Role of Regulatory Science in Reducing Barriers to Generic Drug Product Development

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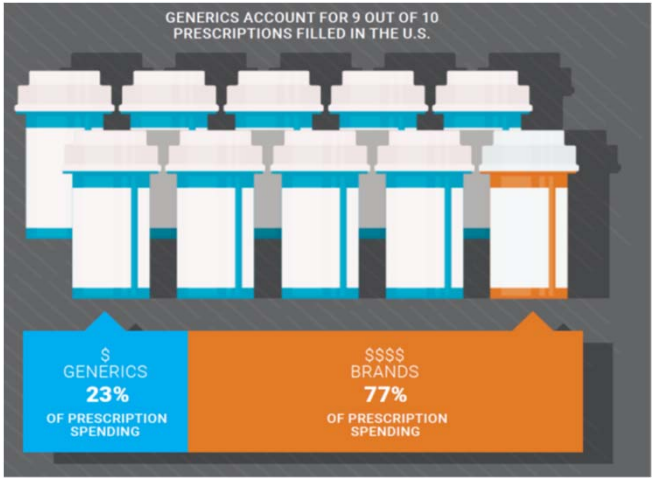
Disclaimer: The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views or policy of the U.S. Food and Drug Administration.

Generic Drugs in the United States

Overall Drug Products

Generic Drugs:

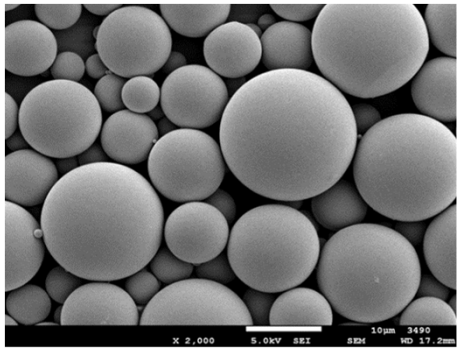
- 90% of prescription
- 23% of spending



Orally inhaled drug products

1 Generic
(approved Jan 30, 2019)

Poly-(lactic-co-glycolic acid) (PLGA) microspheres
Long-acting injectable products



No Generics

However,

~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/2018_aam_generic_drug_access_and_savings_report.pdf

GDUFA: Generic Drug User Fee Amendments

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

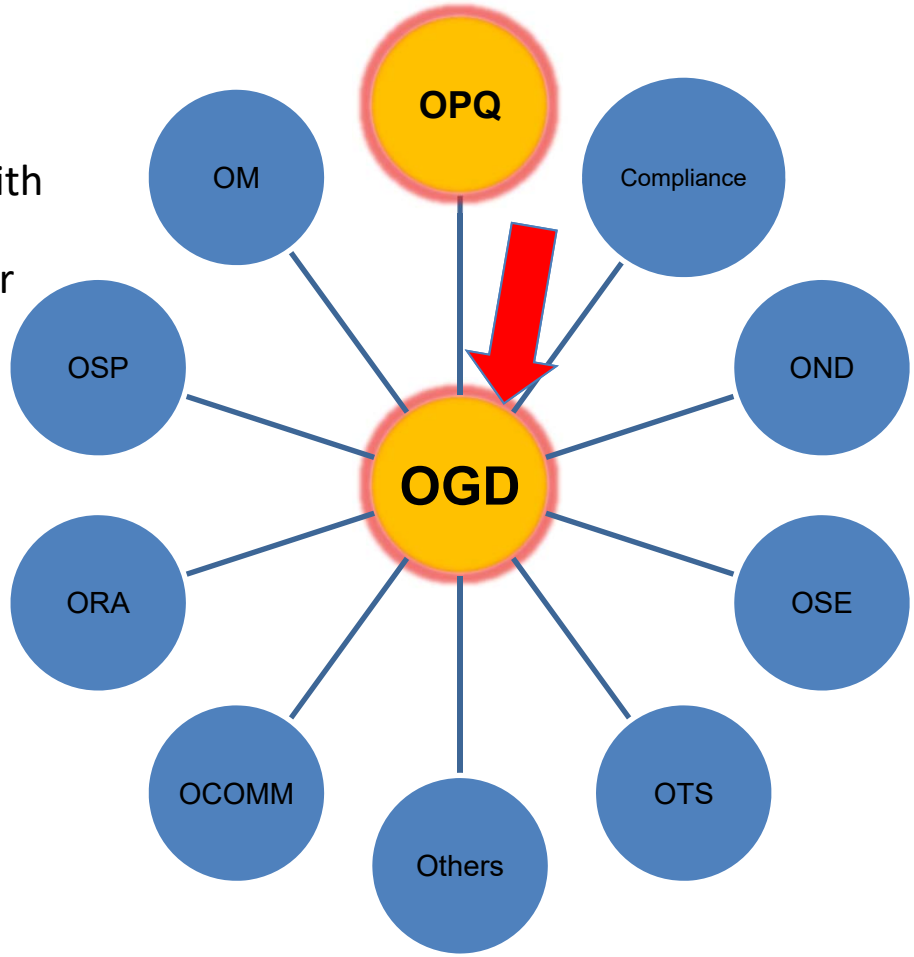
Our Interest

- 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
  - 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

FDA Generic Drug Program

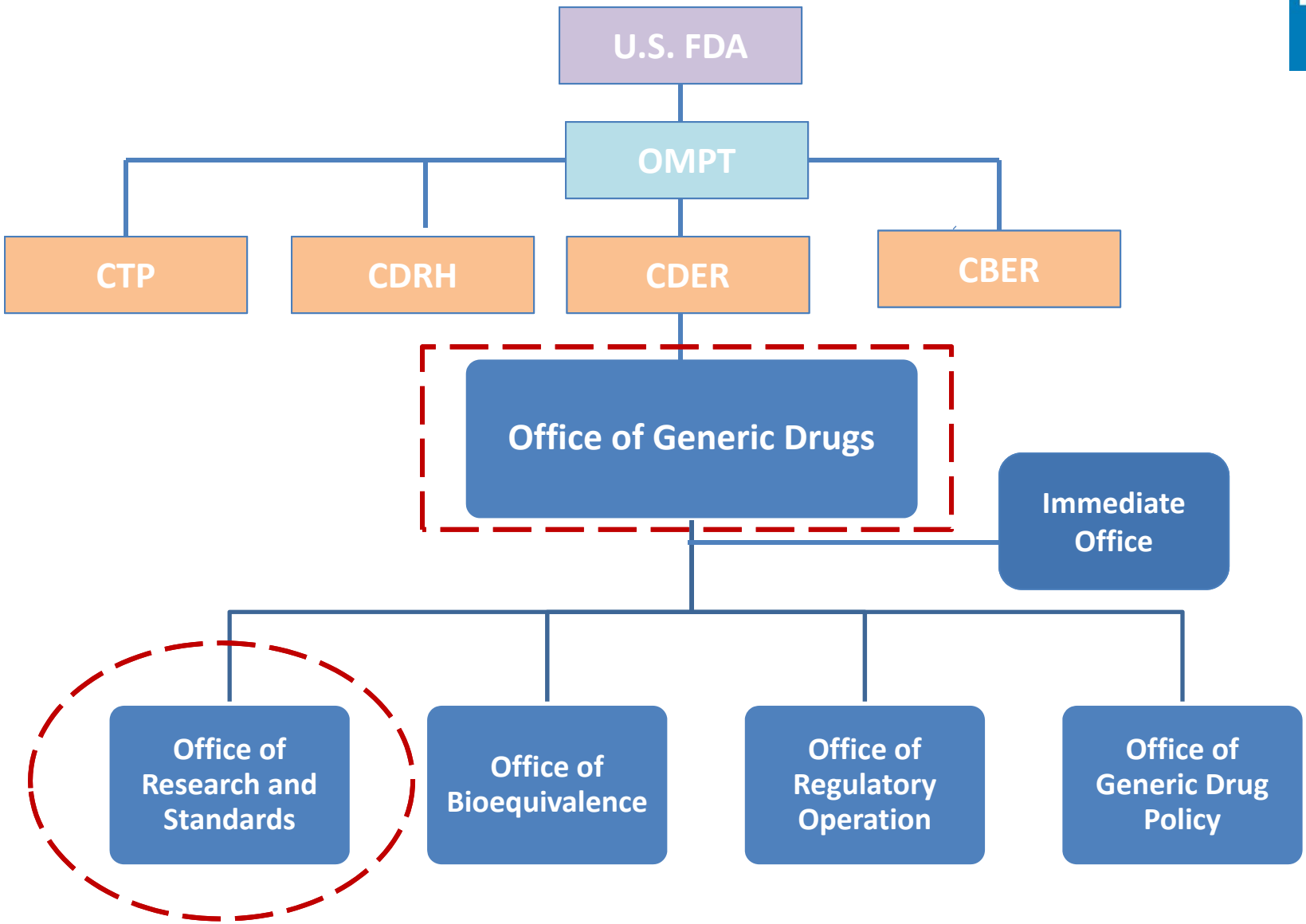
- **The Office of Generic Drugs (OGD)** at CDER, FDA
  - interface for abbreviated new drug application (ANDA) applicants to interact with for the Generic Drug Program,
  - similar to the Office of New Drugs (OND) for new drug applications (NDAs)
- **The Office of Product Quality (OPQ)** and **OGD**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



www.fda.gov

CDER: Center for Drug Evaluation and Research
CBER: Center for Biologics Evaluation and Research
CDRH: Center for Devices and Radiological Health

