Newly Approved Complex Drug Products and Potential Challenges to Generic Drug Development

Lei Zhang, PhD

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

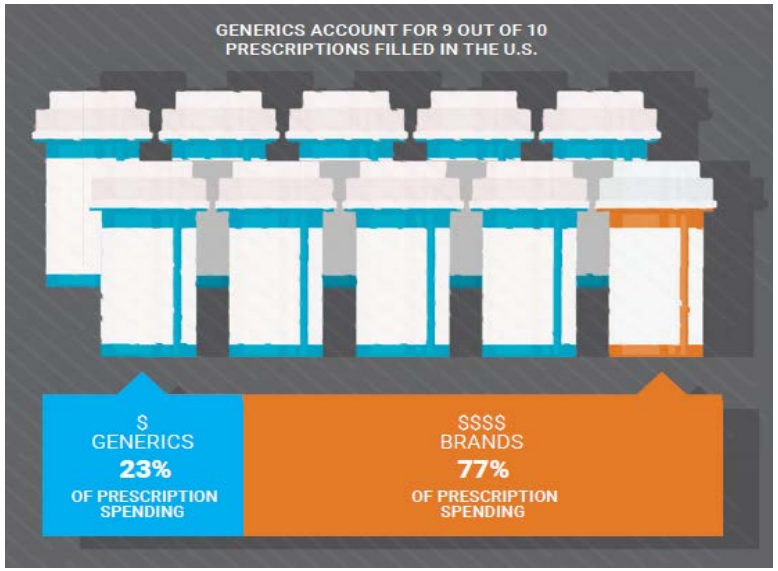
May 1, 2019

Generic Drugs in the United States

Overall Drug Products

Generic Drugs:

