Complex Drug Product Landscape

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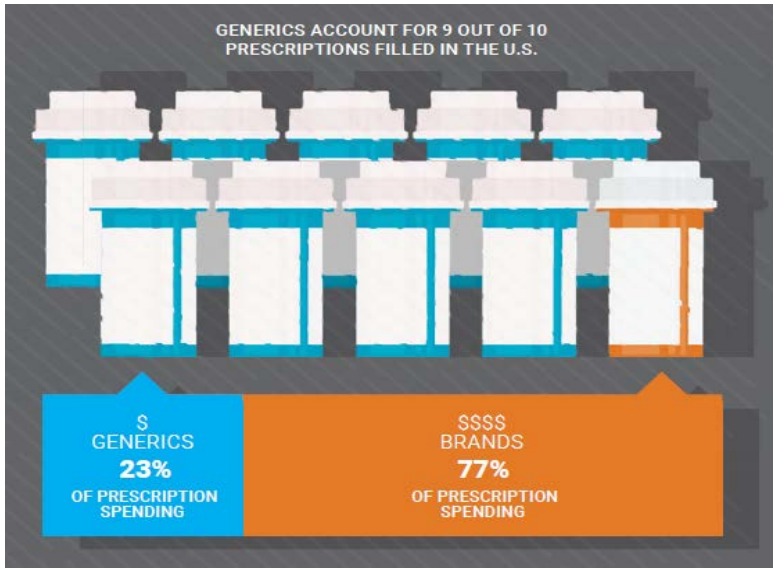
Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Generic Drugs in the United States

Overall Drug Products

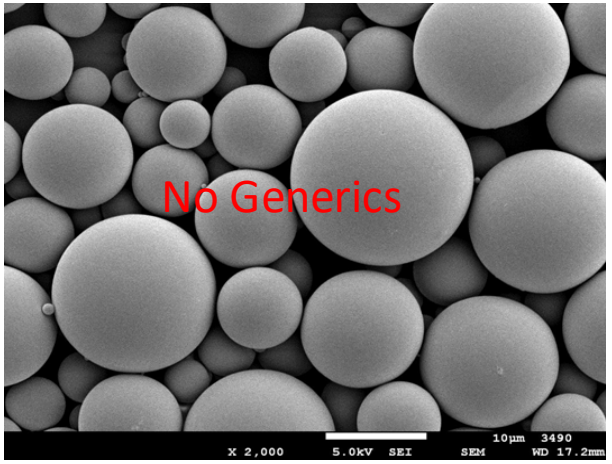


However,

Topical drug products with generics available < 40%
Ophthalmic products with generics available < 50%

Orally inhaled drug products

Poly-(lactic-co-glycolic acid) (PLGA) microspheres



https://accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf

Complex Products

According to the **GDUFA II commitment letter**, complex products generally include products with

1) complex active pharmaceutical ingredients (APIs);
2) complex formulations;
3) complex routes of delivery;
4) complex dosage forms;
5) complex drug-device combination;
6) other products where there is complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

GDUFA: Generic Drug User Fee Amendments

Available at:
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
Complex routes of delivery	• Any non-solution drug product with a non-systemic site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action)
Complex dosage forms/formulations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation
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
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

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

Complex API

A complex API is often a mixture of different components and can contain a distribution of molecular weight (MW), including:

Products that are mixtures of components (often from both semi-synthetic and natural sources), e.g.,

- Conjugated estrogens, heparin, and low MW heparin (e.g., enoxaparin sodium)
- Botanic drug products (e.g., crofelemer)
- Complex oils and oil-derived products (e.g., omega-3 acid ethyl esters)

Products that have a distribution of molecular weight or structures

- Synthetic polymers (e.g., colesevelam HCl)
- Metal complex (e.g., iron sucrose)

Chemically-synthesized polypeptides (majority of chains shorter than 40 amino acids) (e.g., glatiramer acetate)

Peptides (alpha amino acid polymer with a specific, defined sequence that is shorter than 40 amino acids, having higher order structure and potential immunogenicity issues) (e.g., liraglutide)

Oligonucleotides (e.g., eteplirsen)

