

# PQRI Biopharmaceuticals Technical Committee 2020 Webinar Series

## ***The Challenge and the Promise: Developing Complex Drug Products***

Moderator: Ajit Narang, Ph.D., Genentech

Presenters: Wenlei Jiang,, Ph.D., CDER/FDA

Adrian Goodey, Ph.D., Merck and Co., Inc.



# Agenda

## I. Welcome and Overview of Webinar

Moderator: Ajit Narang, Ph.D., Genentech

## II. Complex Drug Product Landscape

Wenlei Jiang, Ph.D., U.S. Food and Drug Administration

## III. The Complexities of Developing Complex Products

Adrian Goodey, Ph.D. Merck & Co, Inc.

## IV. Moderated Q&A Session with the speakers



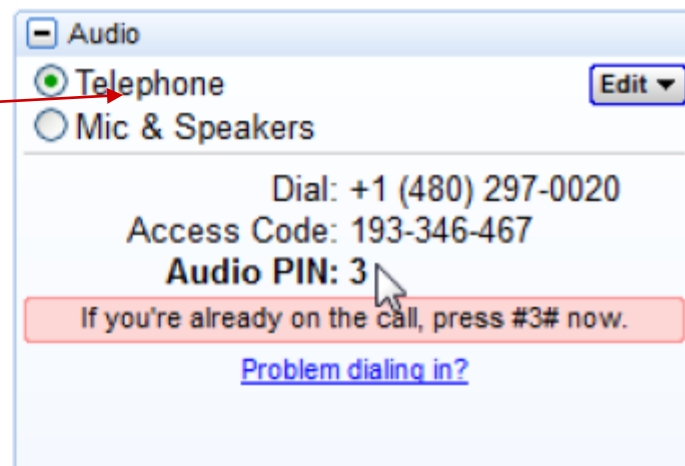
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The recording will be posted on the PQRI website at [www.pqri.org](http://www.pqri.org) after the webinar.

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- **Note:** *Today's presentation is being recorded.*



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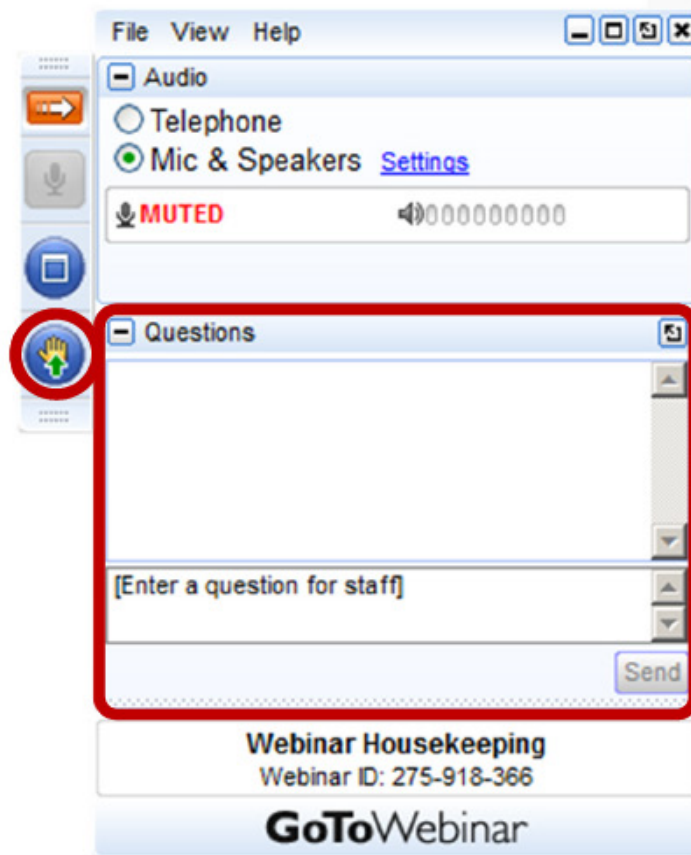
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# Product Quality Research Institute (PQRI)

## Mission:

PQRI is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality, manufacturing, and regulation.