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

Generic Drugs

- Are the same as brand-name drugs (or “innovator” or reference listed drug, RLD) in active ingredients, dosage form, strength, route of administration, quality, performance characteristics, safety, efficacy, and intended use

(Feb 2019, Clinical Pharmacology and Therapeutics Themed Issue)

From FDA website – Understanding Generic Drugs
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

Allowed Difference in Generics

A generic product cannot have *significant differences* that would impact the safety or efficacy profile of the brand-name drugs

- 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

https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/default.htm

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

NDA	ANDA
1. Chemistry, Manufacturing & Controls (CMC)	1. Chemistry, Manufacturing & Controls (CMC)
2. Testing	2. Testing
3. Labeling	3. Labeling
4. Inspection	4. Inspection
5. Animal Studies	
6. Bioavailability	5. Bioequivalence
7. Clinical Studies	

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

Infer **TE**

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

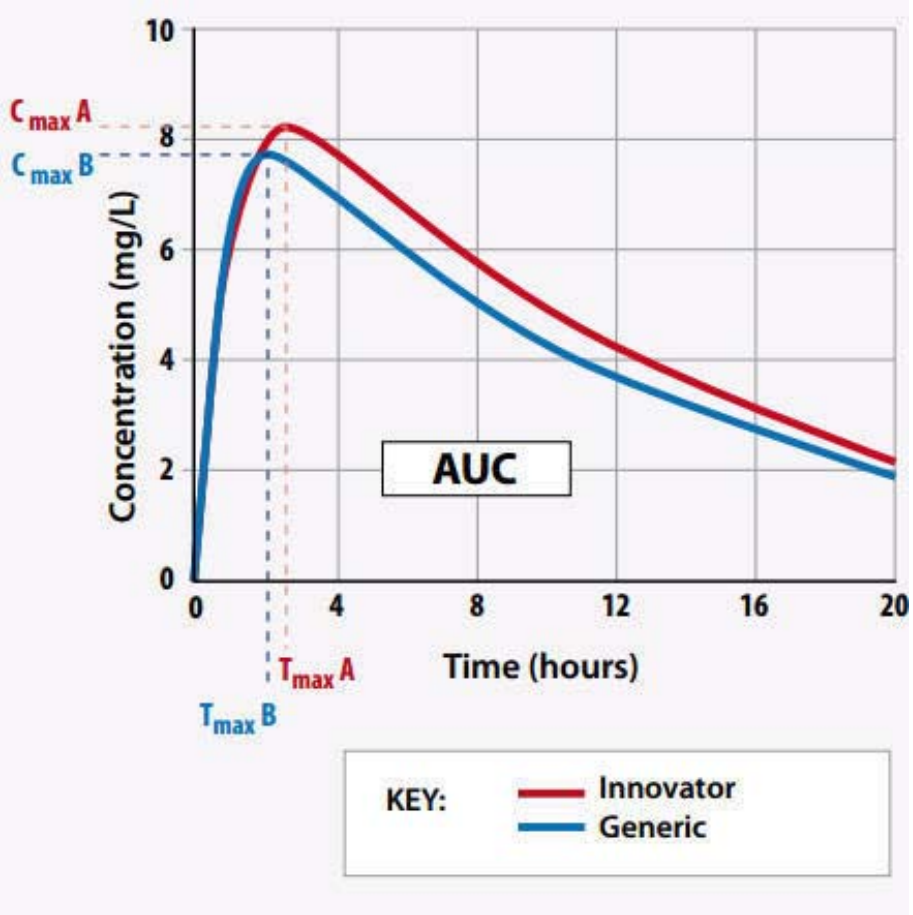
TE: Therapeutic Equivaence

Therapeutic Equivalence (TE)

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

Bioequivalence (BE) Determinations



- For products with systemic site of action, BE via systemic PK endpoints (e.g., C_{max} and AUC) helps infer comparable safety and efficacy

- For products that are locally acting, it is more difficult to assess local exposure
  - The site of action may not be directly correlated with systemic PK
  - Alternative methods

Bioequivalence Approaches

Maybe demonstrated by in vivo or in vitro data or both:

- In vivo pharmacokinetic (PK) study
  - Endpoints: blood, plasma, etc.
- In vivo pharmacodynamic (PD) study
- In vivo comparative clinical endpoint BE study
- In vitro studies
  - Waiver of in vivo studies for certain immediate-release (IR) oral dosage forms
    - Biopharmaceutics Classification System (BCS)-based
    - Additional strength
  - In vitro tests predictive of human in vivo bioavailability (IVIVC) (for extended-release oral dosage forms)
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence

21 CFR 320.22 and 320.24(b)

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”

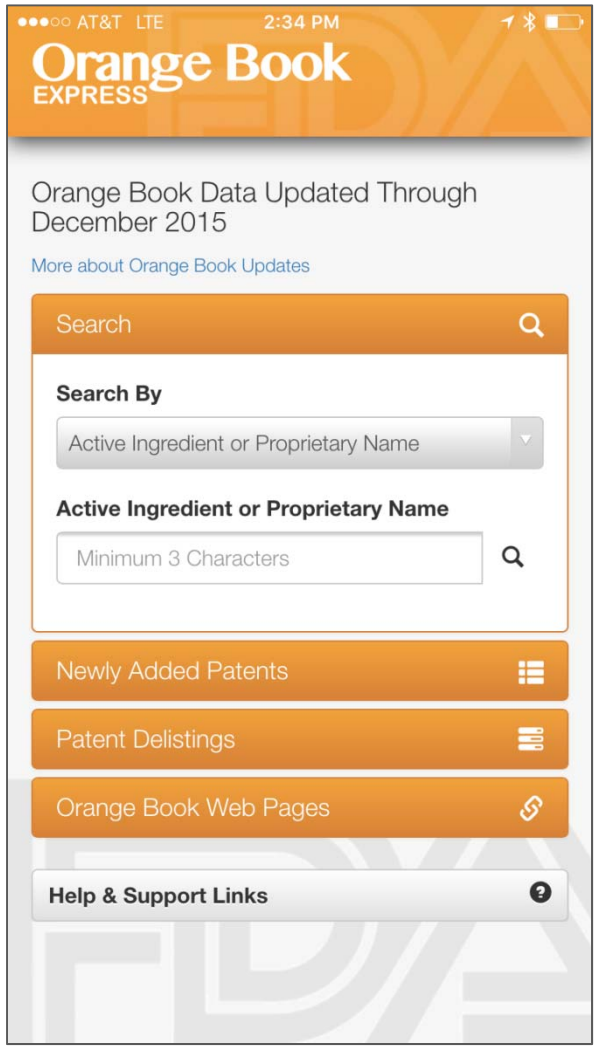
- The first print publication occurred October 1980, and the color orange was selected since it was almost Halloween.