Complex Dosage Forms

Semisolid Dosage Forms

- Creams, lotions, gels, ointment, and foams

Non-oral Nanotechnology Products

- Nano size liposome formulations (e.g., doxorubicin)
- Iron complex formulations (e.g., sodium ferric gluconate)
- Nano-suspension (e.g., paclitaxel)
- Self-assembling nanotubes (e.g., lanreotide acetate)
- Nano-emulsions (e.g., cyclosporine, difluprednate)
- Lipid complex drugs (e.g., amphotericin B lipid complex)

Long-Acting Injectable (LAI) Products

- Suspensions (e.g., aripiprazole LAI suspension)
- Multivesicular liposomes (e.g., bupivacaine liposomes)
- Biodegradable implants/inserts (e.g., leuprolide acetate)
- Microspheres (e.g., risperidone)

Complex Drug-Device Combination Products

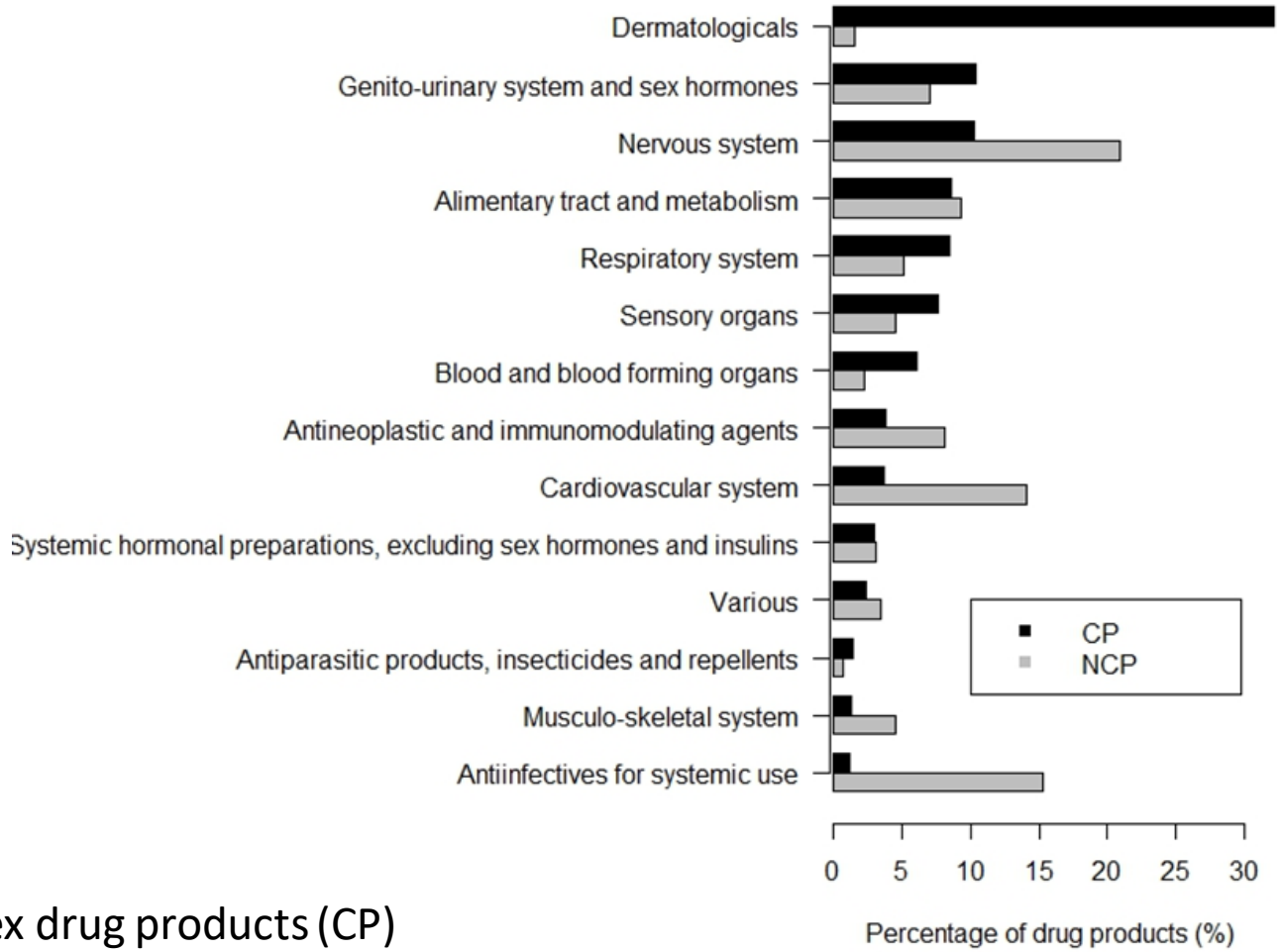
- Pre-filled syringes having a level of complexity, e.g., dual chamber and/or specific labeling unique to the device
- Pre-filled auto-injector products for injectable formulations
- Orally inhaled and nasal drug products (such as metered-dose inhalers, dry powder inhalers, and nasal spray products)
- Iontrophoretic transdermal products
- Transdermal and topical delivery systems (TDS, historically called “patches”)
- Metered-dose pumps for topical and transdermal formulations
- Implants with non-biodegradable device parts
- Intrauterine system