PQRI BTC Webinar  
April 2020

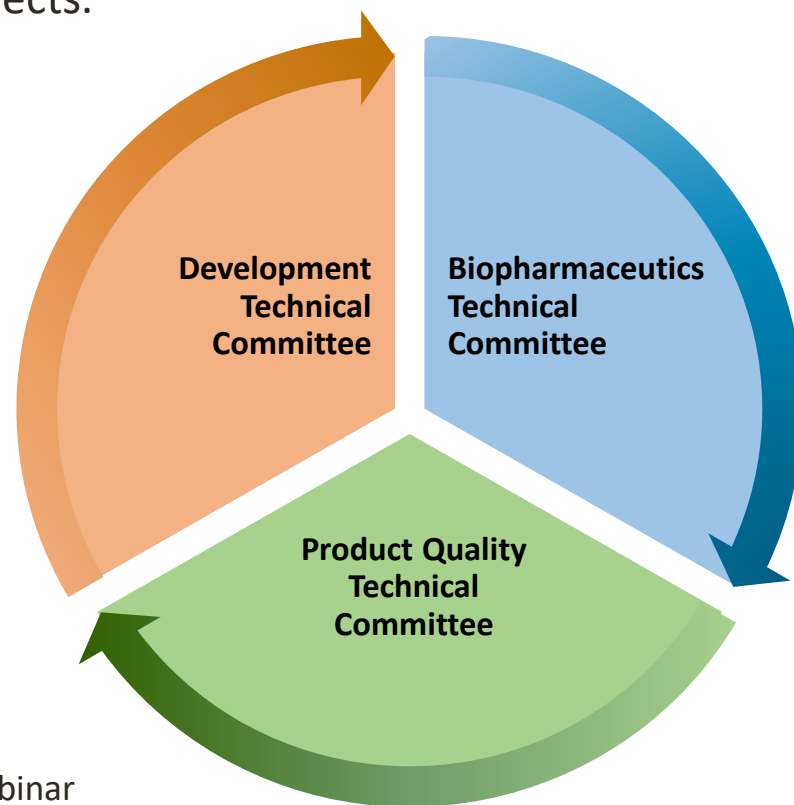


# What Does PQRI Do ?

- Unites thought leaders from regulatory agencies, standard setting bodies, industry and academia to conduct research and share knowledge on emerging scientific and regulatory quality challenges
- Provides a unique, neutral forum to develop broad consensus among a diverse collection of industry organizations and regulatory bodies
- Creates opportunities to accomplish mutual goals that cannot be achieved by individual organizations
- Impacts global regulatory guidance and standards, bringing maximum value to members and patients

# PQRI Structure

- PQRI consists of two governing bodies – a Board of Directors and Steering Committee and three **Technical Committees**,
- Technical Committees each have a broad disciplinary focus that collectively spans the drug product regulatory lifecycle. They establish and provide scientific guidance, direction and oversight to PQRI working groups and research projects.
- Current PQRI Technical Committees:
  - Biopharmaceutics Technical Committee (BTC)
  - Development Technical Committee (DTC)
  - Product Quality Technical Committee (PQTC)
- This webinar is sponsored by the **BTC**.
- The mission of the BTC is to identify, disseminate, and facilitate scientific and technical projects to address gaps in biopharmaceutical aspects of drug development and global regulatory guidance.



# Past BTC Webinar Series

(Posted at <http://pqri.org/biopharmaceutics-technical-committee-btc/>)

## **2019 Webinars**

- ***Holistic QbD to Enable Product Quality Webinar (October 10, 2019)*** Presenters: Ajit Narang, Ph.D., Genentech; Rakhi Shah, Ph.D., FDA; Xavier Pepin, Pharm.D, Ph.D; Divyakant Desai, Ph.D., BMS; Xavier Pepin, Pharm.D, Ph.D., AstraZeneca
- ***The Expanding IVIVC Toolbox to Enable Drug Product Quality and Clinical Pharmacology – Complementary Traditional and PBPK Based Approaches (June 7, 2019)*** Presenters: Xianyuan (Susie) Zhang, Ph.D., FDA and Filippas Kesisoglou, Ph.D., Merck

## **2018 Webinars**

- ***A Science Based Approach to Simplifying the Regulatory Pathway for Topical Drugs (April 9, 2018)*** Presenters: Vinod P. Shah, Ph.D., FAAPS, FFIP and Flavian Radulescu, Ph.D.
- ***Questions about the Proposed Topical Classification System (TCS) and What To Do With It (June 19, 2018)*** Presenter: Sam Raney, Ph.D., FDA
- ***Performance Testing in Quality Control and Product Development, Where are We? (October 23, 2018)*** Presenter: Raimar Löbenberg, Ph.D., University of Alberta
- ***Biowaiver Approaches for Solid Oral Dosage Forms in New Drug Applications (December 6, 2018)*** Presenter: Poonam Delvadia, Ph.D., FDA





# Today's Presenters

Wenlei Jiang, Ph.D., Senior Science Advisor  
US Food and Drug Administration

[Wenlei.Jiang@fda.hhs.gov](mailto:Wenlei.Jiang@fda.hhs.gov)