- All FDA approved drugs products listed
  - NDAs, ANDAs 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-name 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

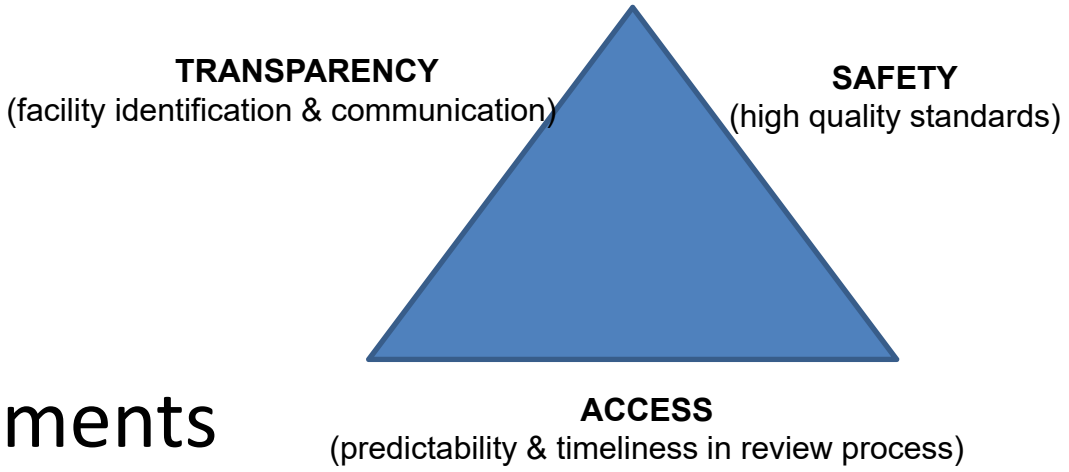
ANDROID APP ON Google play

Generic Drug User Fee Amendments (GDUFA)

- First started in Oct 2012 (GDUFA I)
- 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)

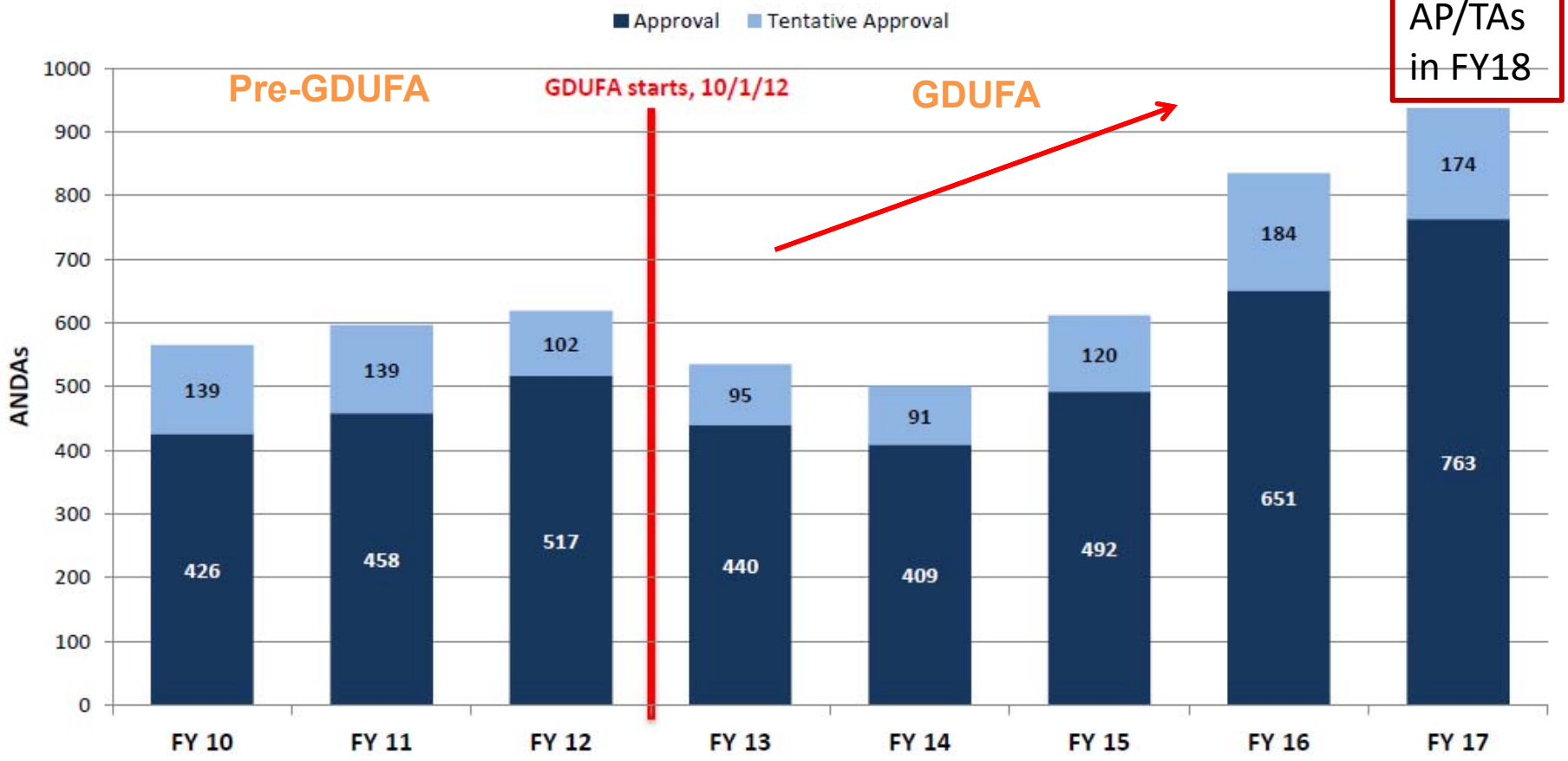
1. Metrics
   - Applications
   - GDUFA Backlog
   - cGMP Inspections
2. Efficiency enhancements
3. **Regulatory science**



cGMP: Current Good Manufacturing Practices

GDUFA Process Improvements Bring Increased Approvals (APs) and Tentative Approvals (TAs)

971 AP/TAs in FY18



GDUFA I Research Outcomes

- Awarded ~100 research grants and contracts
- Published 788 of product-specific Guidances (PSGs)*
  - 495 new and 293 revisions
- Held 65+ pre-ANDA meetings
  - Pre-ANDA meetings are in GDUFA II commitments
- Approved first generic ANDAs linked to GDUFA research projects, e.g.,
  - 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)

***Product-specific guidances identify the evidence needed to support generic drug approval**
https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

GDUFA II

- Second 5-year program
- 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

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 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/formu-lations	• 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

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

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

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 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**

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

- Identify a Single RLD
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength

Pharmaceutical Equivalence (PE)

- Same Labeling
- **Bioequivalence (BE)**
- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls (CMC) Information
- cGMPs (facilities)

PE + BE → TE

Challenges for Complex Generic Drug Products

- Pharmaceutical Equivalence (PE)
  - How to demonstrate active ingredient "sameness"
- Bioequivalence (BE)
  - 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 (TE)
  - 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 (PSGs) on how to demonstrate "sameness" or equivalence (PE, BE, TE)

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 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 molecular entities (NMEs)
- Establishes Pre-ANDA program for complex generic drug products