Complex Routes of Delivery

A local route of delivery is considered complex, while the systemic route of delivery is not considered complex.

Administration Routes	Routes of Delivery	Complex Route of Delivery?
Conjunctival, dental, intracavernous, intracavitary, intracerebral, intra-articular, intracorneal, intracoronal, intradiscal, intraductal, intraovarian, intrapulmonary, intrapleural, intraprostatic, intraspinal, intrasynovial, intrathecal intrameningeal, intralymphatic, intralesional, ophthalmic, oral inhalation, otic, periodontal, transplacental, and transtracheal	Local	Yes
Buccal, nasal, oral, rectal, topical, and vaginal	Either systemic or local	Yes, if the route of delivery is local (not systemic)
Transdermal, intravenous, intramuscular, subcutaneous, and sublingual	Systemic	No

Therapeutic Area Distributions of Approved Drug Products

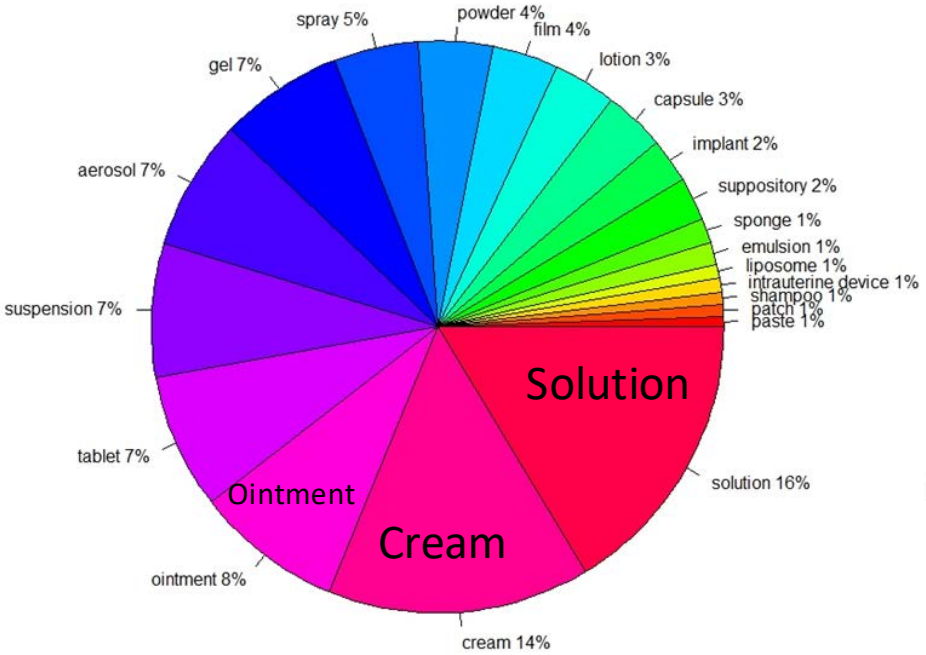


Complex drug products (CP)
Non-complex drug products (NCP)