Dr. Wenlei Jiang currently serves as a Senior Science Advisor in the Office of Research and Standards (ORS)/Office of Generic Drugs (OGD)/Center for Drug Evaluation and Research (CDER). She has been championing regulatory research in the areas of generic nanomaterials, narrow therapeutic index drugs, and modified release products to support review standards development and ensure post-market safety and efficacy of these drug products. Currently she is leading complex drug product classification and research, as well as promoting global bioequivalence harmonization. She also serves as Chair at Product Quality Research Institute (PQRI) Biopharmaceutical Technical Committee. Prior to joining FDA, she was at Novartis Pharmaceutical Corporation where her responsibilities included formulation development of conventional liquid and solid dosage forms, and advanced parenteral drug delivery systems. She received her PhD in Pharmaceutics and Pharmaceutical Chemistry from The Ohio State University.



PQRI BTC Webinar  
April 2020



# Today's Presenters

Adrian Goodey, Ph.D., Principal Scientist  
Merck Research Laboratories  
[adrian.goodey@merck.com](mailto:adrian.goodey@merck.com)



Adrian Goodey is a Principal Scientist in the Analytical Sciences group within Merck Research Laboratories, focusing on specialty dosage forms. In this role, Dr. Goodey leads the development of drug products delivered via alternate routes of administration, including inhalers, nasal sprays and sub-dermal implants. Prior to joining the pharmaceutical industry in 2007, Dr. Goodey earned a B.Sc. in chemistry from Emory University, completed a PhD in chemistry from the University of Texas at Austin, and then served as an ACS/PRF Alternative Energy Postdoctoral Fellow at the Pennsylvania State University. Dr. Goodey currently chairs the IPAC-RS Cascade Impactor working group. His research interests include advancing the science of aerodynamic particle sizing and the development of clinically relevant analytical methods for pharmaceutical testing. To date, he has authored fourteen peer-reviewed scientific articles and two patents.



# Complex Drug Product Landscape

Wenlei Jiang, Ph.D.

Senior Science Advisor

Office of Research and Standards  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
U.S. FDA

Apr 28, 2020

Product Quality Research Institute (PQRI) Biopharmaceutical Technical Committee (BTC)  
Webinar Series

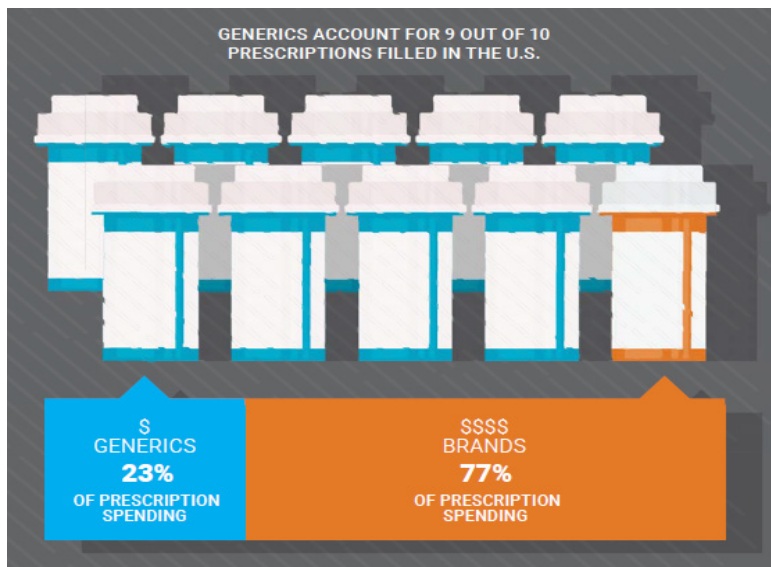
# Disclaimer

- 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



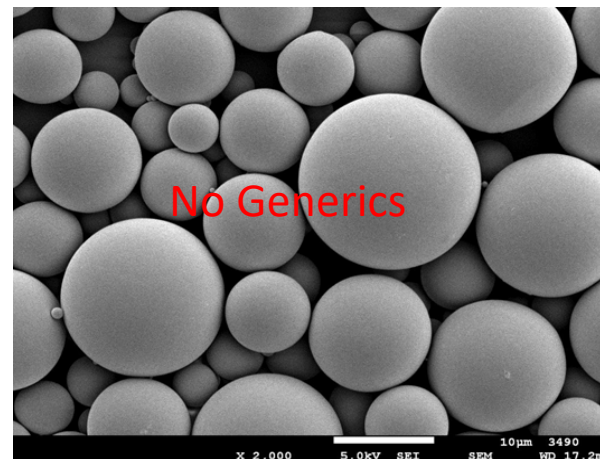
## Overall Drug Products



## Orally inhaled drug products



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



## However,

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

# 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  
pharmaceutic  
al 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/formula  
tions*

