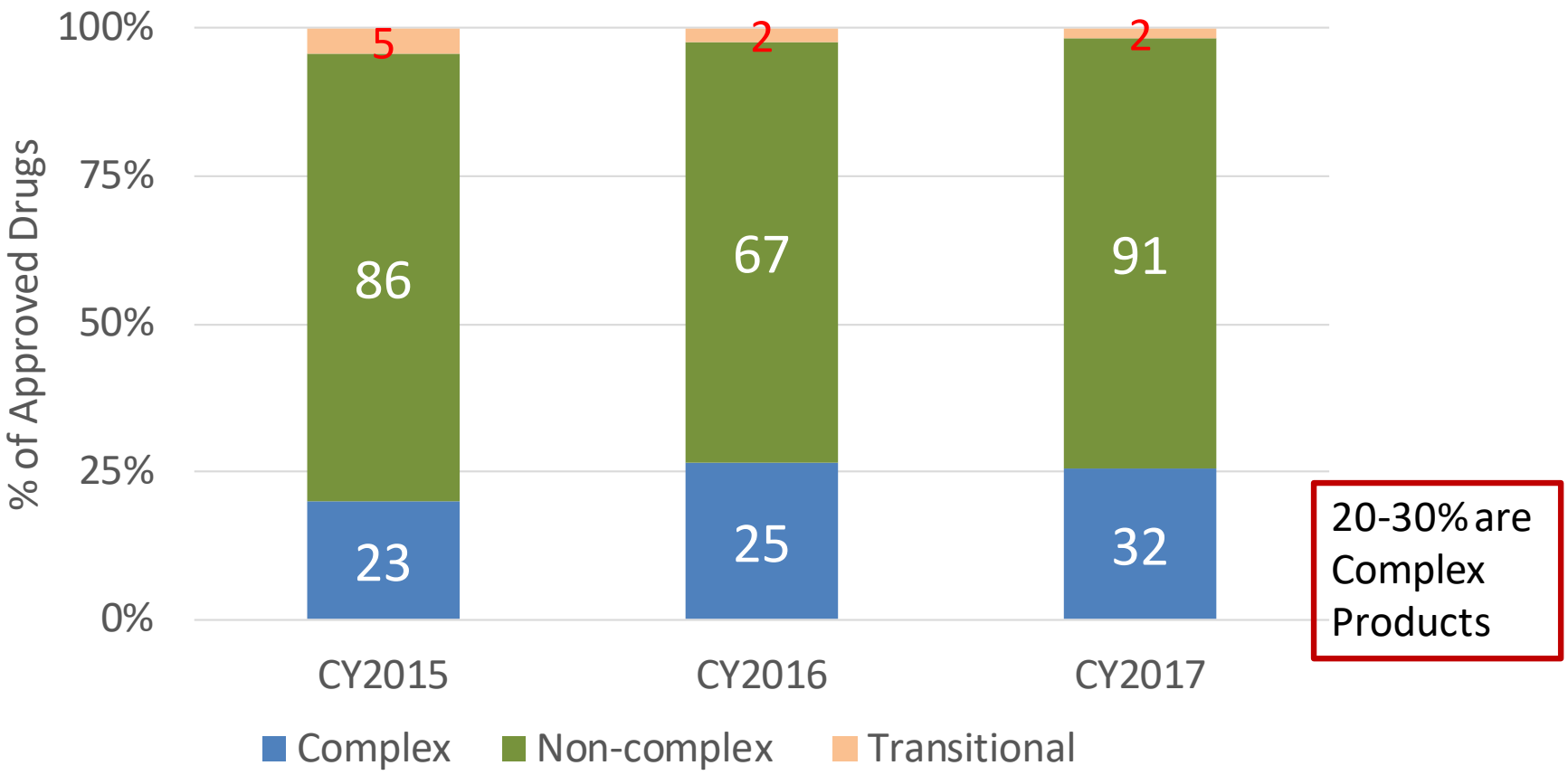
Complex Route of Delivery

- 4 generics for Acyclovir Topical Ointment, 5% (8 Total ANDAs approved)
  - All ANDAs approved based upon a characterization-based BE method
- First generics approved (have PSGs)
  - Estradiol Vaginal Cream USP, 0.01% (12/2017)
  - Butenafine Hydrochloride Cream, 1% (11/2017)
  - Hydrocortisone Butyrate Lotion, 0.1% (11/2017)
  - Dapsone Gel, 5% (10/2017)

Complex Drug-Device Combination

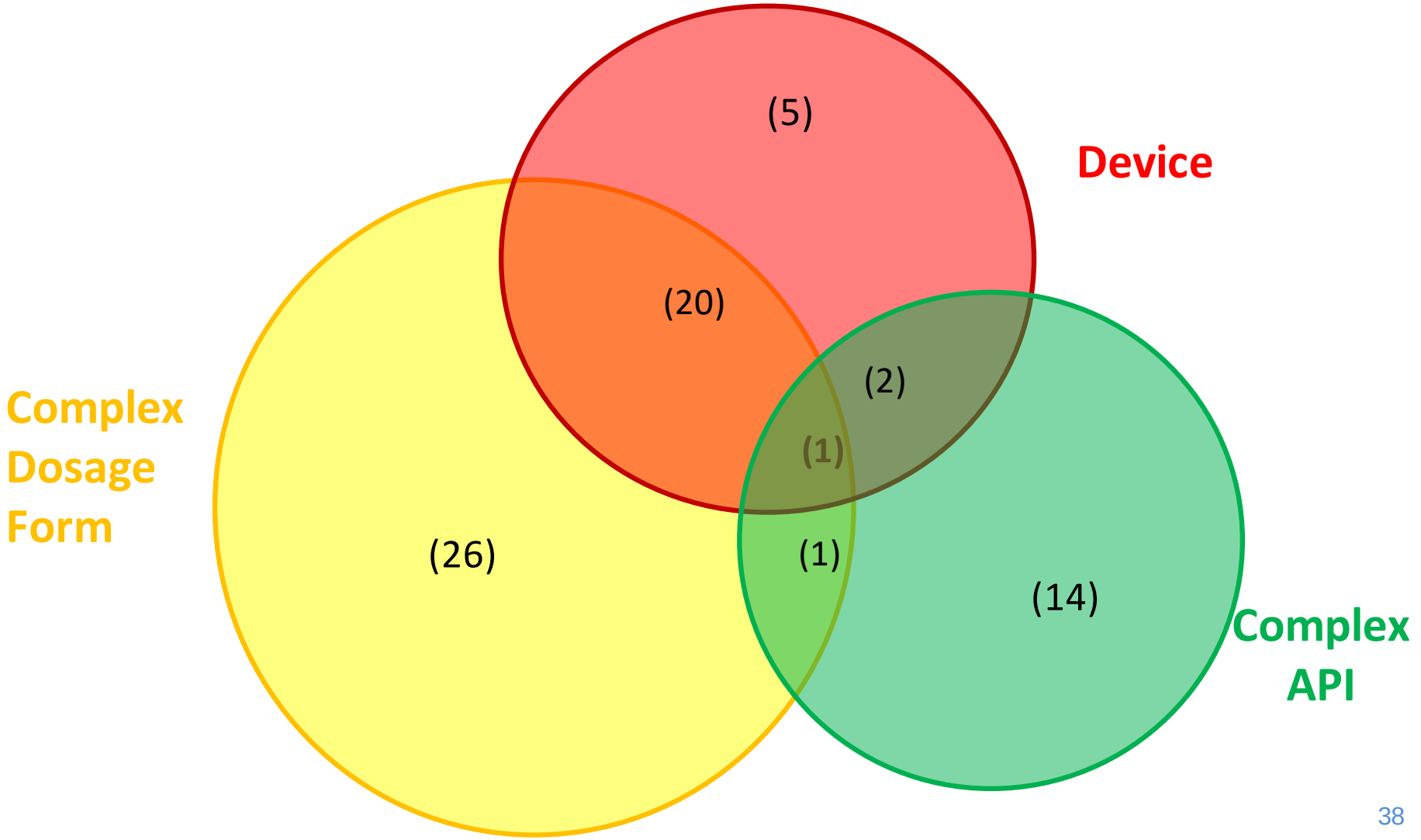
- Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, 137mcg/50mcg (4/2017)
- Epinephrine auto-injector (8/2018)