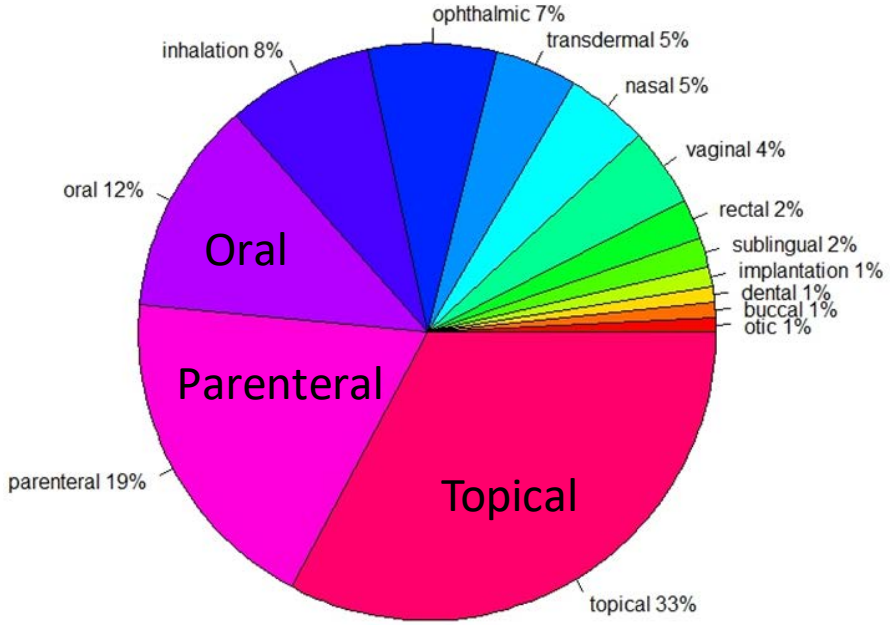
Year 1939-2017 FDA Approved Drug Database