- 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

# 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



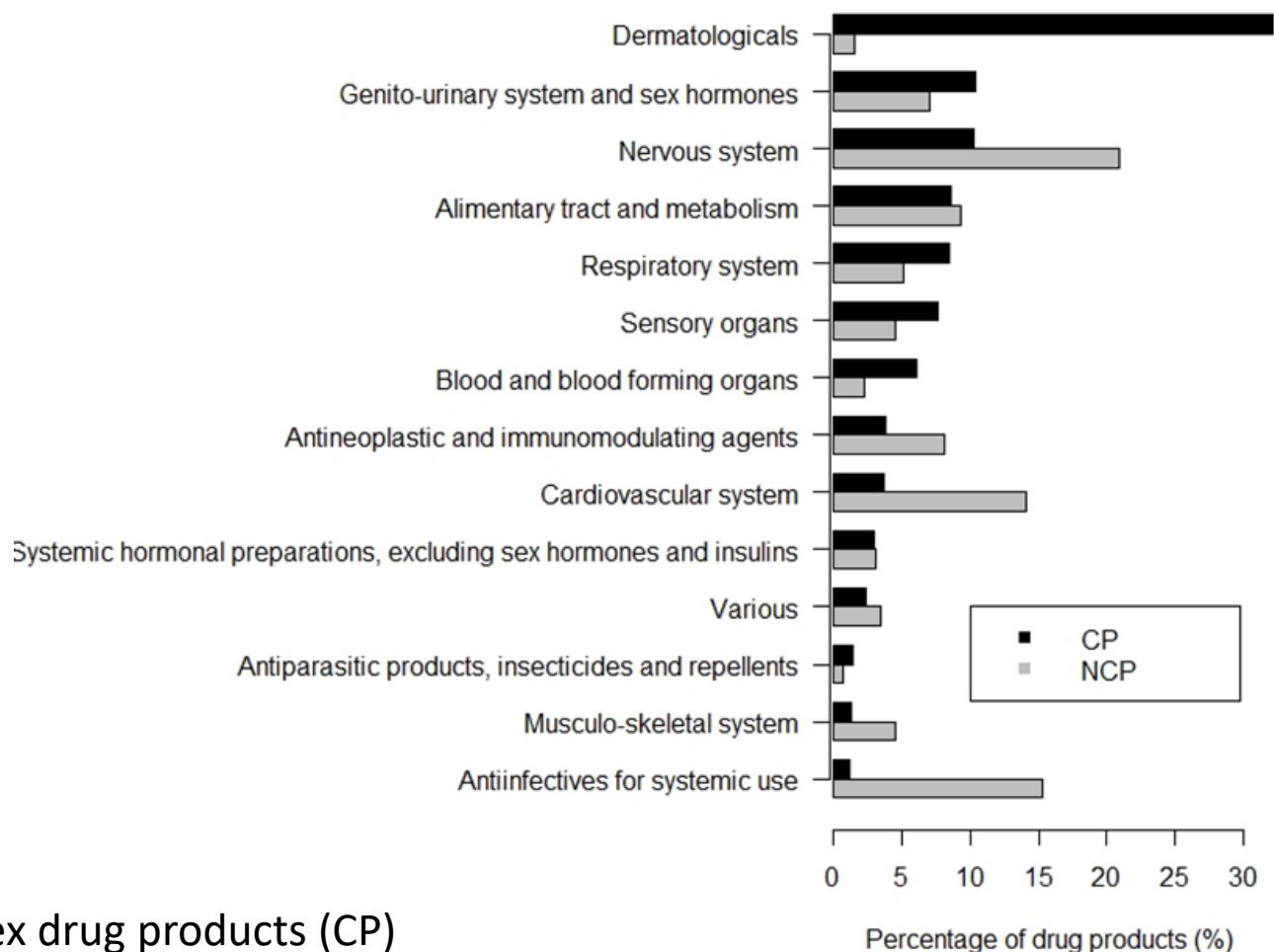
- Pre-filled syringes having a level of complexity, e.g., dual chamber and/or specific labeling unique to the device
- Pre-filled auto-injector products for injectable formulations
- Orally inhaled and nasal drug products (such as metered-dose inhalers, dry powder inhalers, and nasal spray products)
- Iontophoretic 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, intracoronary, 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)