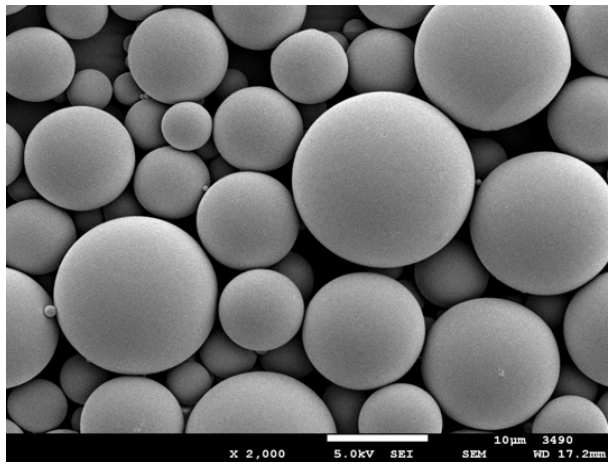
- 90% of prescription
- 23% of spending



Orally inhaled drug products

1 Generic

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



No Generics

However,

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

~30% are Complex Products Per GDUFA II Commitment Letter Definition*

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

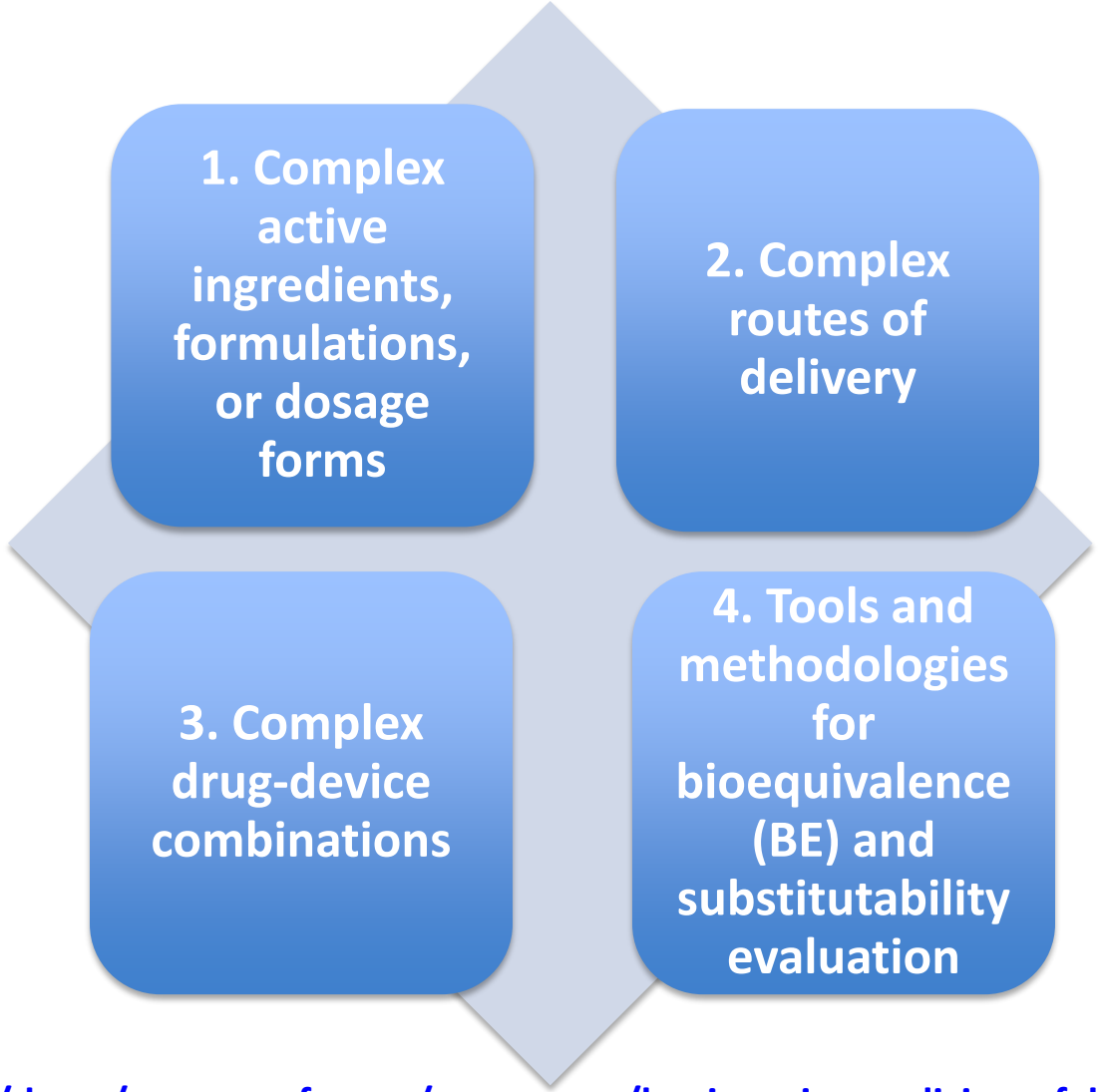
Complex Products

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/formulations	• 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