Complex Drug Products in Approved NDAs 2015-2017

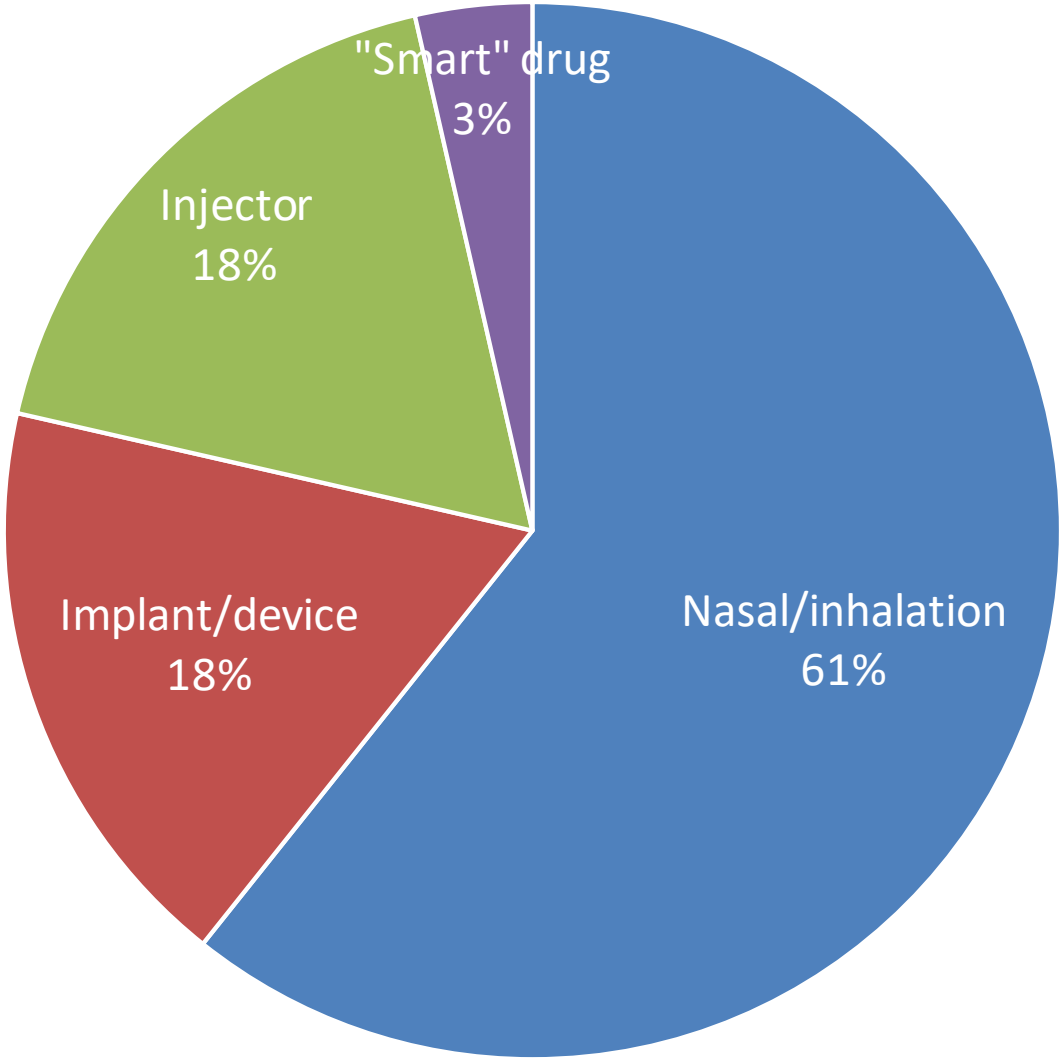


*Numbers noted on the bar graph are the number of approved NDAs, and the height of the graph is normalized

Intersections of Complex Dosage Form, Drug-Device Combination and Complex API of Complex NDA Drug Products 2015-2017



Complex NDA Drug Products with Device Components 2015-2017



Examples of Recently Approved Complex APIs

- Peptides
  - BYDUREON BCISE (also drug-device combination)