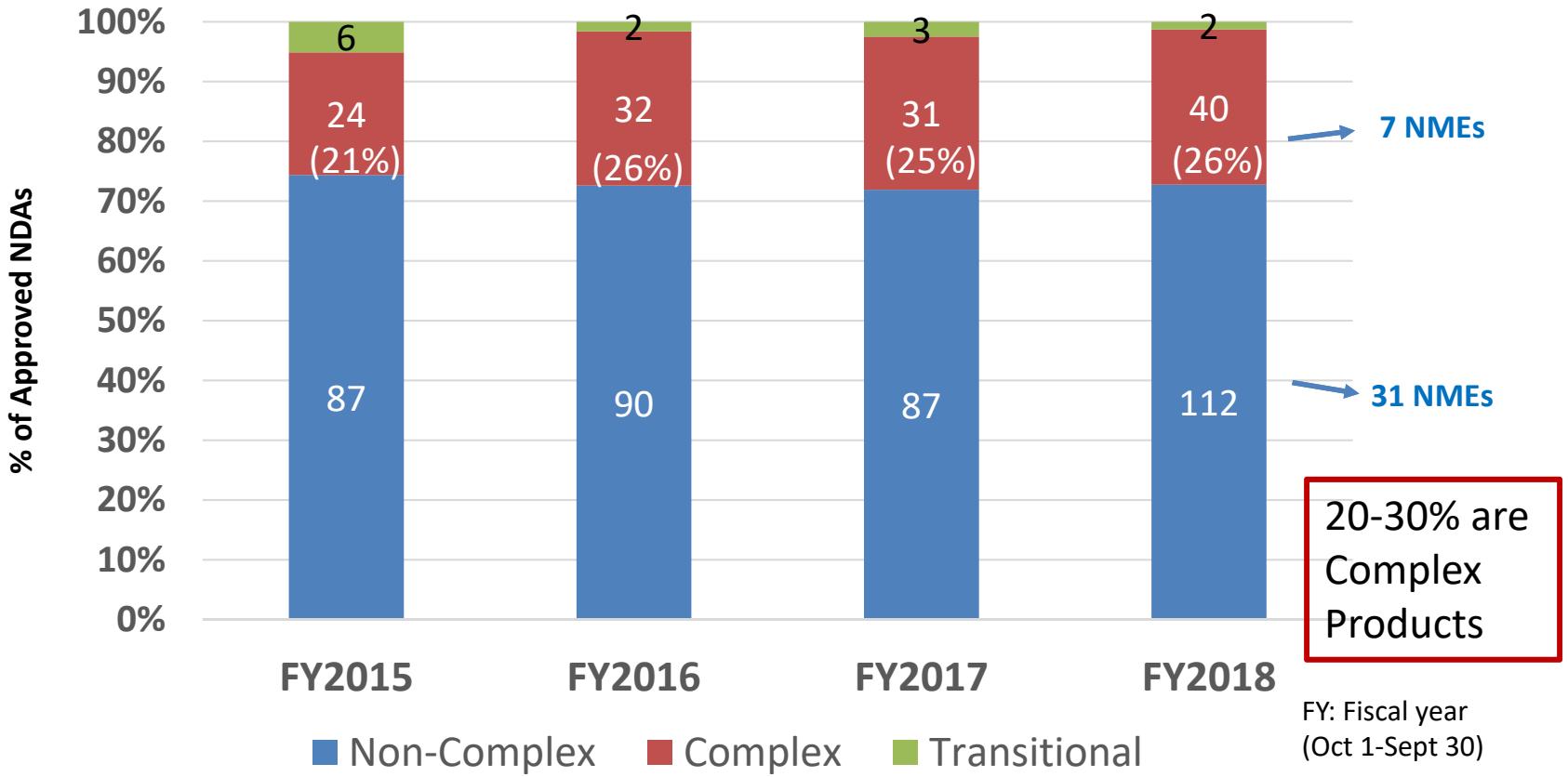
GDUFA Regulatory Science Program

- 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

Complex Drug Products in Approved NDAs FY2015-2018



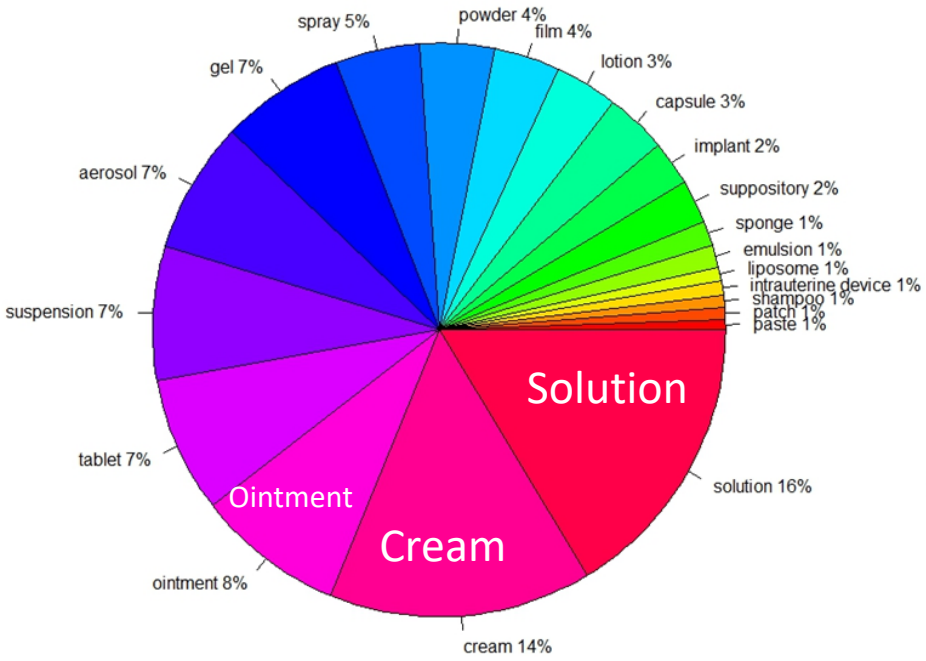
FY: Fiscal year
(Oct 1-Sept 30)

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

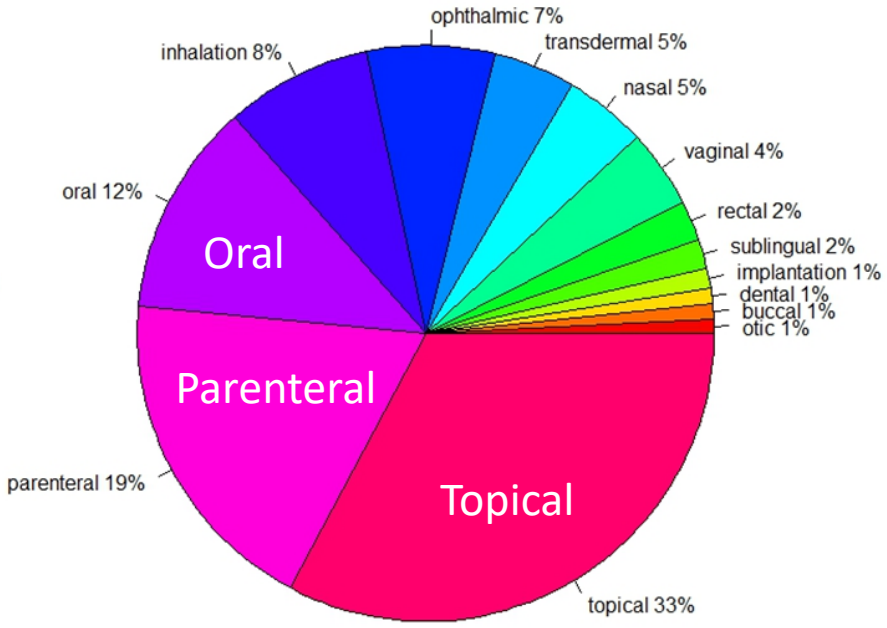
NDA: New Drug Application; NMEs: New Molecular Entities

Distribution of Complex Drug Products Based on Dosage Forms and Administration Routes

Dosage Form



Rout of Administration



Data in these figures are up to 2017

Courtesy: Wenlei Jiang

GDUFA Regulatory Research

The 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

FY19 Research Priorities

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

Complex Drug Products

https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm567695.htm

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)
  - ONPATTRO (Patisiran)

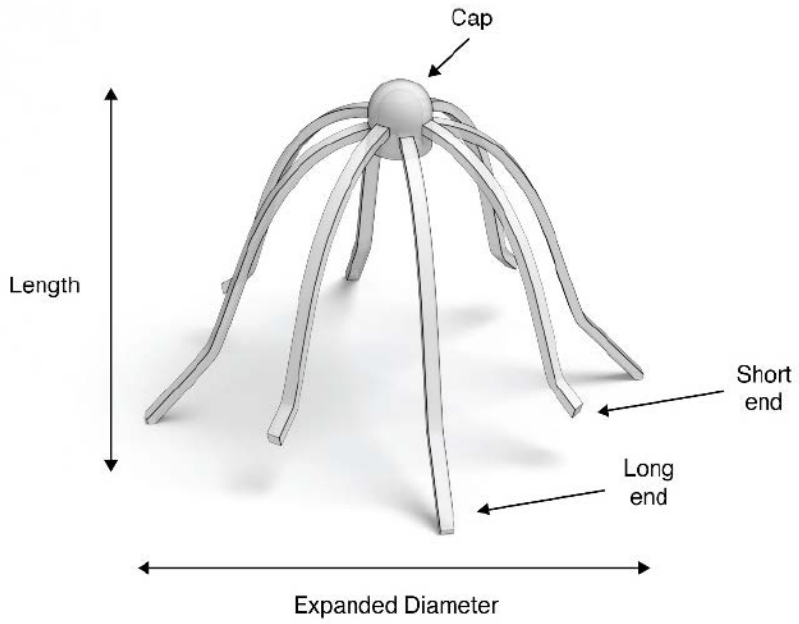
Challenges:
- Characterizations for establishing identity
- Impurity analysis for related-substances

Examples of Complex Drug-Device Products

- **New device: Respimat device**
  - Four drug products approved in this device
    - No PSG has been issued
  - A new inhalation drug delivery device and commonly referred to as "Soft Mist Inhaler"
  - The device actuates a mist cloud of solution over 1.5 seconds (as opposed to a 10-minute nebulized product or a few millisecond actuated metered dose inhaler)
  - Active FDA research toward developing BE standards

SINUVA (Mometasone Furoate)

- New dosage form: New approach to treat Nasal Polyp Disease
- Approved: 12/08/2017 (NDA 209310)
- API: Mometasone furoate
- Dosage Form/Route: Implant; implantation
- An implant that elutes drug over time to the local site of action
- **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