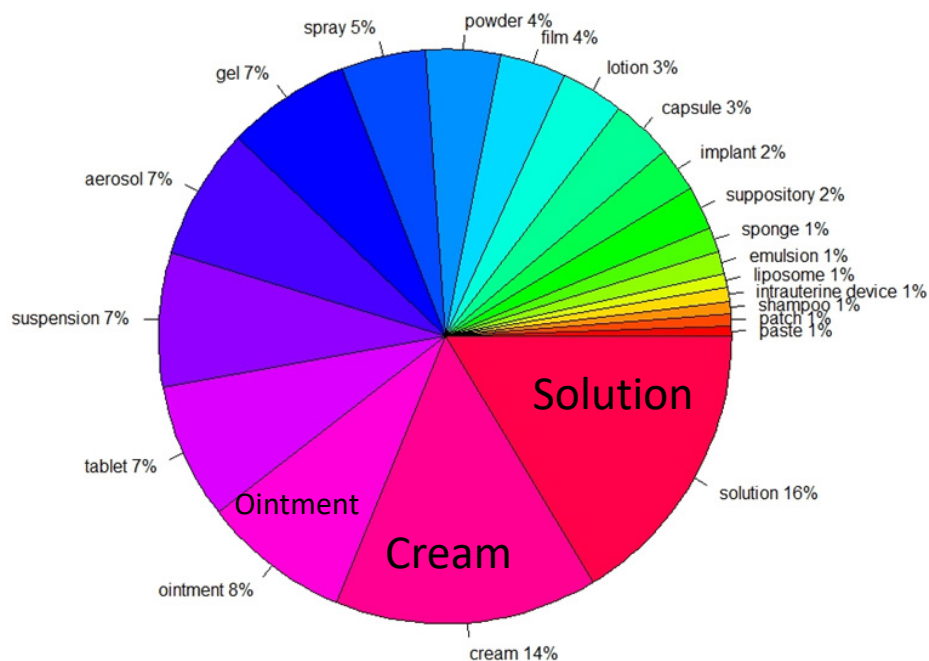
Non-complex drug products (NCP)

Year 1939-2017 FDA Approved Drug Database

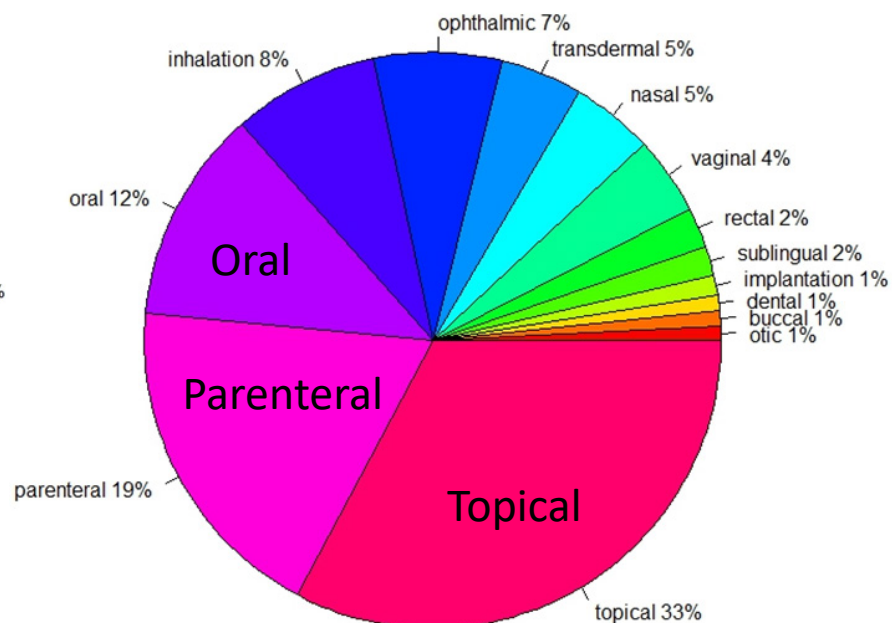
# Distribution of Complex Drug Products Based on Dosage Forms and Administration Route