FY2019 GDUFA Research Science Priority Areas

15 priority areas under 4 broad categories



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

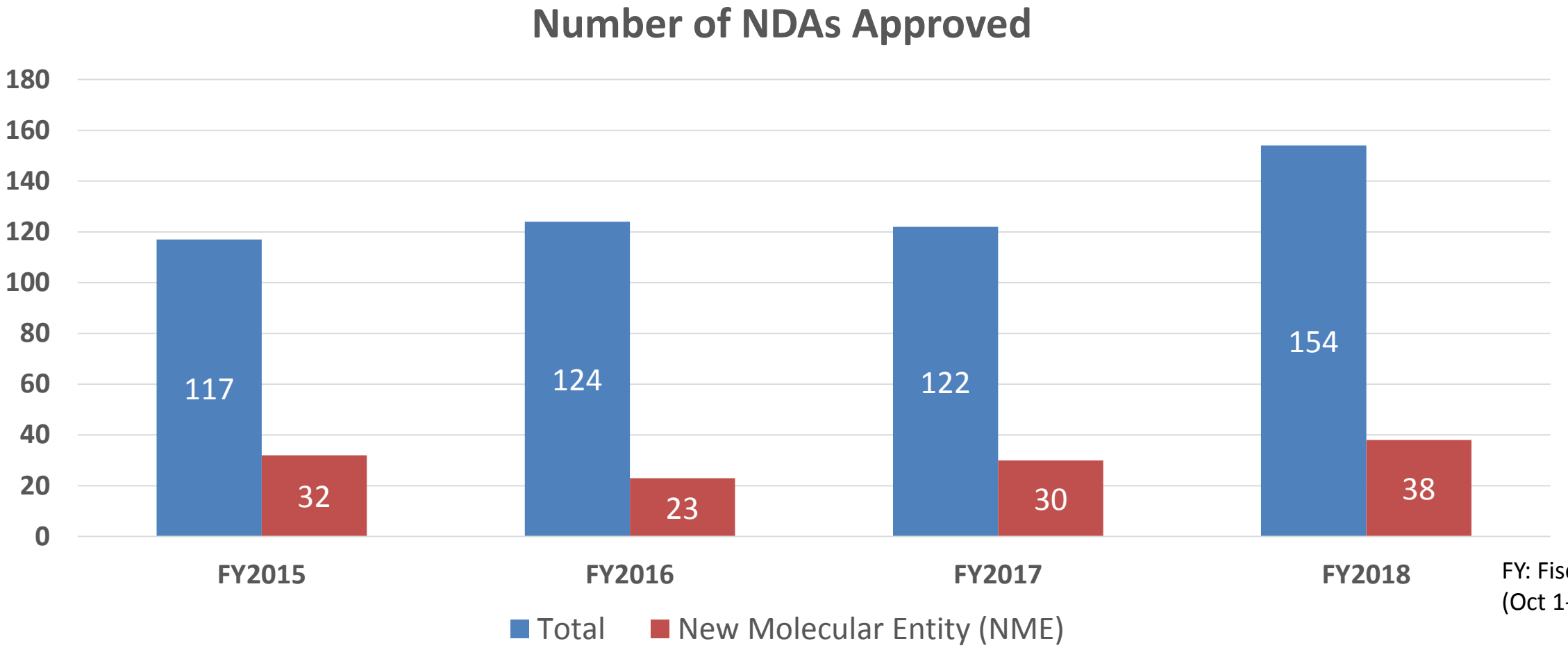
Questions for the Panel

- Do these research priorities address the scientific challenges to developing generics of recently approved complex NDAs (NMEs and Non-NMEs)?

- To aid in this analysis, we will review the landscape.