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

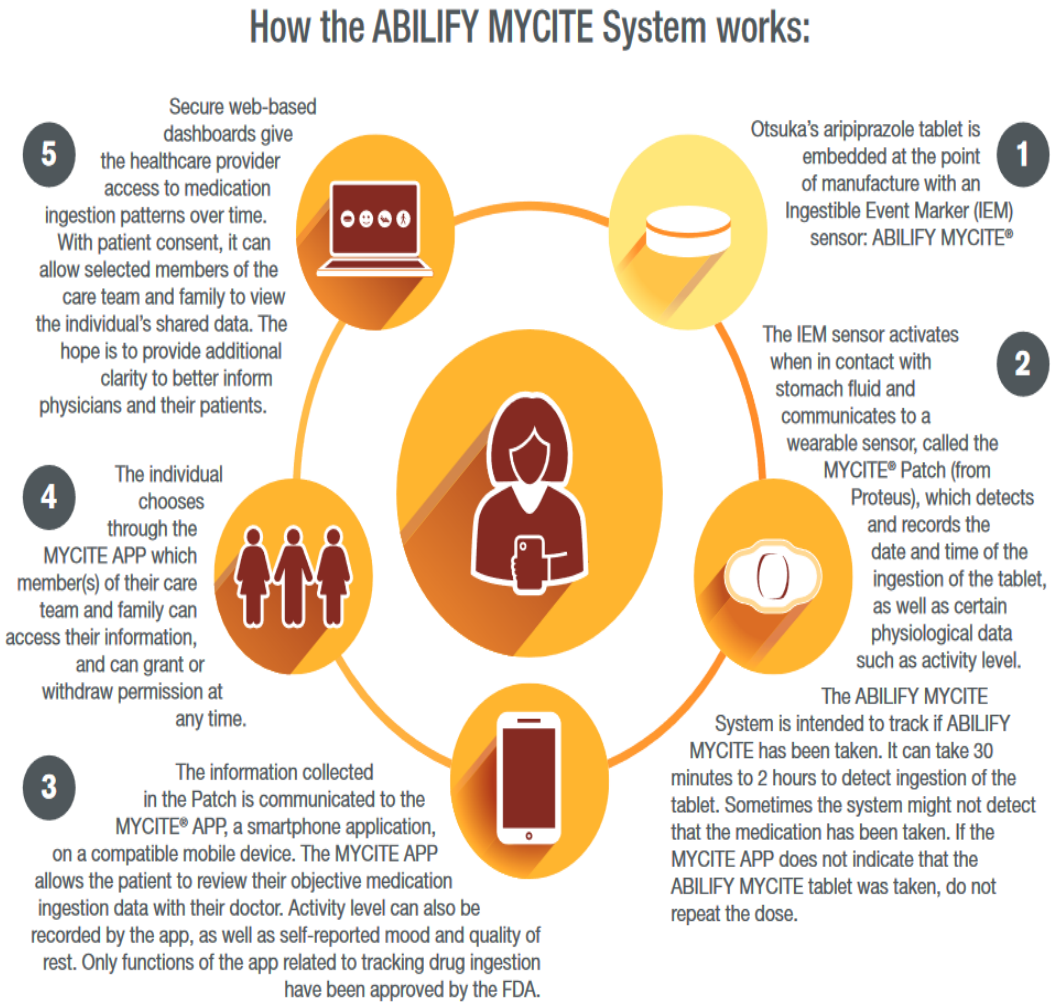
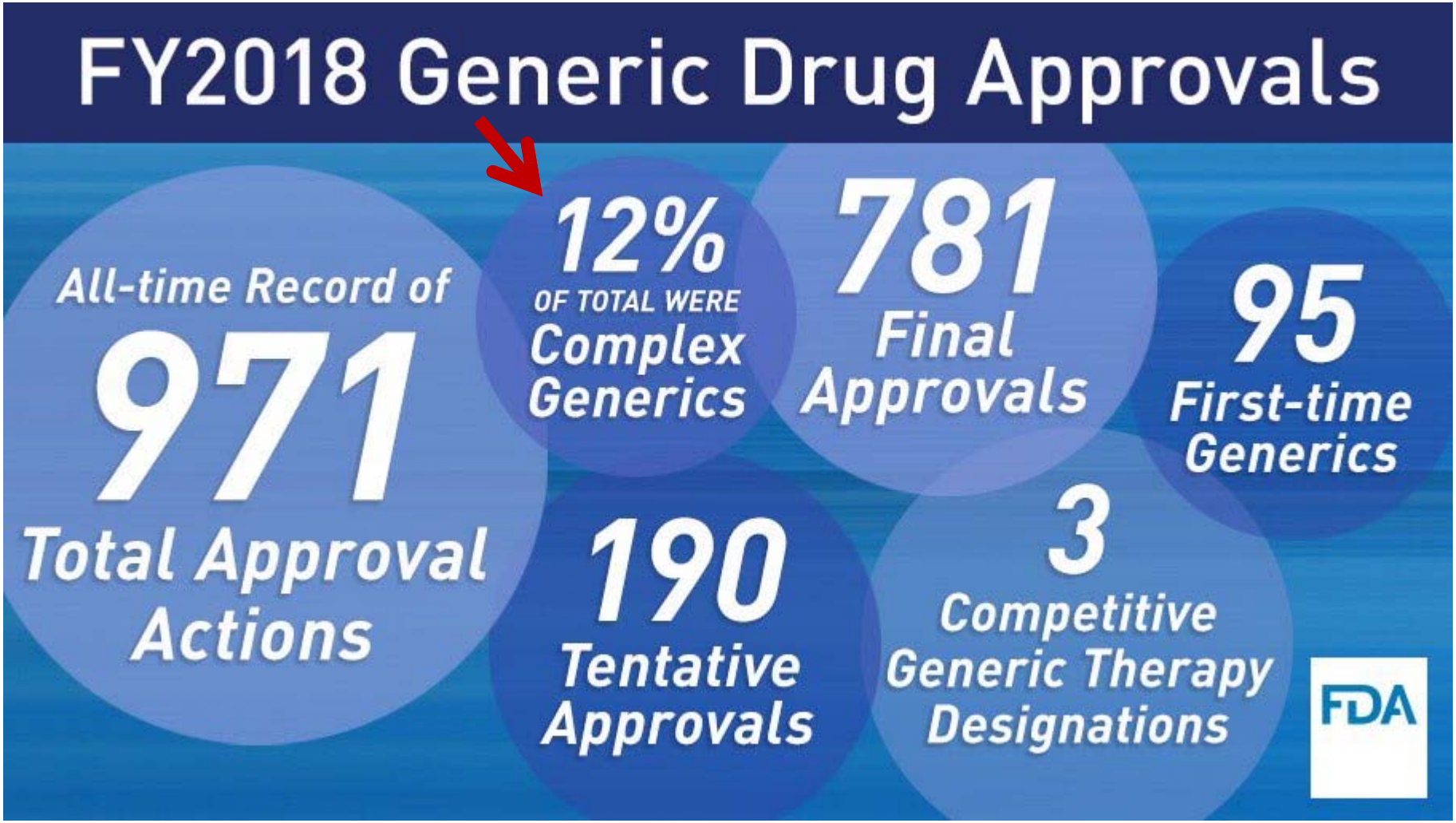