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

Dosage Form

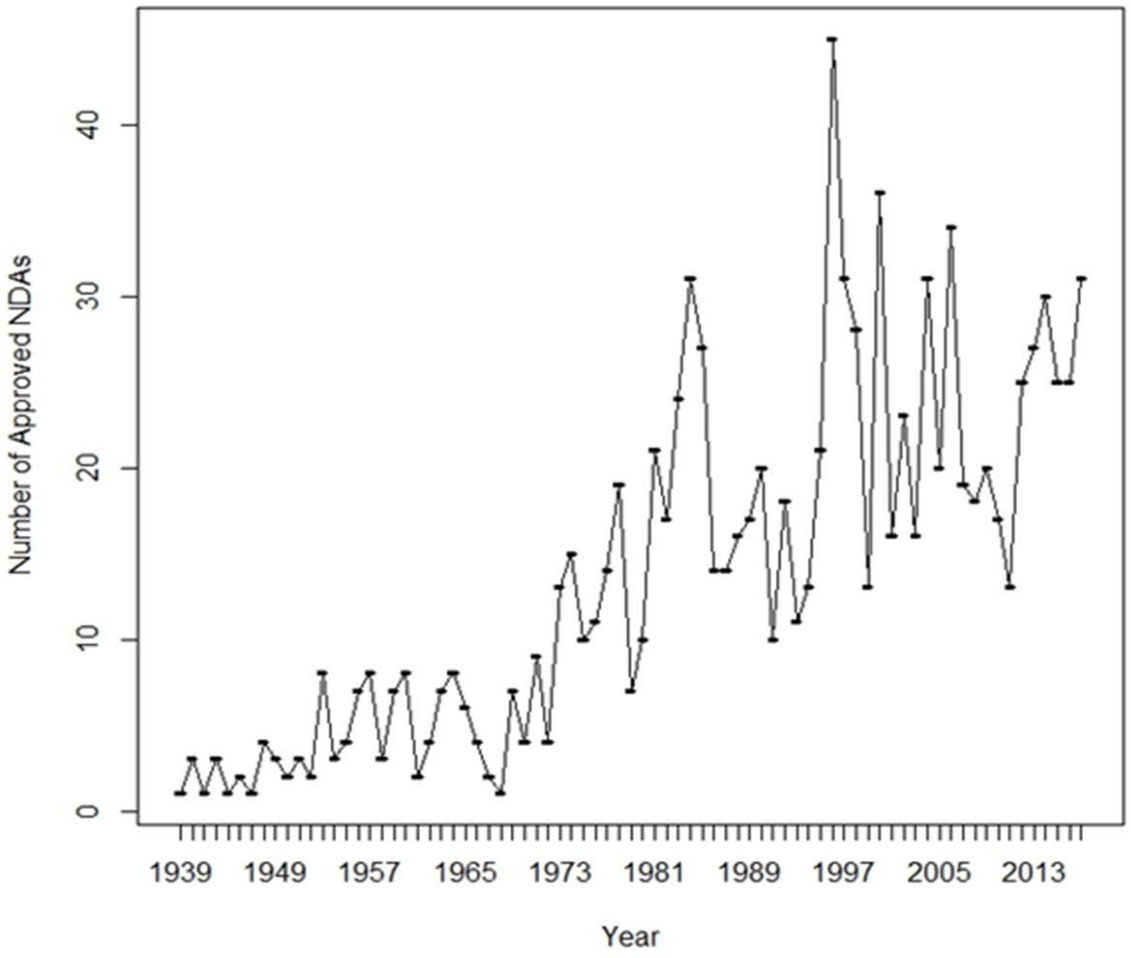


Administration Route



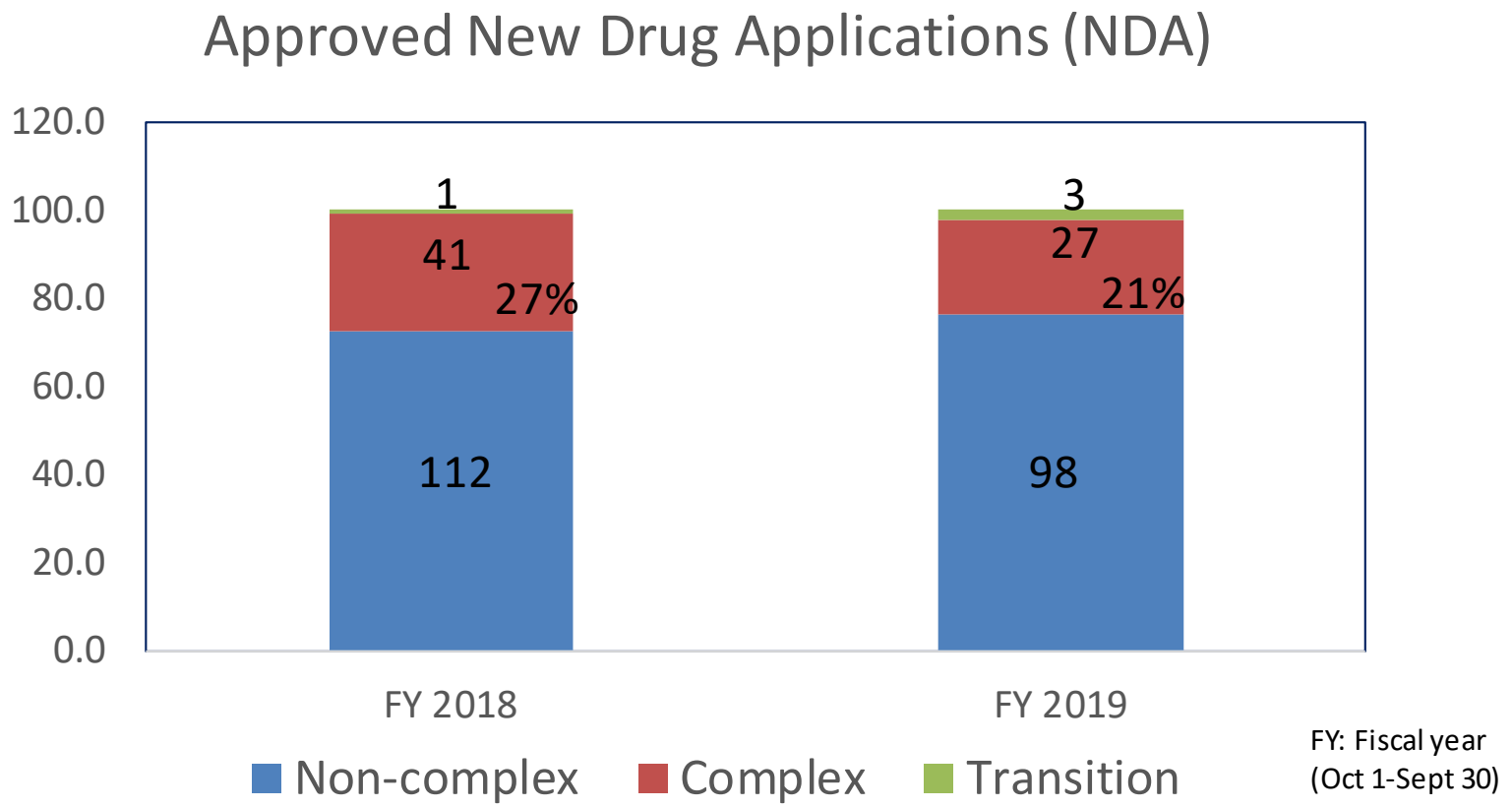
Year 1939-2017 FDA Approved Drug Database