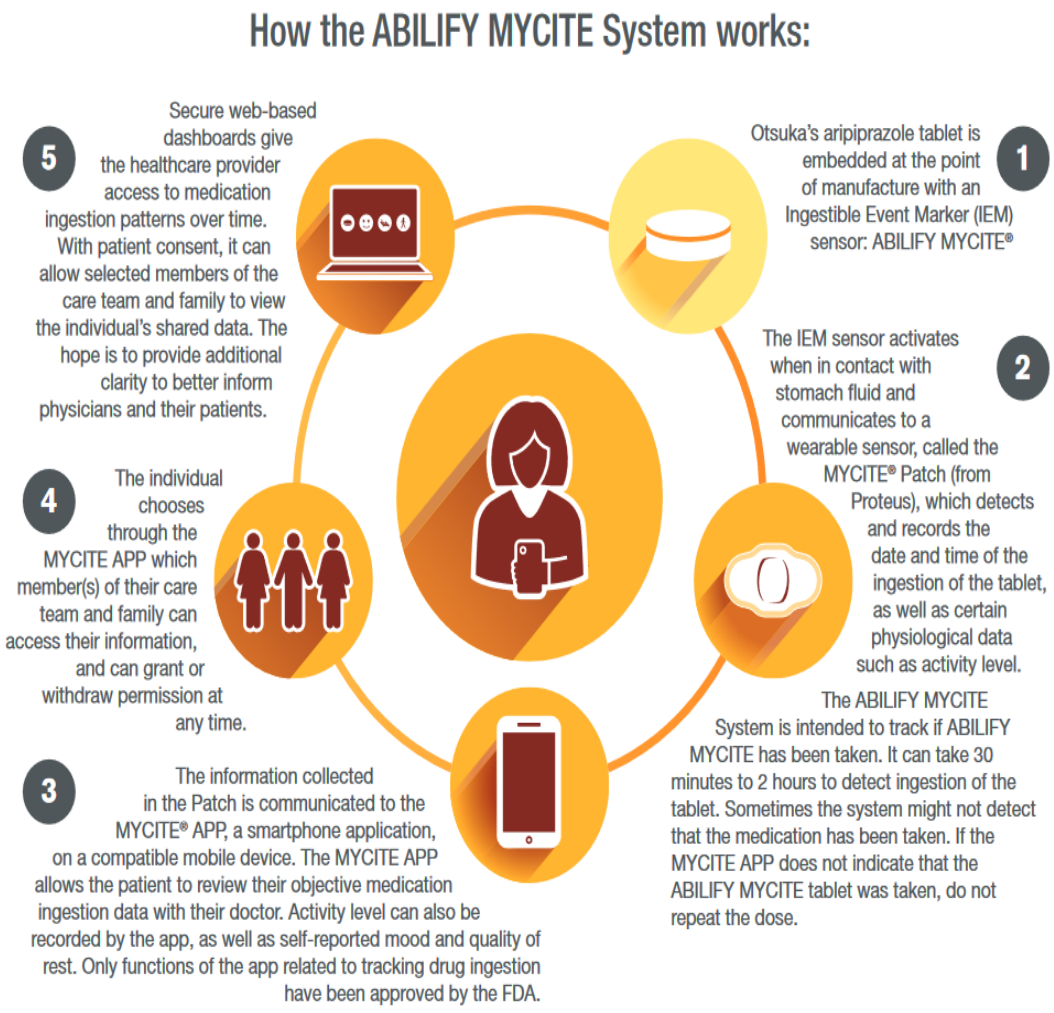
Challenges:
- Peptide-related impurity analysis
- Non-clinical immunogenicity assessments on impurities
- Drug-device combinations

- Oligonucleotides
  - EXONDYS 51 (Eteplirsen)
  - SPINRAZA (Nusinersen)

Challenges:
- Characterizations for establishing identity
- Impurity analysis for related-substances

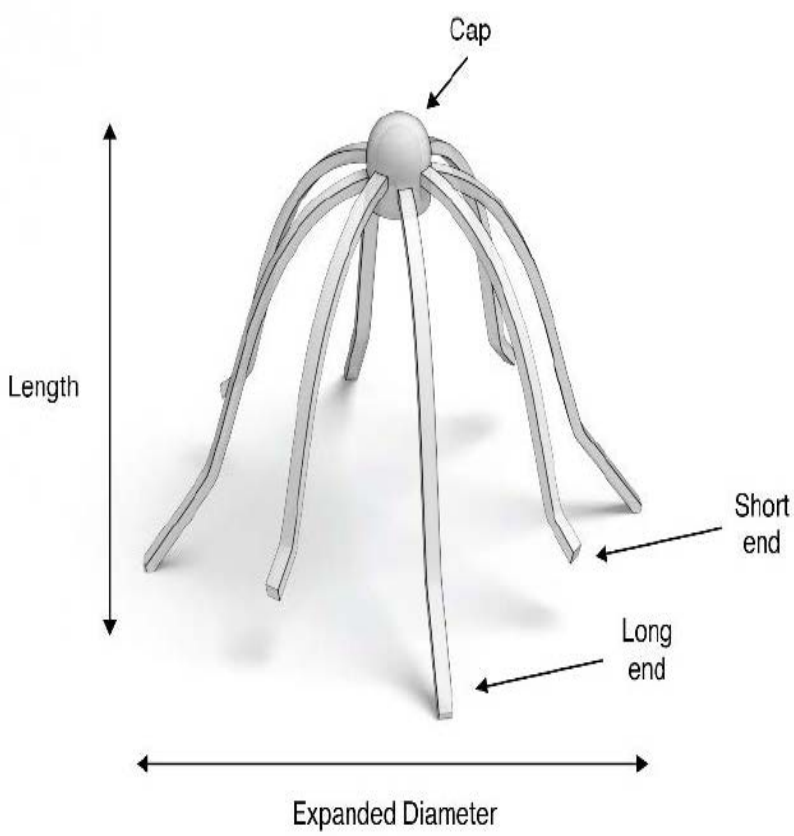
Smart Pill ABILIFY MYCITE

- First digital ingestion tracking system approved (NDA 207202) in the U.S.
- Approved: 11/13/2017
- API: ARIPIPRAZOLE
- Dosage Form/Route: TABLET;ORAL
- **Indication:** Treatment of adults with schizophrenia; bipolar I disorder; major depressive disorder
- **Complexity:** Drug-device combination