Image source: Proteus Digital Health

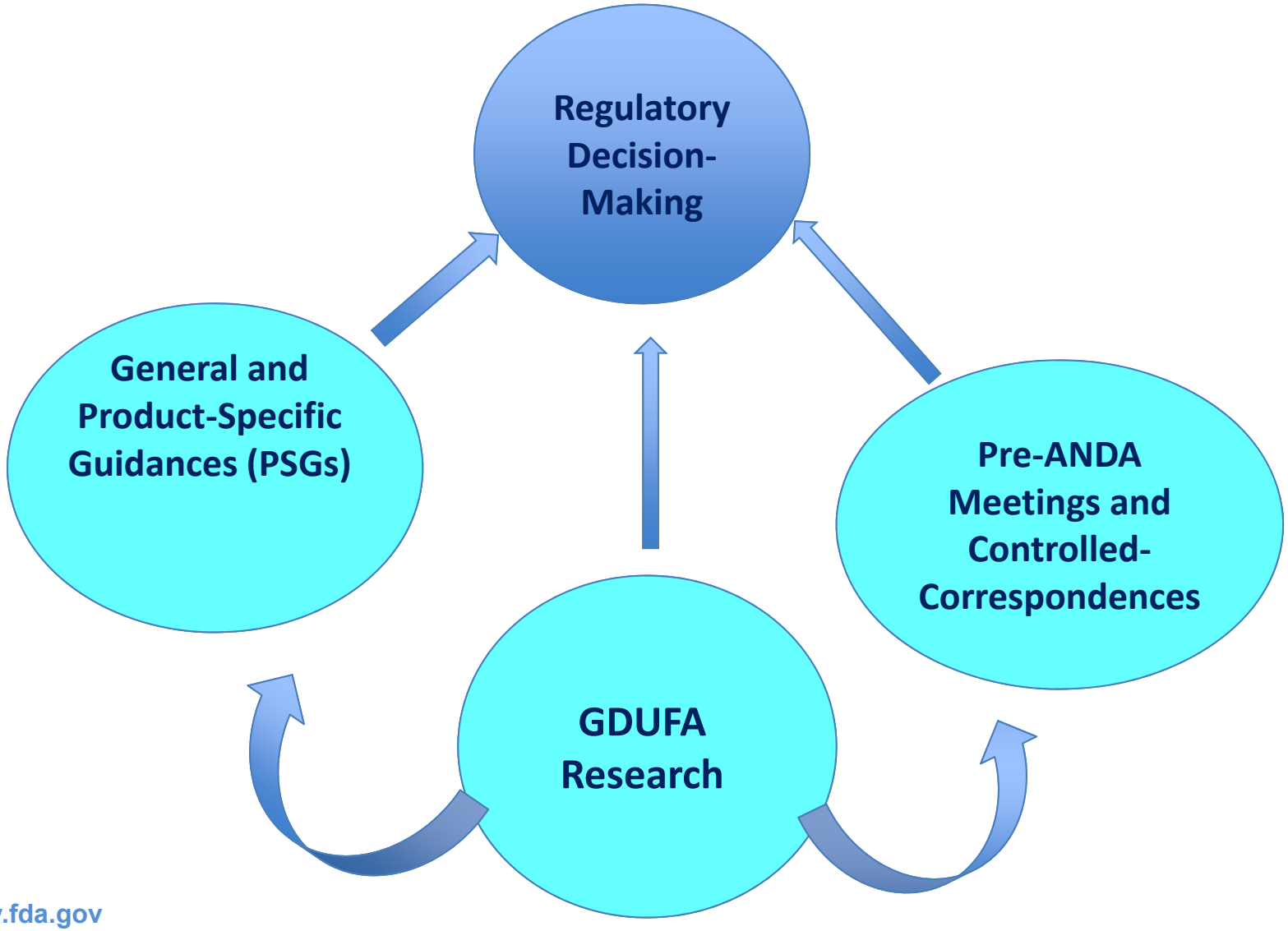
In FY 2018, ~30% approved New Drugs (NDAs) are complex products.



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

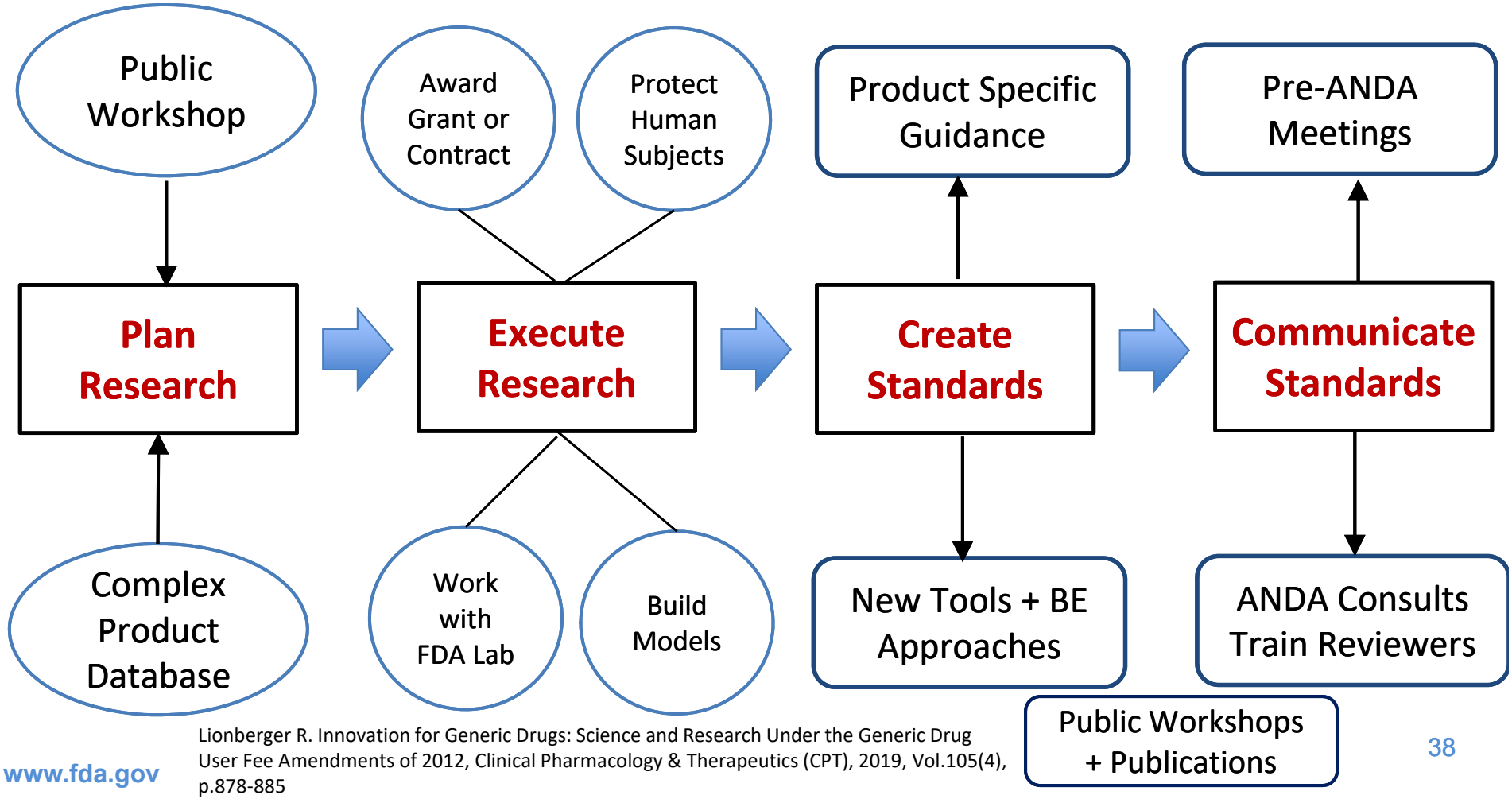
www.fda.gov

Science-Informed Regulatory Policy and Decision-Making



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**



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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: -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: -Research-