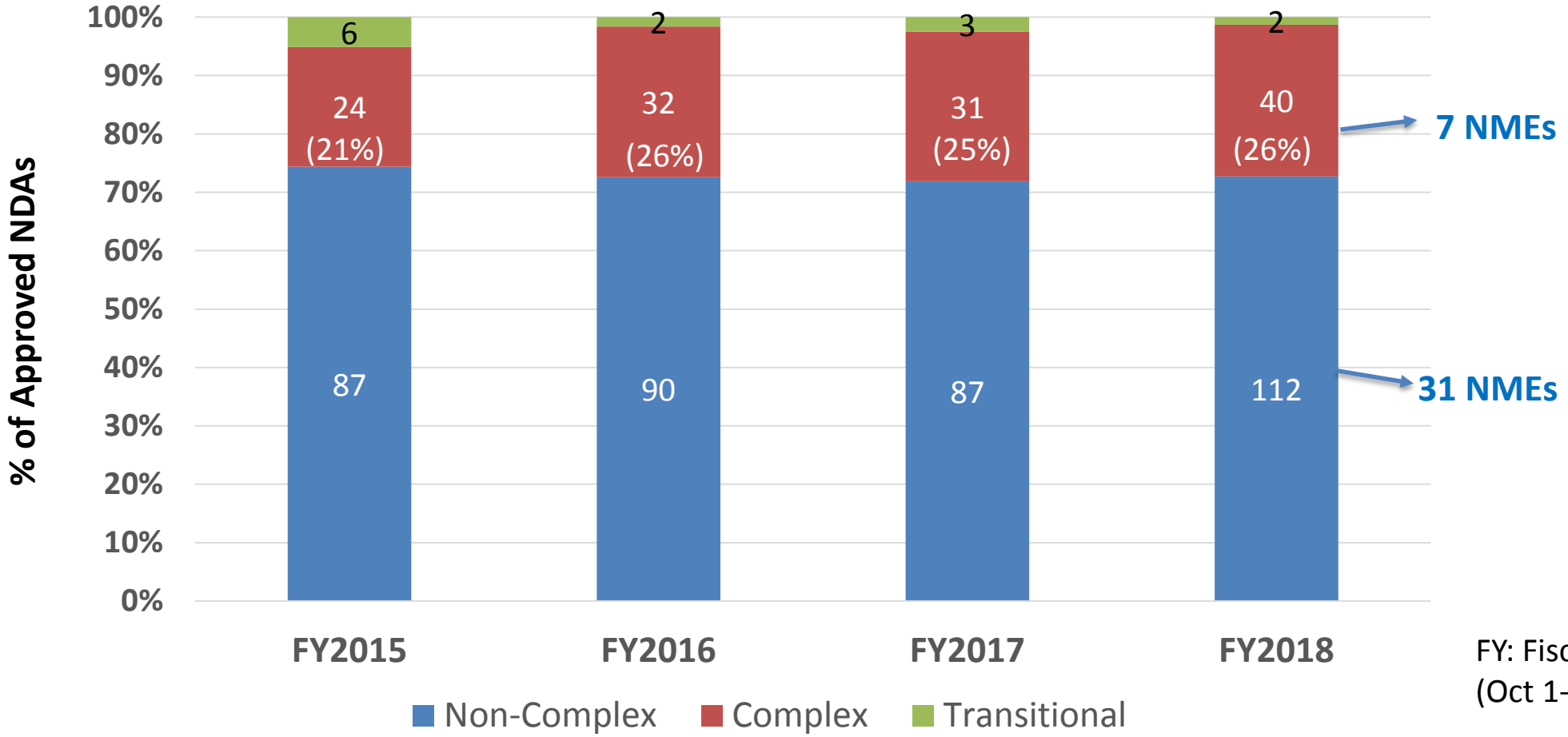
NMEs: New Molecular Entities

Approved New Drug Applications (NDAs) FY2015-2018



FY: Fiscal year
(Oct 1-Sept 30)

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

NMEs: New Molecular Entities

Product-Specific Guidances (GDUFA II Goals)

Product-specific guidances identify the evidence needed to support generic drug approval

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

PSGs Published in FY2018

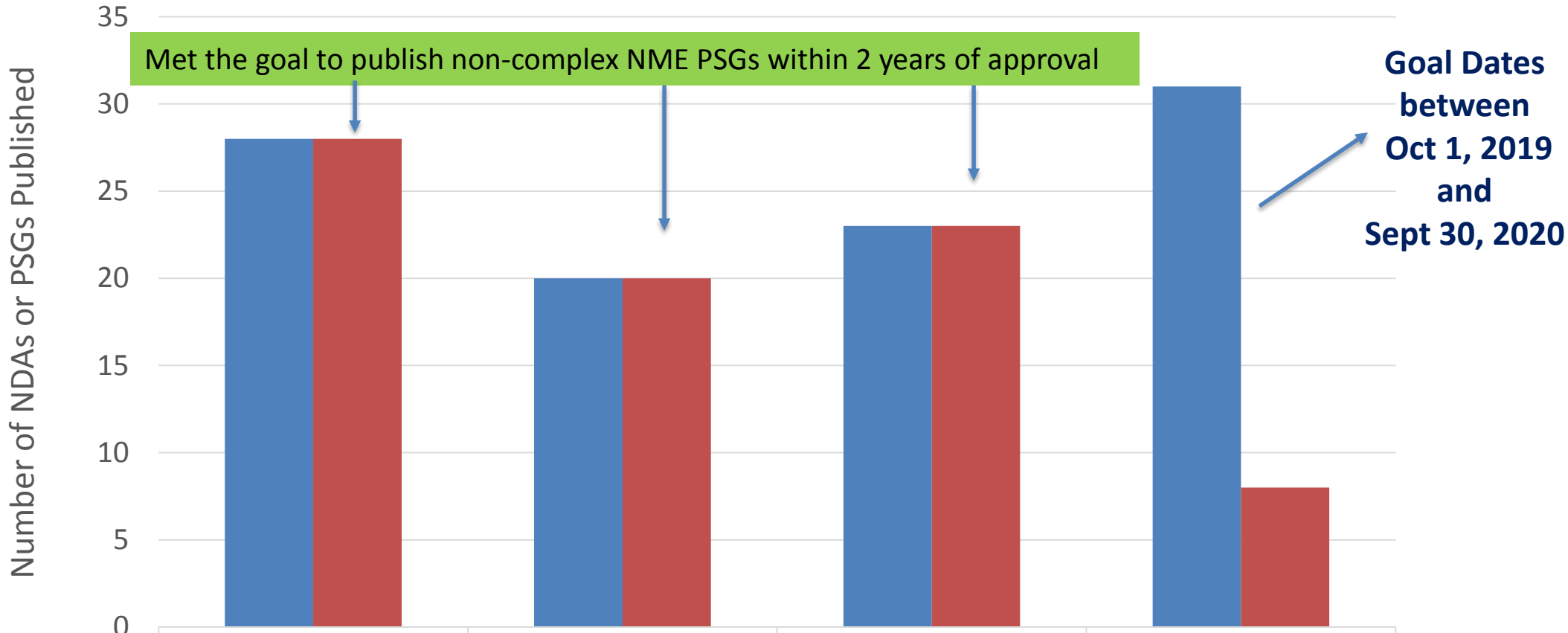
Total Number of PSGs	New	Revised	Complex	Non-Complex
208	136	72	75 (36%)	133 (64%)