SINUVA

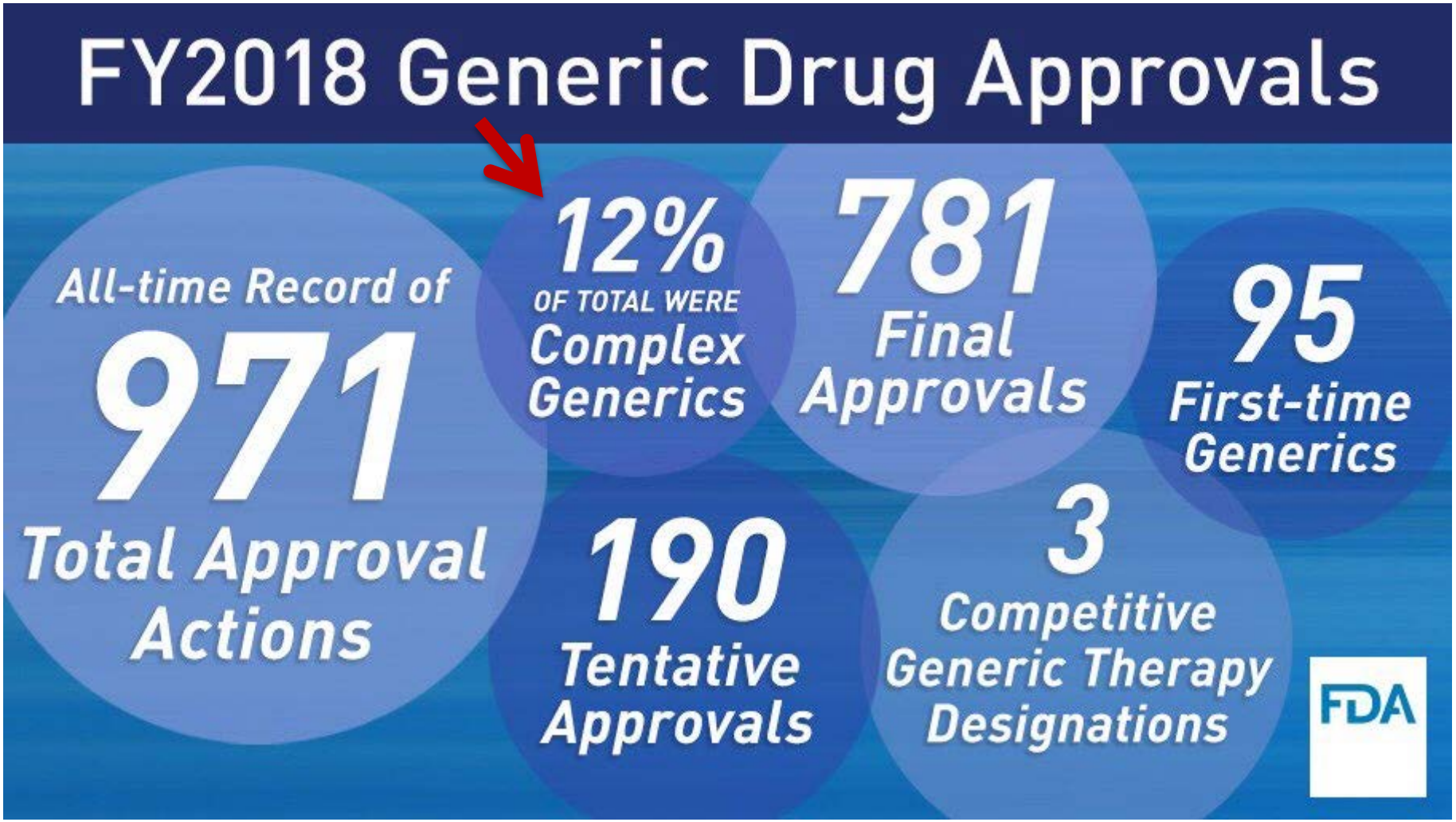
- New Approach to Treating Nasal Polyp Disease
- Approved: 12/08/2017 (NDA 209310)
- API: Mometasone furoate
- Dosage Form/Route: Implant; implantation
- **Sinus Implant**: corticosteroid-eluting implant indicated for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery
- **Complexity**: Complex dosage form (i.e., extended release implant); drug-device combination



STIOLTO RESPIMAT

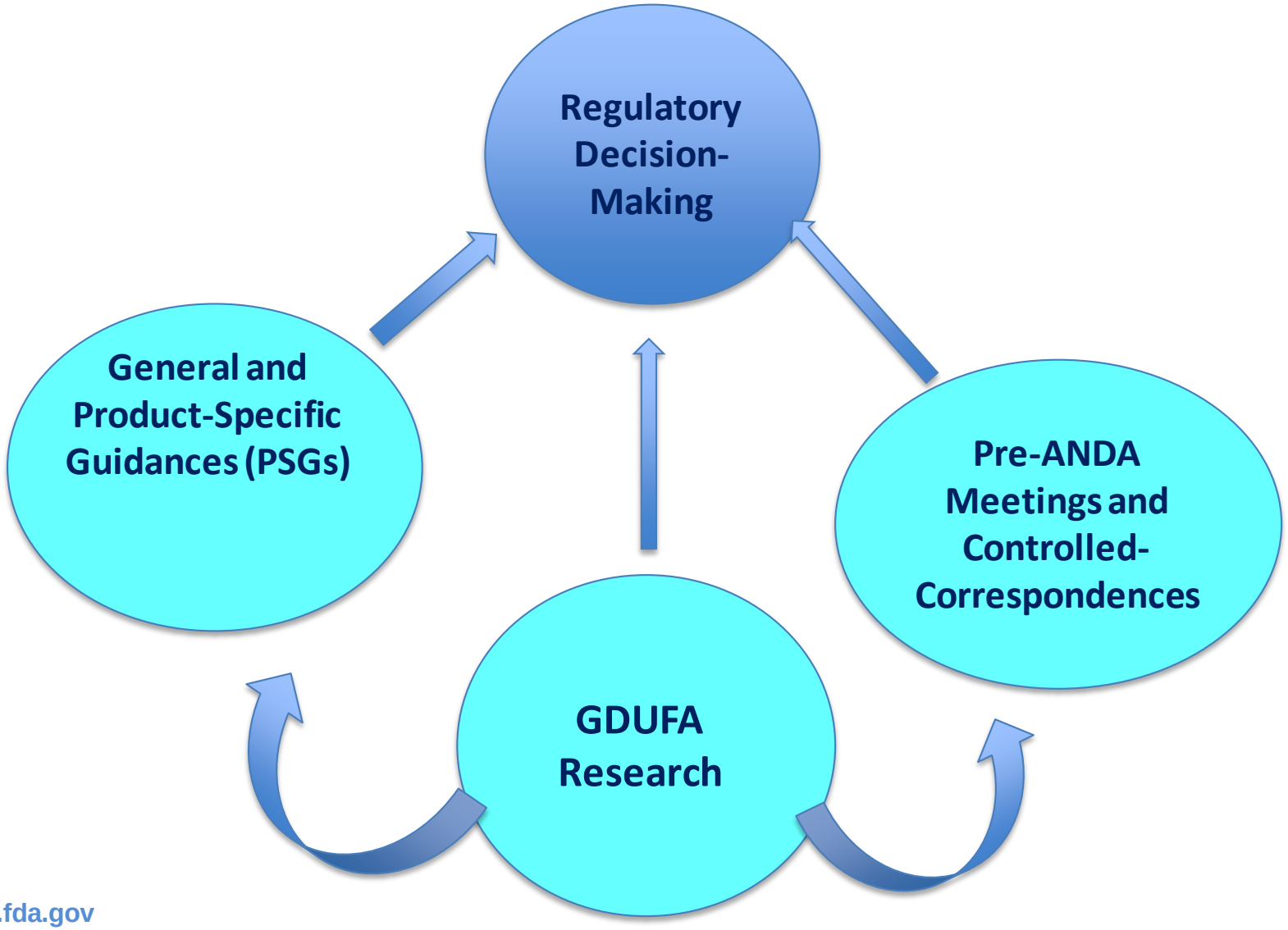
- New approach to inhalation spray
- Approved: 05/21/2015 (NDA 206756)
- API: Tiotropium bromide and olodaterol
- Dosage Form/Route: inhalation spray
- **Complexity**: Respimat is a new inhalation drug delivery device and commonly referred to as "Soft Mist Inhaler"