Dosage Form

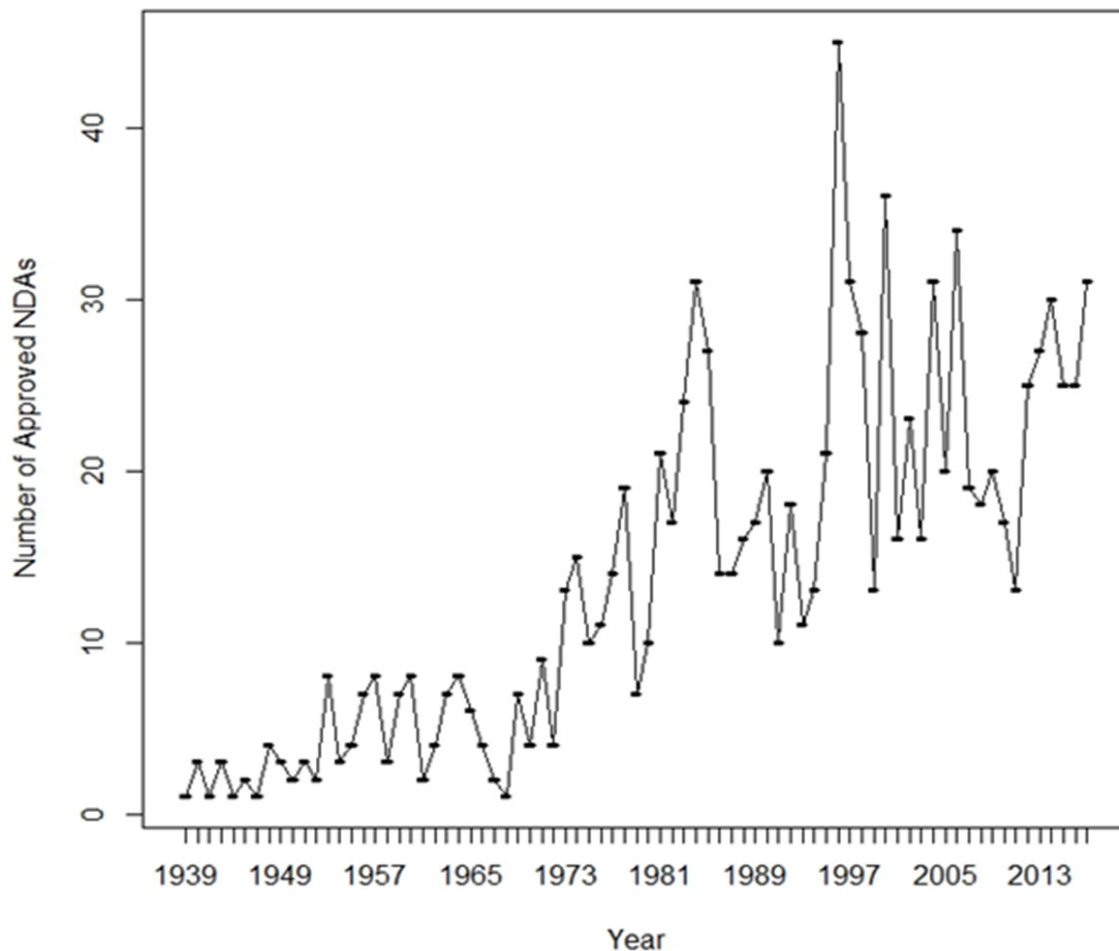


Administration Route



Year 1939-2017 FDA Approved Drug Database

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

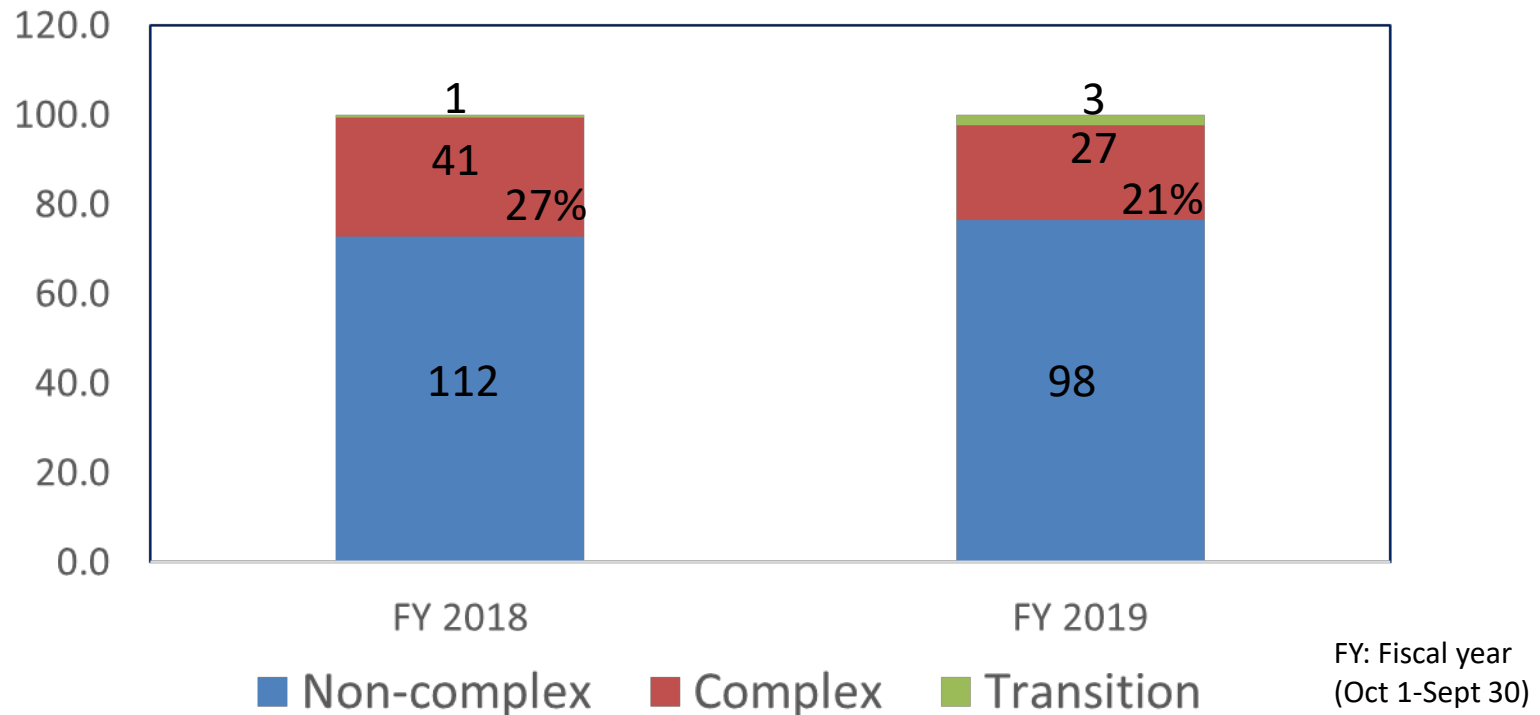


Year 1939-2017 FDA Approved Drug Database

# Approved Complex and Non-complex NDAs



## Approved New Drug Applications (NDA)

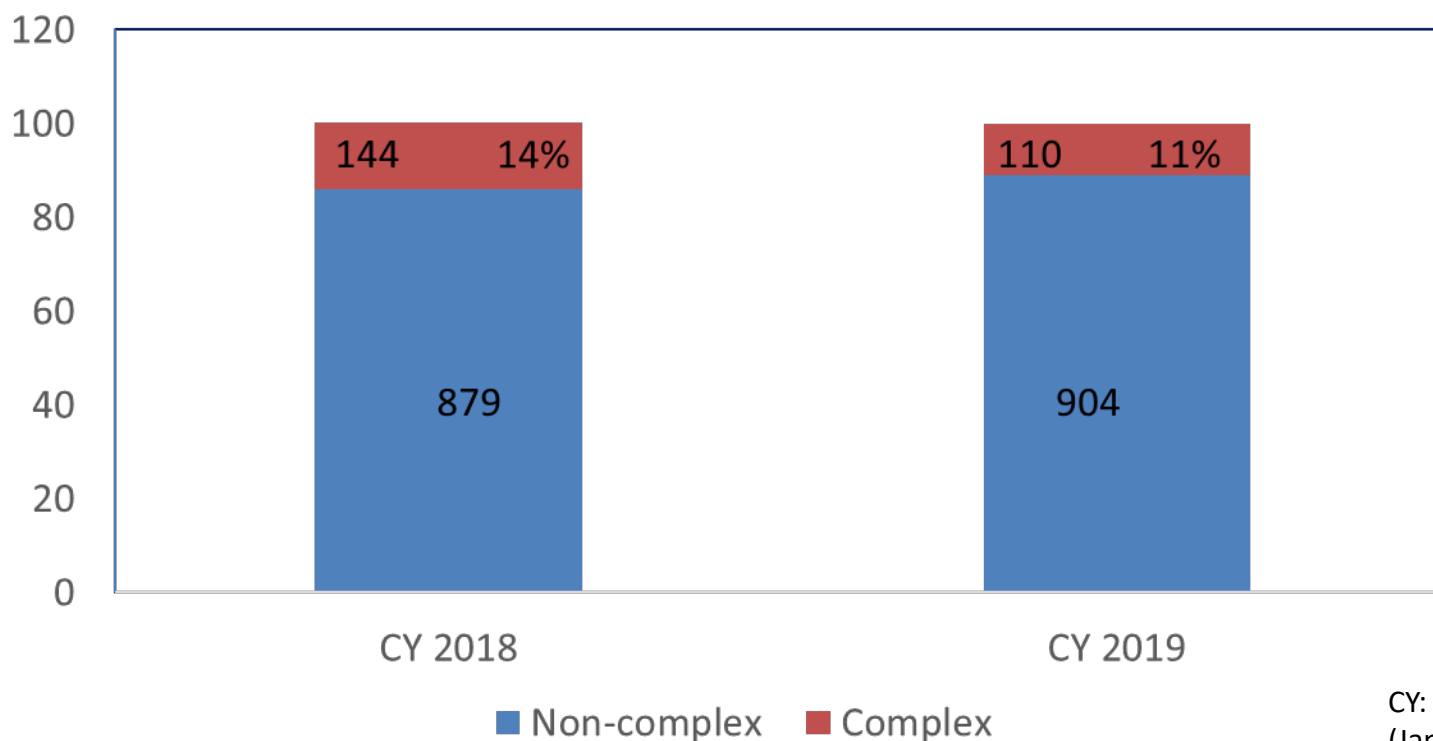


Transition products: Certain protein products originally approved via a new drug application will need approval via a biologic license application after March 23, 2020. For example, albumin-conjugated drugs, insulin-containing drugs, urokinase, and alglucerase will be transitioned into a biologic license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

# 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](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:

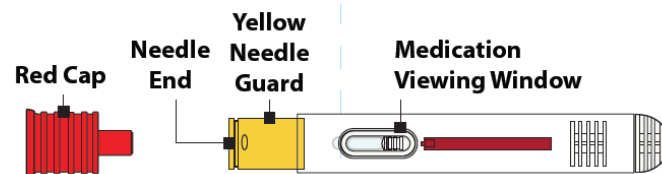


**Complex drug-device combination:**

Auto-injector  
(complex)



Prefilled syringe (non-complex)



# 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.

*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>

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