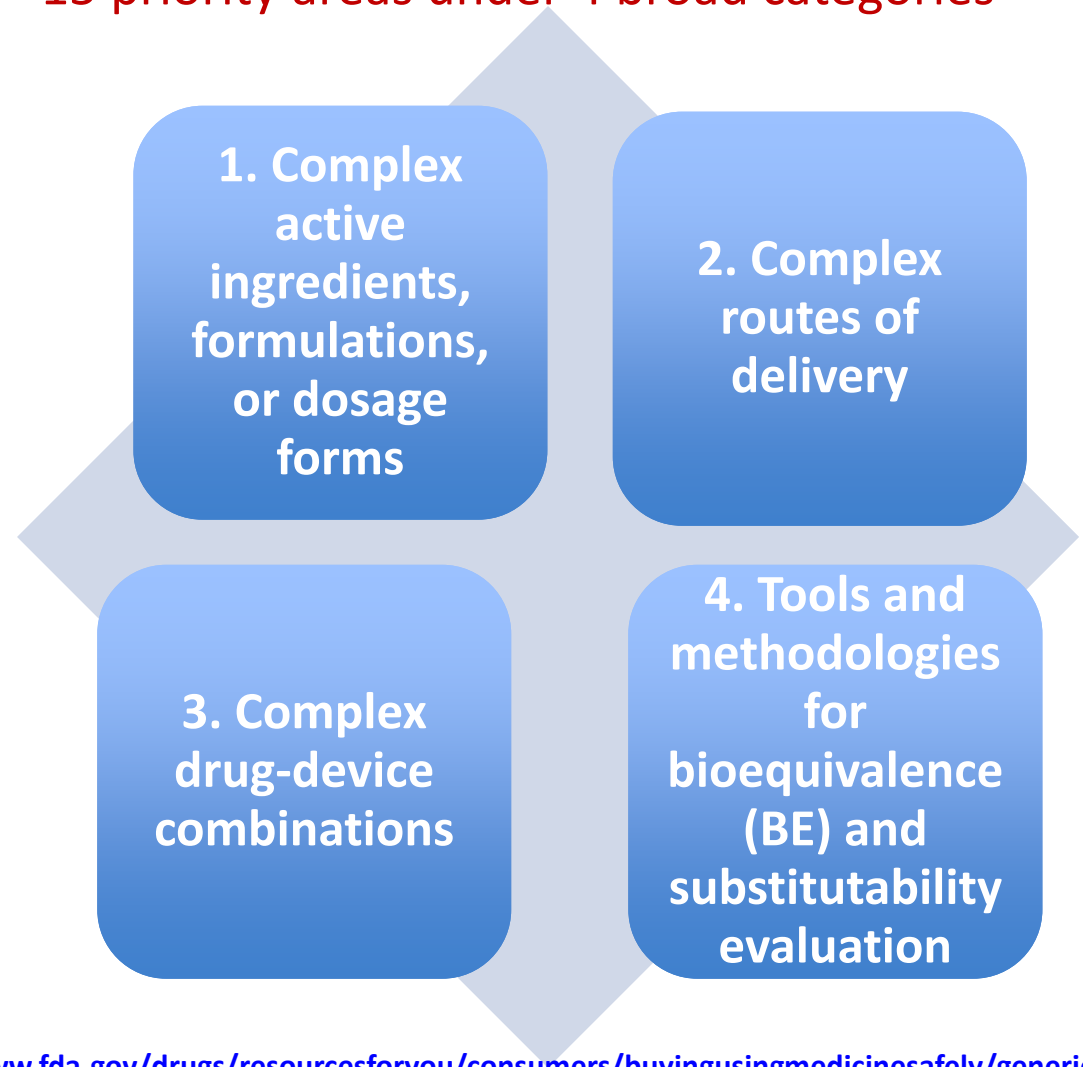
- Reporting
  - Annually, FDA will report on its website the extent to which GDUFA regulatory science-funded projects
    - Support the development of generic drug products
    - Generate evidence needed to support efficient assessment and timely approval of ANDAs
    - Evaluate generic drug equivalence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

GDUFA Science and Research Website

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

FY2019 GDUFA Research Science Priority Areas

15 priority areas under 4 broad categories



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

FY18 GDUFA Research Priority
(#14) Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations

- **FDA Internal Research**
  - Bi-phasic dissolution systems
  - Impact of excipients on drug solubility, passive permeability, and intestinal metabolism and transport
  - A database on commonly observed excipients in IR products for BCS Class III drug substances

- **Ongoing Grants and Contracts Funded in FY2017**
  - Effect of excipients on intestinal drug transporters (PI: Kathy Giacomini)

Zhang L, FY2018 Generic Drug Regulatory Science Initiatives Public Workshop, May 24, 2018
https://www.fda.gov/downloads/Drugs/NewsEvents/UCM608740.pdf

Effect of Excipients on Drug Product Absorption

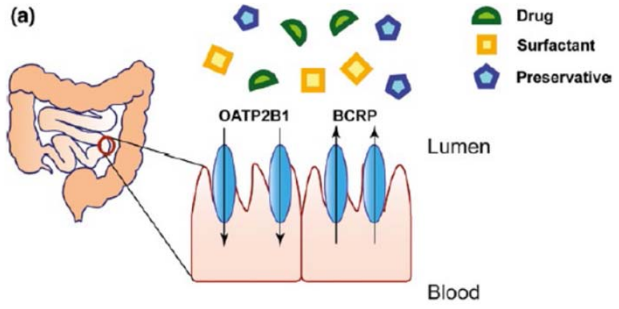
- Research was conducted to comprehensively determine the effects of excipients on oral drug absorption to support mechanistic understanding-based formulation strategy for developing generic oral drug products

- Excipients' impact on bioavailability of BCS Class 3 drugs (Contracts: HHSF223200910020C and HHSF223200810041C)
  - Univ. of Maryland

Vaithianathan S, et al., J Pharm Sci. 105(2):996-1005, 2016; Vaithianathan S, et al., J Pharm Sci. 105(4):1355-1357, 2016.

- FDA-UCSF/Stanford CERSI project (Grants: U01FD004979/U01FD005978)
  - UCSF

Zou L, et al., *Clin Pharm Ther*. 105 (2)323-325, 2019; Irwin JJ, et al., *Clin Pharm Ther*. 101 (3) 320-323, 2017



BCS3 drugs: Cimetidine and Acyclovir

14 excipients were selected from a list of 20 most common excipients in oral products; **12** common excipients were found not impact cimetidine and acyclovir absorption in humans.

Excipient	Recommended maximum allowable amount for a class 3 biowaiver (mg)	Maximum excipient amount studied here (mg)	Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg	Maximum amount (mg) in Inactive Ingredient Database
Microcrystalline Cellulose	Qualitatively same and quantitatively v similar	600	100mg (20%-90%)	1385.3
Hydroxypropyl Methyl Cellulose	Qualitatively same and quantitatively v similar	40	10mg (2%-5%)	444.4
Sodium Lauryl Sulfate	50	50	4.5mg (0.5%-2.5%)	51.69
Corn Starch	900	900	150mg (25%-75%)	1135
Sodium Starch Glycolate	200	200	12mg (4%)	876
Colloidal Silicon Dioxide	40	40	1.5mg (0.1%-1%)	100
Dibasic Calcium Phosphate	600	600	150mg (25%-75%)	635.5
Crospovidone	100	100	10mg (2%-5%)	340
Lactose	900	900	240mg (80%)	1020
Povidone	70	70	7.5mg (0.5%-5%)	240
Stearic Acid	80	80	6mg (1%-3%)	72
Pregelatinized Starch	200	200	150mg (5%-75%)	435.8
Croscarmellose Sodium	120	120	37.5mg (0.5%-25%)	180
Magnesium Stearate	40	40	7.5mg (0.25% to 5%)	400.74

Vaithianathan S, et al., J Pharm Sci. 105(2):996-1005, 2016; Vaithianathan S, et al., J Pharm Sci. 105(4):1355-1357, 2016.

Save the Date!

FY 2019 Generic Drug Regulatory Science Initiatives Public Workshop

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Meeting Information

Date:

Wednesday, May 1, 2019, from 8:30 - 4:30pm

Location:

FDA White Oak Campus, 10903 New Hampshire Ave. Bldg. 31, Rm. 1503 Sections B&C Silver Spring, MD 20993

Background:

FDA will hold a public workshop that will provide an overview of the current status of the regulatory science initiatives for generic drugs and will provide an opportunity for public input on research priorities in these topic areas. FDA is seeking input from a variety of stakeholders—industry, academia, patient advocates, professional societies, and other interested parties—as it fulfills its commitment under the reauthorization of the Generic Drug User Fee Amendments (GDUFA) to develop an annual list of regulatory science initiatives specific to generic drugs. FDA will take the information it obtains from the public workshop into account in developing the fiscal year (FY) 2020 Regulatory Science Plan. The workshop will be held on May 1, 2019, at the FDA White Oak Campus, 10903 New Hampshire Avenue Building 31, Great Room Sections B & C, Silver Spring, MD 20993.FDA wants your input. You may submit ideas on generic drug research topics to be included on the FY 2020 Regulatory Science Plan by emailing GDUFARegulatoryScience@fda.hhs.gov.

Additional details are available in the Federal Register Notice.