In FY 2018, ~30% approved new drugs are complex products.



Lower % of complex products were approved as generics. There is a gap that needs to be filled up by additional research.

Science-Informed Regulatory Policy and Decision-Making



Pre-ANDA Program for Complex Products

- Pre-ANDA Meetings
- Product Development
- Pre-Submission
- Mid-Review Cycle

Goals of the Pre-ANDA Program Under GDUFA II

- Clarify regulatory expectations for prospective applicants early in product development
- Assist applicants to develop more complete submissions
- Promote a more efficient and effective ANDA assessment process
- Reduce the number of review cycles required to obtain ANDA approval, particularly for Complex Products

Pre-ANDA Program for Complex Products:
1. Research

- Scope
  - FDA conduct internal and external research to support fulfilment of submission assessment and pre-ANDA commitments
- Public Workshops
  - Annually, FDA will conduct a public workshop to solicit input from industry and stakeholders for inclusion in an annual list of GDUFA II Regulatory Science initiatives
  - Interested parties may propose regulatory science initiatives via email to genericdrugs@fda.hhs.gov
  - After considering industry and stakeholder input, FDA will post the list on FDA's website
  - Industry GDUFA II regulatory science working group
    - Meet with FDA twice yearly on current and emerging challenges and concerns

Pre-ANDA Program for Complex Products:
1. Research

- Reporting
  - Annually, FDA will report on its website the extent to which GDUFA regulatory science-funded projects
    - Support the development of generic drug products
    - Generate evidence needed to support efficient assessment and timely approval of ANDAs
    - Evaluate generic drug equivalence
- Venues for communications of results
  - Webinars and workshops (e.g., five FDA workshops October 2017-May 2018)

GDUFA Science and Research Website

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Pre-ANDA Program for Complex Products:
2. Guidance

- In addition to general guidances, Product-Specific Guidances (PSGs) provide clear and direct advice to ANDA applicants
- Product-specific guidances identify the methodology for developing drugs and generating evidence needed to support generic drug approval
  - ~1,600 PSGs are currently available as of September 2018
  - New PSGs are issued every quarter
  - More PSGs for complex products are under development

Product-Specific Guidances for Generic Drug Development:
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Pre-ANDA Program for Complex Products:
2. Guidance

For NCE Products (non-complex)	For Complex Products	For Other Products
• FDA will issue PSGs for 90% of NCE NDAs approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date	• There are Pre-ANDA meetings for complex products without a PSG or guidance • FDA will strive to issue PSGs for complex products as soon as scientific recommendations are available	• Based on requests from the regulated industry and public health priorities

NCE: New Chemical Entity; NDA: New Drug Application

Pre-ANDA Program for Complex Products:
2. Guidance

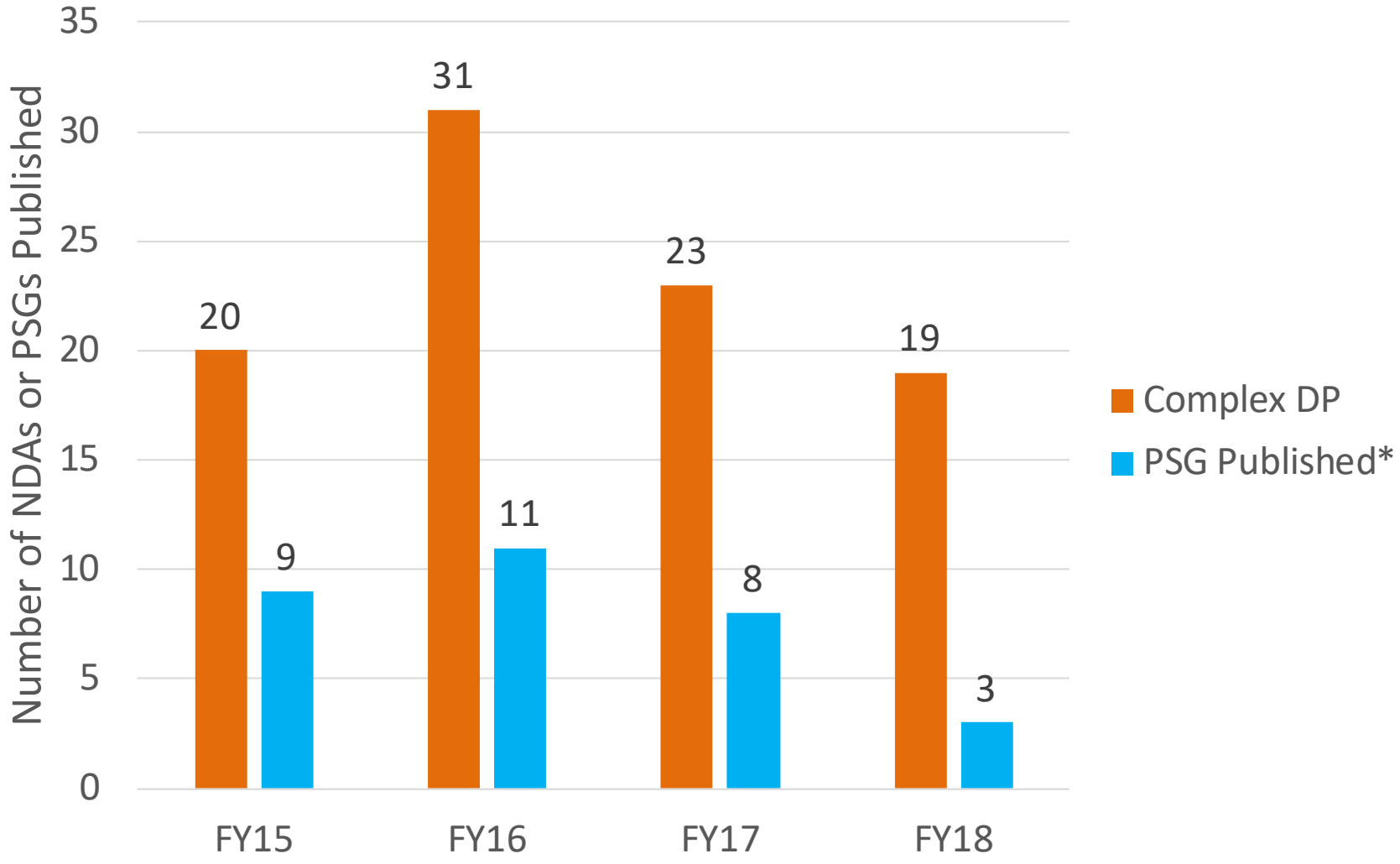
Timely PSGs to optimize ANDA reviews for all product categories