# 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

# 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
<a href="#">Abacavir Sulfate</a>	<b>Final</b>	Oral	Tablet	<a href="#">020977</a>	05/2008
<a href="#">Abacavir Sulfate; Dolutegravir Sodium; Lamivudine</a>	Draft	Oral	Tablet	<a href="#">205551</a>	06/2015
<a href="#">Abacavir Sulfate; Lamivudine</a>	Draft	Oral	Tablet	<a href="#">021652</a>	11/2007
<a href="#">Abacavir Sulfate; Lamivudine; Zidovudine</a>	<b>Final</b>	Oral	Tablet	<a href="#">021205</a>	05/2008
<a href="#">Abemaciclib</a>	Draft	Oral	Tablet	<a href="#">208716</a>	09/2018
<a href="#">Abiraterone Acetate</a>	Draft	Oral	Tablet	<a href="#">202379</a>	07/2018
<a href="#">Acalabrutinib</a>	Draft	Oral	Capsule	<a href="#">210259</a>	02/2019
<a href="#">Acamprosate Calcium</a>	Draft	Oral	Tablet, Delayed Release	<a href="#">021431</a>	05/2017
<a href="#">Acarbose</a>	<b>Final</b>	Oral	Tablet	<a href="#">020482</a>	08/2017
<a href="#">Acetaminophen</a>	Draft	Oral	Tablet, Extended Release	<a href="#">019872</a>	02/2011

# 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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# Pre-ANDA Meetings for Complex Products



Meeting Type	Meeting Focus	Product Stages