FY: Fiscal Year
(Oct 1-Sept 30)

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

PSG Development for Recent Non-complex NMEs (FY2015-2018 NDA Approval Cohorts)

As of Feb 2019



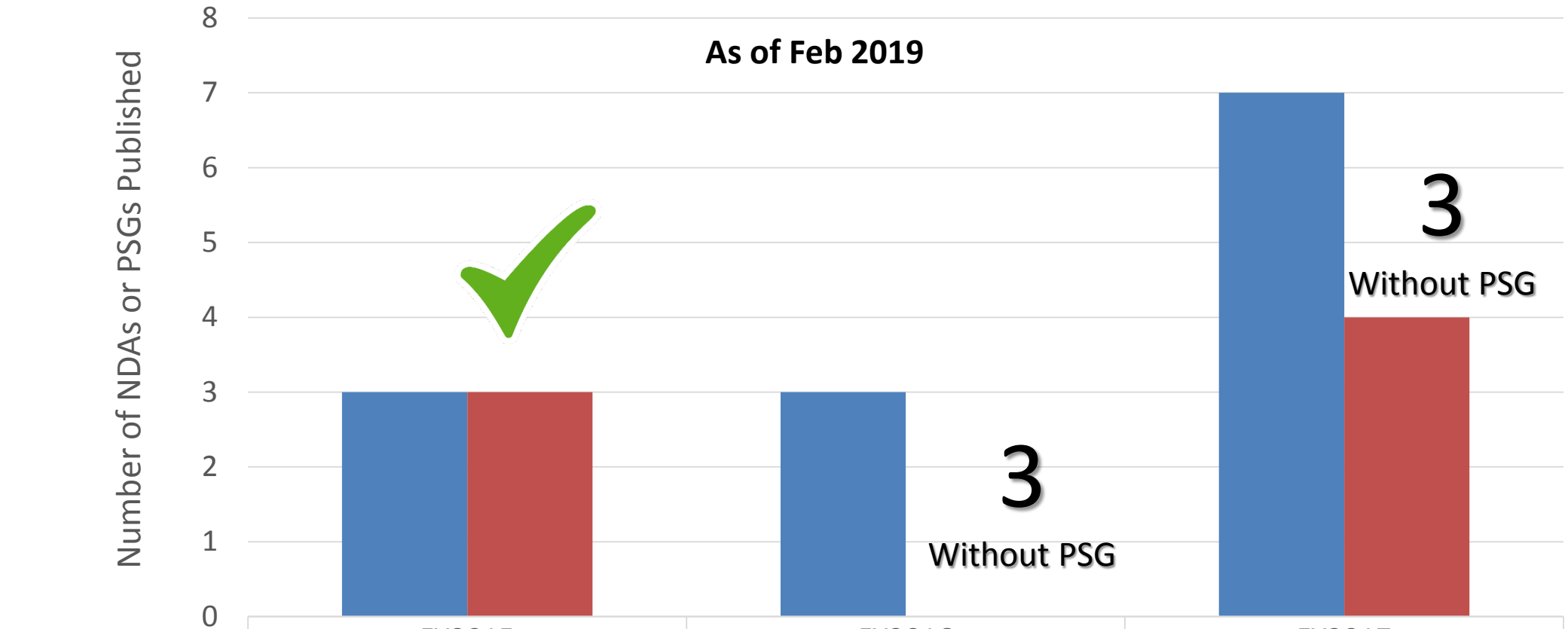
FY: Fiscal Year (Oct 1-Sept 30)

* Prior to FY18: Number includes PSG published and drug products may be eligible for "biowaiver" under 21 CFR 320.22(b)
Starting FY18 (GDUFA II), we will publish PSGs for all non-complex NMEs within 2 years of approval.