- Provide guidance to applicants early in development
- Coordination between guidance revisions and review
- Keep guidance up to date

Timely PSGs to enable access to generics in all product categories

- Communicate research results
- Manage our pre-ANDA meeting capacity

PSG Development for Recent Complex Drug Products



* Number includes PSG published, drug products that are covered under FDA general guidance and may be eligible for "biowaiver" under 21 CFR 320.22(b)

Pre-ANDA Program for Complex Products:
3. Pre-ANDA Meetings

- Pre-ANDA meetings accelerate access to generic complex products through early engagement with the FDA
- Three types of meetings:
  - Product development meetings
  - Pre-submission meetings
  - Mid-review cycle meetings

Draft Guidance: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578366.pdf

GDUFA II Pre-ANDA Metrics*

- Ten months into the program, 65 pre-ANDA meeting requests have been submitted
- 40 have been granted, 25 denied
  - Denied meetings are given a path forward, such as re-submit as a control or re-submit your meeting request with the following information (inadequate meeting package)

*Data as of 7/31/2018

Most Common Types of Products for Pre-ANDA Meeting Requests Received

- Topicals
- Ophthalmics
- Inhalation
- Injectables (complex)

Pre-ANDA Program for Complex Products:
4. Controlled Correspondence (Controls)

Standard Controls: 60 days

- Use for requests for information on a specific element of generic drug development (e.g., Q1/Q2)
- Or use for information on certain post-approval submission requirements

Complex Controls: 120 days

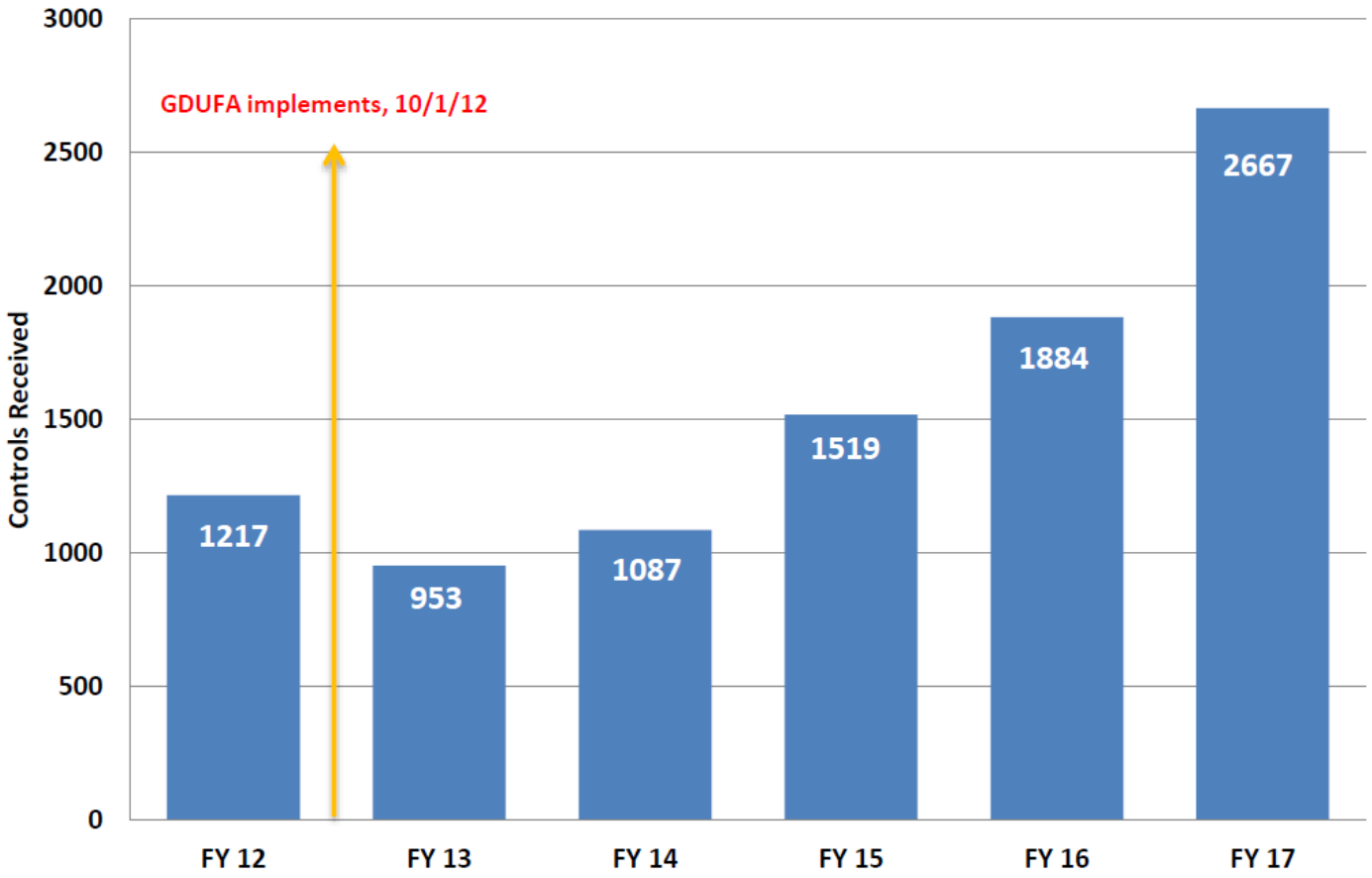
- Evaluation of clinical content
- Review of protocols for drugs that reference-listed drugs with REMS ETASU
- Alternate BE within the same study type

REMS: Risk Evaluation and Mitigation Strategies; ETASU: Elements to Assure Safe Use

Draft Guidance: Controlled Correspondence Related to Generic Drug Development:
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf

Control Correspondence Received

Generic drug product development questions



* Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Numbers reflect controls submitted that are accepted for review, as per Controls Guidance for Industry.