Product Development Meeting	<ul style="list-style-type: none"><li>• Help ANDA applicant engage early with FDA about scientific exchange of an individual product development program, e.g. alternative bioequivalence approach</li></ul>	During complex generic product development stage
Pre-submission Meeting	<ul style="list-style-type: none"><li>• Discuss and explain the format and content of an ANDA to be submitted</li></ul>	6-12 months before ANDA submission
Mid-review-cycle meeting	<ul style="list-style-type: none"><li>• Provide the applicant an update about the application review status</li></ul>	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

# Thank you!

Any Questions?

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[genericdrugs@fda.hhs.gov](mailto:genericdrugs@fda.hhs.gov)

# Thank you for attending the webinar!

For more information on PQRI, visit our website at:

[www.pqri.org](http://www.pqri.org)

Questions? Contact the PQRI Secretariat at:

[PQRIsecretariat@pqri.org](mailto:PQRIsecretariat@pqri.org)

## Call for Volunteers

If you or your company is a member of a PQRI member organization (CHPA, FDA, Health Canada, IPEC-Americas, PDA or USP) and you would to participate in any of the PQRI Technical Committees, please contact the PQRI Secretariat ([PQRIsecretariat@pqri.org](mailto:PQRIsecretariat@pqri.org)) for further information.