Approved New Drug Applications (NDAs) Considered as Complex Drug Products



Year 1939-2017 FDA Approved Drug Database

Approved Complex and Non-complex NDAs



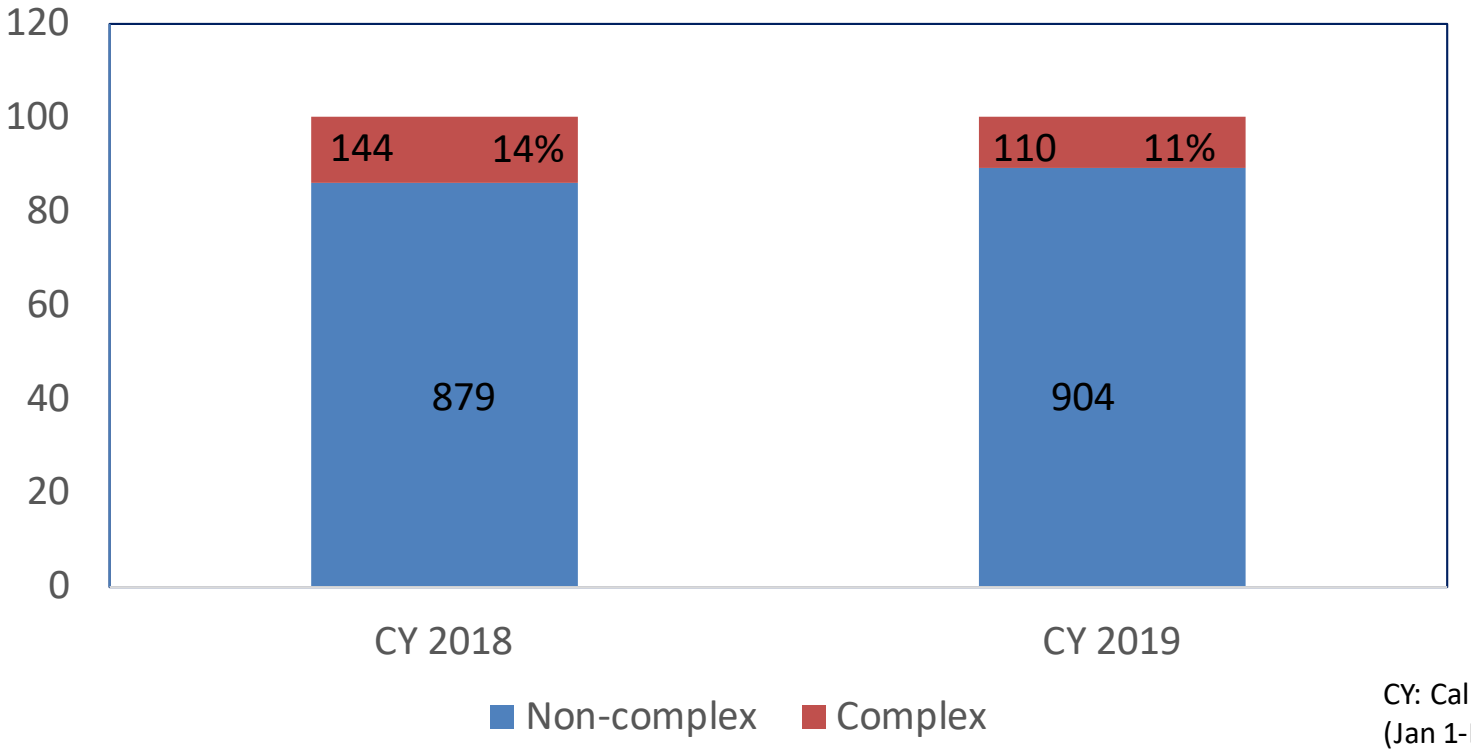
FY: Fiscal year
(Oct 1-Sept 30)