FY2015-2017 NDA Approval Cohorts
Complex Products

1. NMEs
2. Overall

PSG Development for Recent NME Complex Drug Products (FY2015-2017 NDA Approval Cohorts)

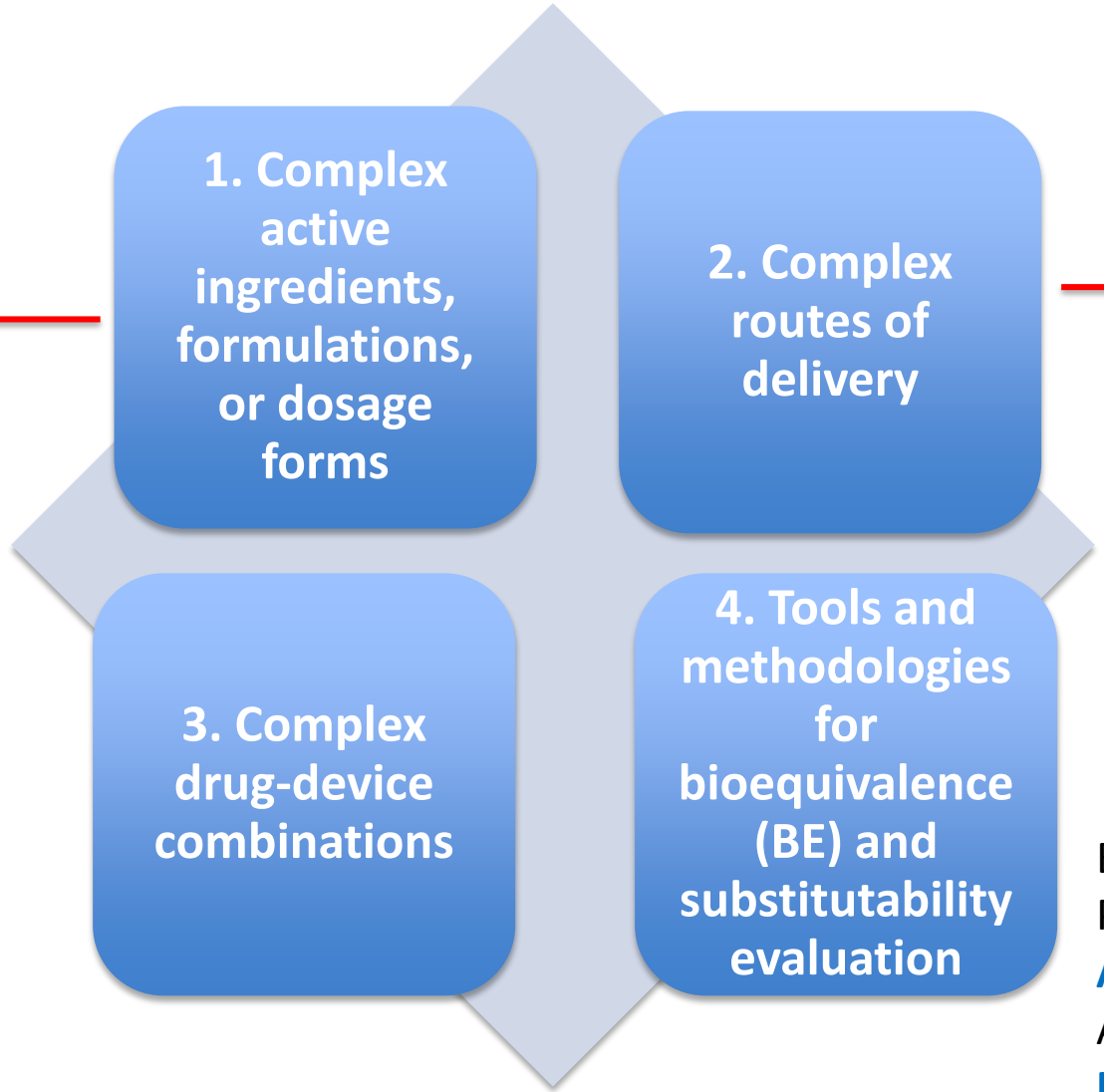


	FY2015	FY2016	FY2017
Complex NMEs	3	3	7
PSG Published*	3	0	4

* Prior to FY18: Number includes PSG published and drug products may be eligible for "biowaiver" under 21 CFR 320.22(b)
Starting FY18 (GDUFA II), we will publish PSGs for all non-complex NMEs within 2 years of approval.