One of topics for discussion:
The value to the generic industry in expanding BCS class 3 waivers to non-Q1/Q2 formulations

https://www.fda.gov/Drugs/NewsEvents/ucm624723.htm

Pre-ANDA Program for Complex Products:
-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
  - 1,682PSGs are currently available as of February 2019
  - 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:
-Guidance-

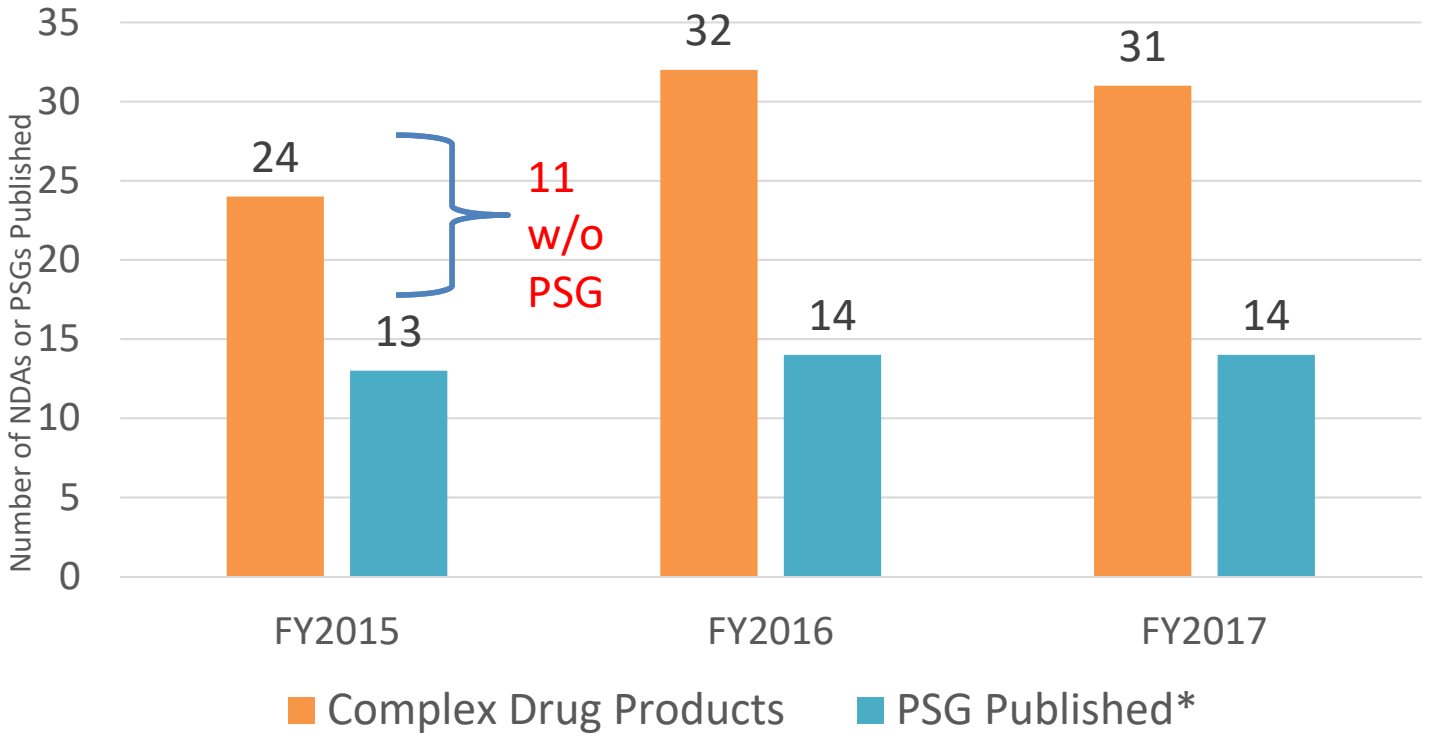
Timely PSGs to optimize ANDA reviews for all product categories

- 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 (FY2015-2017 NDA Approval Cohorts)



* 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)

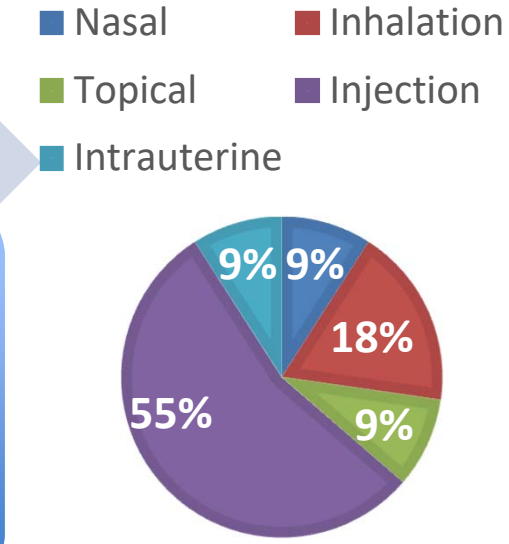
Recent Non-NME Complex Drug Products Without PSG FY2015 (N=11)

1. Complex active ingredients, formulations, or dosage forms

10/11 (91%)
3 Complex APIs
2 Long-acting Injectables

2. Complex routes of delivery

45% COMPLEX ROUTE OF DELIVERY



3. Complex drug-device combinations

5/11 (45%)

4. Tools and methodologies for bioequivalence (BE) and substitutability evaluation

Pre-ANDA Meetings for Complex Drug Products

Meeting Type	Meeting Focus	Product Stages
Product Development Meeting	• Help ANDA applicant engage early with FDA about scientific exchange of an individual product development program, e.g. alternative bioequivalence approach	During complex generic product development stage
Pre-submission Meeting	• Discuss and explain the format and content of an ANDA to be submitted	6-12 months before ANDA submission
Mid-review-cycle meeting	• Provide the applicant an update about the application review status	During ANDA review

Improve quality of ANDA submissions and reduce the number of review cycles required to obtain ANDA approval, particularly for complex generic products

Value Added:
Pre-ANDA Program for Complex Products

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

- Companies were unclear with regard to regulatory expectation
- Submitted ANDAs missed key aspects
- Numerous review cycles and delay

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

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

Ensure high quality submissions and reduce review cycles

Examples of ANDAs for Complex Products 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)

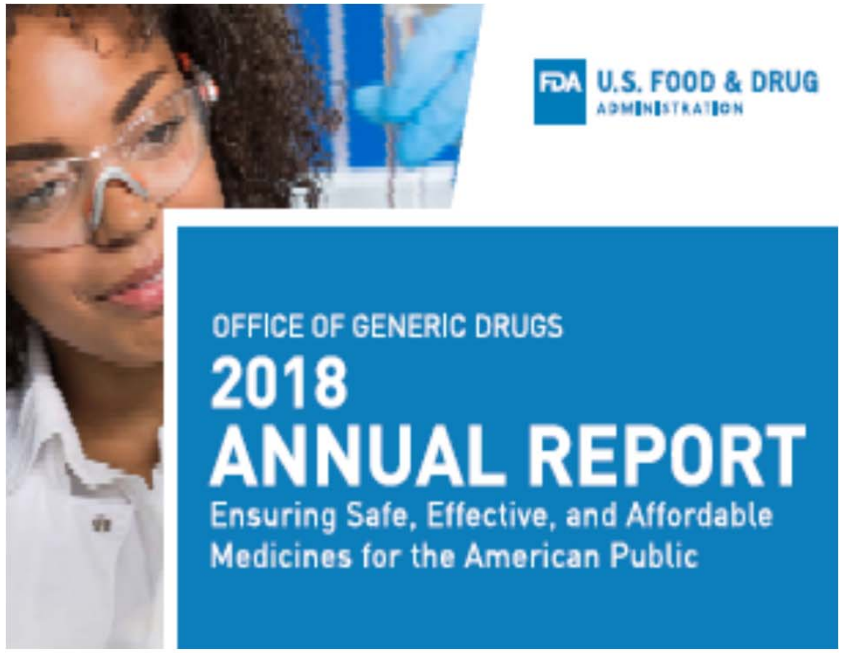
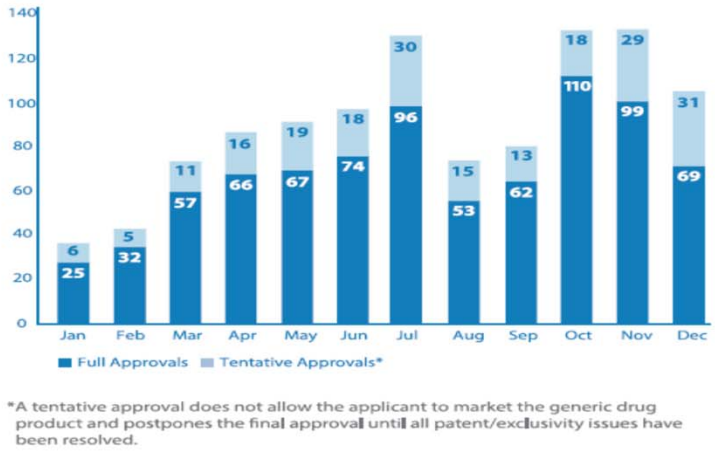


Figure 1. 2018 Generic Drugs Approved



*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.

https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm631710.htm

2018:

- Approval or tentative approval of > 1,000 generic drugs
- 10% first generics
  - 18% were for complex generic drugs
- 14% of all generics approvals were for complex generic drugs

FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D., on 2019 efforts to advance the development of complex generics to improve patient access to medicines

For Immediate Release

Jan 30, 2019

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630160.htm

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Any Questions?

Contact: leik.zhang@fda.hhs.gov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