Transition products: Certain protein products originally approved via a new drug application will need approval via a biologic license application after March 23, 2020. For example, albumin-conjugated drugs, insulin-containing drugs, urokinase, and alglucerase will be transitioned into a biologic license application after March 23, 2020.

https://www.fda.gov/media/119229/download

Approved Complex and Non-complex ANDAs

Tentatively and Fully Approved Abbreviated New Drug Applications (ANDAs)



CY: Calendar year (Jan 1-Dec 31)

ARIKAYCE (Amikacin)

- **NDA 207356 Amikacin liposome inhalation suspension** approved on 9/28/2018
- **Dosage Form/Route:** liposome suspension/oral inhalation
- **Indication:** Treatment of *Mycobacterium avium* complex (MAC) lung disease in adults who have limited or no alternative treatment options

Complex formulation:
Liposome suspension

Complex route of delivery:
Oral inhalation to lung

Complex drug-device combination:
Administer by nebulization only with the Lamira™ Nebulizer System.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207356s004lbl.pdf

GVOKE (Glucagon)

- **NDA 212097 GVOKE auto-injector and pre-filled syringe** approved on 9/10/2019
- **Dosage Form/Route:** Solution/Subcutaneous
- **Indication:** Treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above

Complex API: Glucagon, a polypeptide containing 29 amino acids

Its molecular formula is $C_{153}H_{225}N_{43}O_{49}S$ with the following structure:

NH_2 - His - Ser - Gln - Gly - Thr - Phe - Thr - Ser - Asp - Tyr - Ser - Lys -
1 2 3 4 5 6 7 8 9 10 11 12

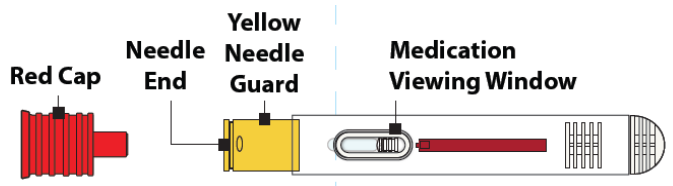
Tyr - Leu - Asp - Ser - Arg - Arg - Ala - Gln - Asp - Phe - Val - Gln - Trp -
13 14 15 16 17 18 19 20 21 22 23 24 25

Leu - Met - Asn - Thr - COOH
26 27 28 29

Complex drug-device combination:

Auto-injector (complex)

Prefilled syringe (non-complex)



https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210134s000lbl.pdf

First Generic Fluticasone Propionate and Salmeterol Inhalation Powder

FDA approved first generic Advair Diskus on 01/30/2019 for the twice-daily treatment of asthma in patients aged four years and older and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

"Today's approval of the first generic drug product for one of the most commonly prescribed asthma and COPD inhalers in the U.S. is part of our longstanding commitment to advance access to lower cost, high quality generic alternatives," said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630151.htm

Thank you so very, very much for this – you have no idea how this generic brand will change the lives of untold numbers of people who were struggling to pay for their asthma medicine…
I paid $398.96 for my inhaler back in January, and today, when the cashier at the pharmacy told me that my total was only $188.65, I almost broke down in tears! …
Again, thank you from the bottom of my heart!"
– anonymous patient

https://www.fda.gov/drugs/generic-drugs/2019-office-generic-drugs-annual-report#Accomplishments

First Generic of Proventil HFA (Albuterol Sulfate) Metered Dose Inhaler (MDI)

FDA Approved First Generic of a Commonly Used Albuterol Inhaler to Treat and Prevent Bronchospasm on Apr 8, 2020.