Value Added:
Pre-ANDA Program for Complex Products

Previously work often "back-loaded", e.g.,

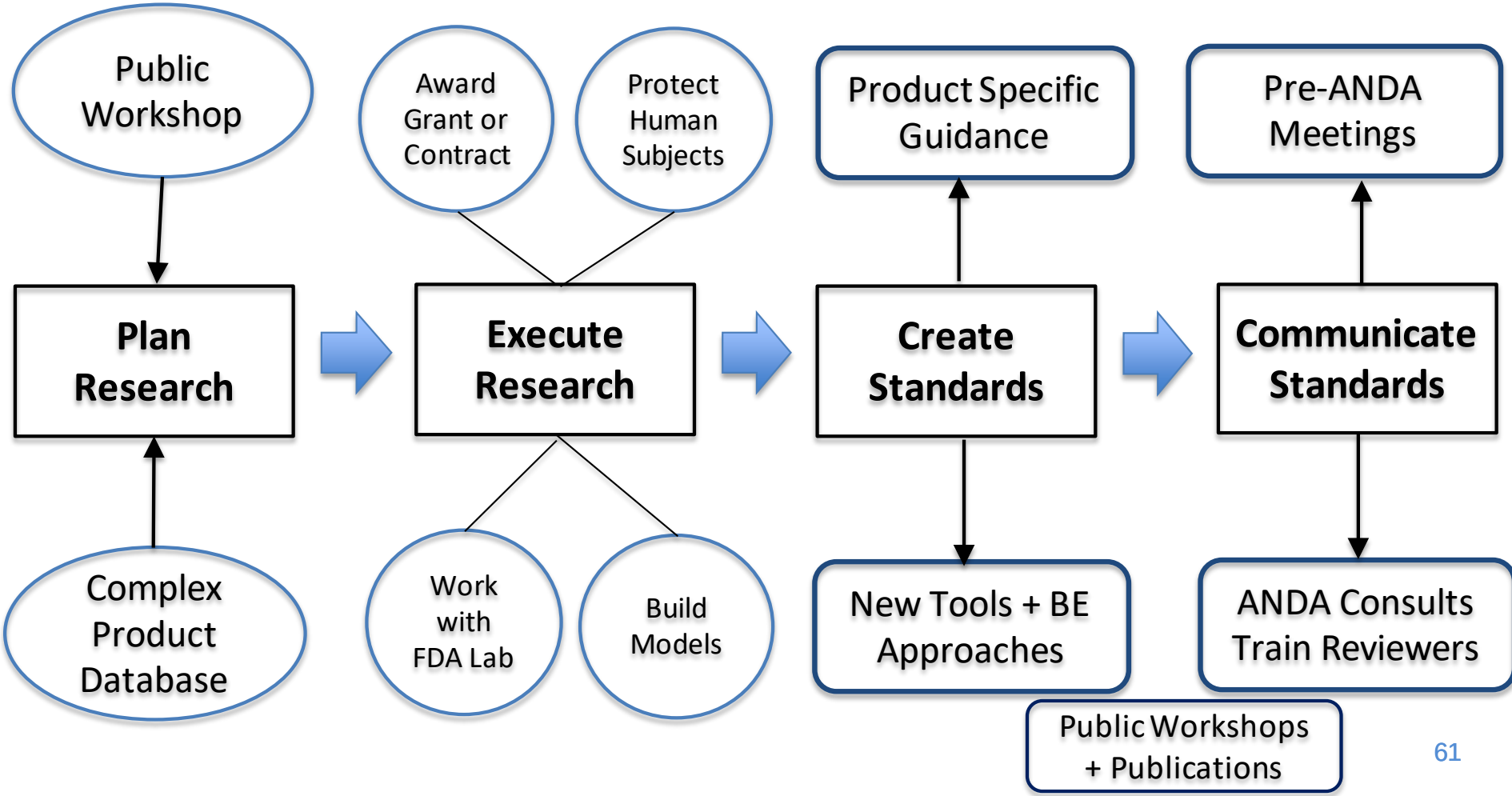
- FDA did not issue PSGs far enough in advance due to workloads and resources
- Companies were unclear with regard to regulatory expectations, and they submitted ANDAs that missed key aspects
- FDA started grappling with the tough issues after ANDA was received
- Numerous review cycles and delay

Now move to "Front Load", e.g.,

- Timely **PSGs** for both NCEs and Complex Products
- **Research** supports the pathways for generic product developments and standards recommendation for demonstrating therapeutic equivalence
- **Pre-ANDA meetings** to discuss issues and regulatory expectations
- Ensure high quality submissions and reduce review cycles