The U.S. Food and Drug Administration today approved the first generic of **Proventil HFA (albuterol sulfate)** Metered Dose Inhaler (MDI), 90 mcg/Inhalation, for the treatment or prevention of bronchospasm in patients four years of age and older who have reversible obstructive airway disease, as well as the prevention of exercise-induced bronchospasm in this age group.

"The FDA recognizes the increased demand for albuterol products during the novel coronavirus pandemic," said FDA Commissioner Stephen M. Hahn, M.D. "We remain deeply committed to facilitating access to medical products to help address critical needs of the American public."

https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-commonly-used-albuterol-inhaler-treat-and-prevent-bronchospasm

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

FY20 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

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

GDUFA Regulatory Research Communications

- FY 2019 GDUFA Science and Research Report **NEW**
- FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop (May 4, 2020) **NEW (Virtual Meeting)**
- FY 2018 GDUFA Science and Research Outcomes
- Impact Story: Developing New Ways to Evaluate Bioequivalence for Topical Drugs
- Nanotechnology Characterization Laboratory Unveils New Technical Services for Drug Developers (March 9, 2018)

Collaboration Opportunities
See a listing of available grant and fellowship opportunities

Priorities & Projects
Learn more about FDA generic drug research priorities, public workshops, and awarded projects

Guidances & Reports
View FDA generic drug research publications, including product-specific guidances and annual reports

Research Publications & Resources
Browse FDA generic drug research published in scholarly journal articles, presentations, and posters

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

Product-Specific Guidance Development

Total number of currently published Product-Specific Guidances: ~ 1800

Active Ingredient (link to Specific Guidance)	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Abacavir Sulfate	**Final**	Oral	Tablet	020977	05/2008
Abacavir Sulfate; Dolutegravir Sodium; Lamivudine	Draft	Oral	Tablet	205551	06/2015
Abacavir Sulfate; Lamivudine	Draft	Oral	Tablet	021652	11/2007
Abacavir Sulfate; Lamivudine; Zidovudine	**Final**	Oral	Tablet	021205	05/2008
Abemaciclib	Draft	Oral	Tablet	208716	09/2018
Abiraterone Acetate	Draft	Oral	Tablet	202379	07/2018
Acalabrutinib	Draft	Oral	Capsule	210259	02/2019
Acamprosate Calcium	Draft	Oral	Tablet, Delayed Release	021431	05/2017
Acarbose	**Final**	Oral	Tablet	020482	08/2017
Acetaminophen	Draft	Oral	Tablet, Extended Release	019872	02/2011

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

Upcoming Product-Specific Guidances for Complex Generic Drug Product Development Introduction

This web page provides information related to upcoming new and revised product-specific guidances (PSGs) to support the development and approval of safe and effective complex generic drug products.

Planned New PSGs for Complex Generic Drug Products

Updated 3/02/2020

Active Ingredient(s)	Route of Administration	Dosage Form	RLD Application Number
ACYCLOVIR; HYDROCORTISONE	TOPICAL	CREAM	022436
APREPITANT	INTRAVENOUS	EMULSION	209296
BIVALIRUDIN	INTRAVENOUS	SOLUTION	211215
BREMELANOTIDE ACETATE	SUBCUTANEOUS	SOLUTION	210557

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https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development

Pre-ANDA Meetings for Complex 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

Summary

Complex product classification criteria helped

- Clarification of complex product concept
- Standardization of the classification process

Complex product distribution in different dosage forms, administration routes, therapeutic areas, and complexity categories

FDA promotes complex generic drug development

- Fund research studies
- Translate these research results into product-specific guidance
- Provide pre-ANDA meeting opportunities

Acknowledgements

- Complex Drug Product Working Group
- Office of Research and Standards
- Office of Generic Drugs

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Any Questions?

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