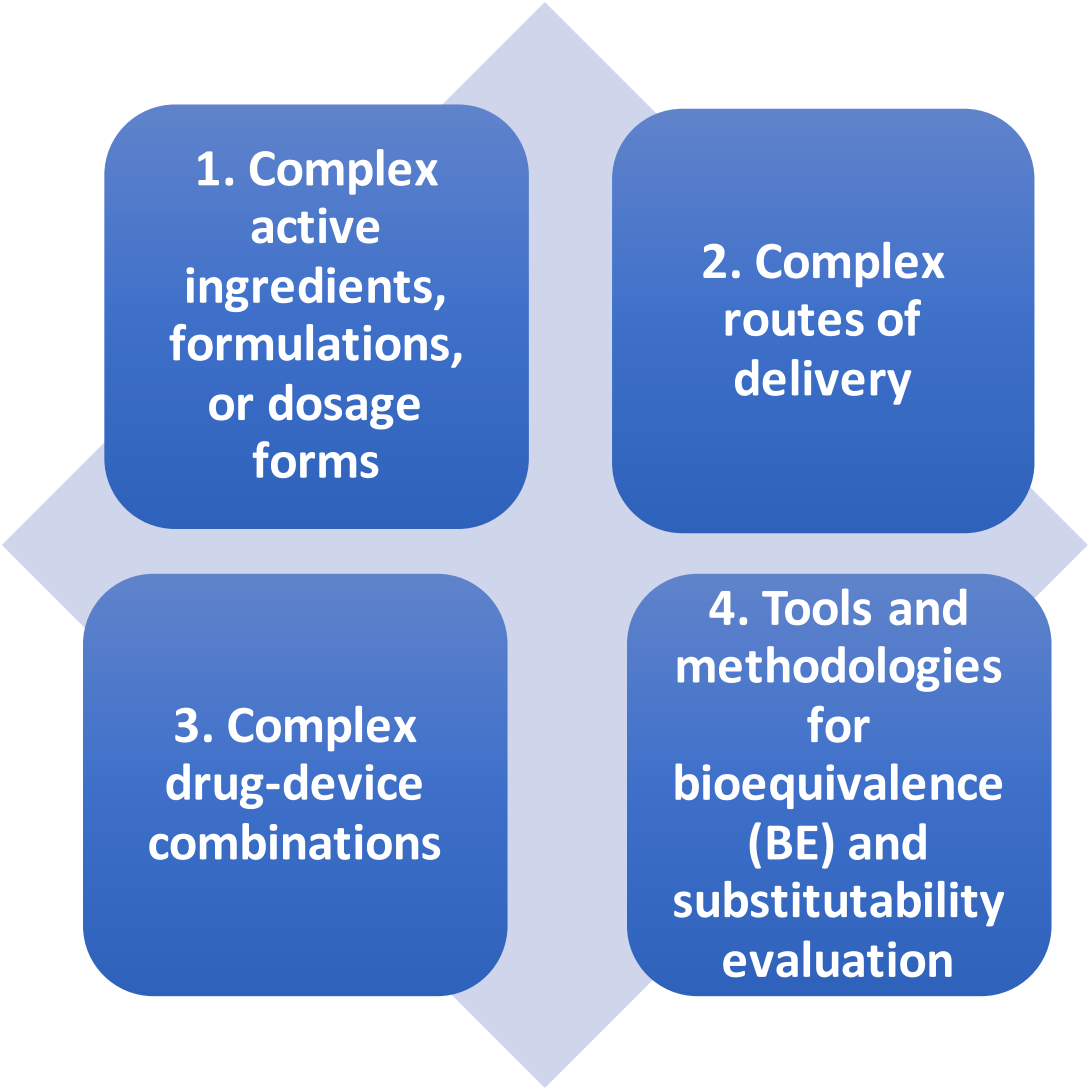
Office of Research and Standards (ORS) Operational Model

- ORS in OGD is a multidisciplinary **Office** that plans and conducts **Research** and translates the results into generic drug **Standards**



FY2018 GDUFA Research Science Priority Areas

15 priority areas under 4 broad categories



https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Developing Methods to Support BE Evaluation

- Q1, Q2, Q3 approaches
  - Qualitative, quantitative and physicochemical sameness
- In vitro testing (Q3) Methodologies
  - Release testing
  - Permeation
  - Raman spectroscopy
  - Computational fluid analysis
  - Microsampling strategies
  - Others
- Improved Study Design

  (directly the result of better understanding of drug product performance attributes)
- Modernized Statistical approaches
- Clinical Pharmacology tools
  - Modeling
  - Simulation

ALL WITH THE INTENT TO…..
compile and align orthogonal evidence to conclude "sameness"/Equivalence

Challenges in Establishing BE Standards for Complex Generics

- Completeness of analytical characterization
  - How many characterizations are needed?
- How similar is equivalent?
  - Equivalence test (statistical criteria)
  - Quality range approach (mean ± X SD)
  - Qualitative comparison (visual displays)
  - Quantitative comparison (statistical methodology)
- Bridging in vitro to in vivo

GDUFA II Complex Product Workshops

- Oct 2-3, 2017: Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review
  - https://www.fda.gov/Drugs/NewsEvents/ucm554182.htm
- Oct 6th, 2017: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
  - https://www.fda.gov/Drugs/NewsEvents/ucm552461.htm
- Oct 20th, 2017: Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access
  - https://www.fda.gov/Drugs/NewsEvents/ucm557252.htm
- Jan 9th, 2018: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products
  - https://www.fda.gov/Drugs/NewsEvents/ucm576064.htm
- Sept 12-13, 2018: Complex Generic Drug Product Development Workshop
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm615104.htm

FDA Commissioner's Blog on Generic Drug Harmonization October 18, 2018

FDA Voices

- FDA Voices on Policy
- FDA Voices on Consumer Safety and Enforcement
- FDA Voices on Medical Products
- FDA Voices on Food
- FDA Voices on Tobacco

Advancing Toward the Goal of Global Approval for Generic Drugs: FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

October 18, 2018

By: Scott Gottlieb, M.D.

Too many Americans struggle with the high cost of drugs. In some cases, patients go without needed medicines. This is why drug pricing is a matter of public health. And it's why FDA launched a Drug Competition Action Plan that focuses on three key areas designed to facilitate more generic competition, promote patient access, and improve the economics of developing generic medicines.

While we've made substantial progress in fostering more competition by resolving obstacles that can make it difficult to win approval of generic versions of certain complex drugs, increasing the speed of generic approvals, and closing down ways that branded companies game the system to prolong drug monopolies, there's still more work to be done.

So we're opening up some new policy fronts when it comes to our Drug Competition Action Plan. And we're re-launching that plan for 2019 with some additional initiatives. Chief among them is a new effort that FDA has proposed to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), a key international body comprised of other regulatory authorities and the pharmaceutical industry: The pursuit of common global development standards for generic drugs.

FDA Commissioner Scott Gottlieb, M.D.

https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm623665.htm

Key Objectives of My Fellowship

Learn EMA's approach on Generics and Hybrids

- Learn EMA's process and principles in developing guidelines related to generics include product-specific bioequivalence guidelines
- Understand possible reasons for the observed differences in BE recommendations

Explore a possible pilot project on complex generics using the Parallel Scientific Advice (PSA) mechanism

- Understand the PSA process, logistics, and timeline
- Establish connection
- Identify benefit and develop criteria for using this mechanism

Identify opportunities for future interaction and convergence

- Interact with the CPN group, PKWP, and QWP on guidance development for generics
- Create opportunities for global development of generics

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