Recent NME Complex Drug Products Without PSG FY2016 (N=3)

- Eteplirsen
- Patiromer
- Aripiprazole lauroxil

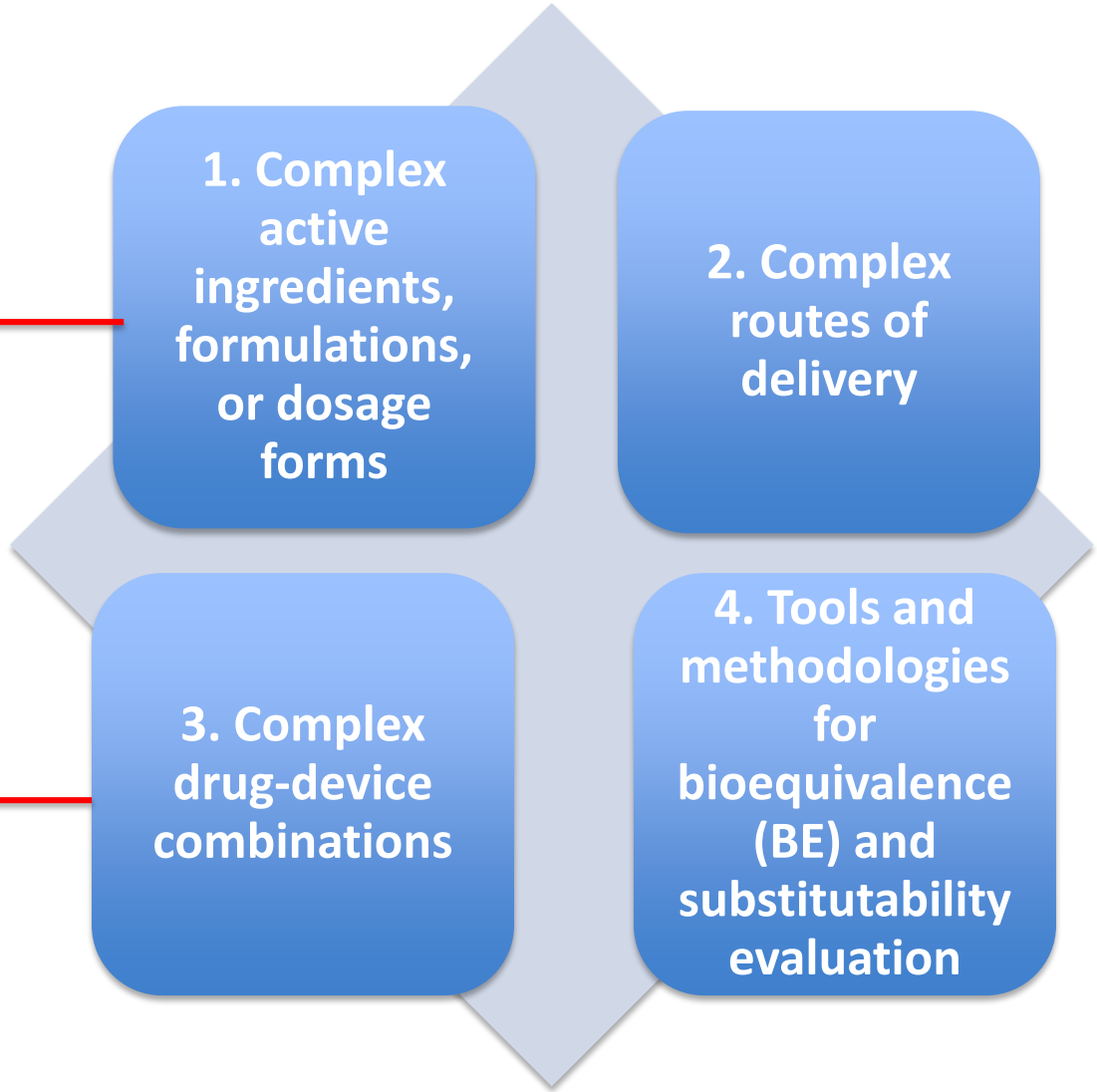


Patiromer

ETEPLIRSEN **(Complex API)**
PATIROMER SORBITEX CALCIUM (**Complex API; Complex Route of Delivery)**
ARIPIPRAZOLE LAUROXIL **(Complex Dosage Form)**

Recent NME Complex Drug Products Without PSG FY2017 (N=3)

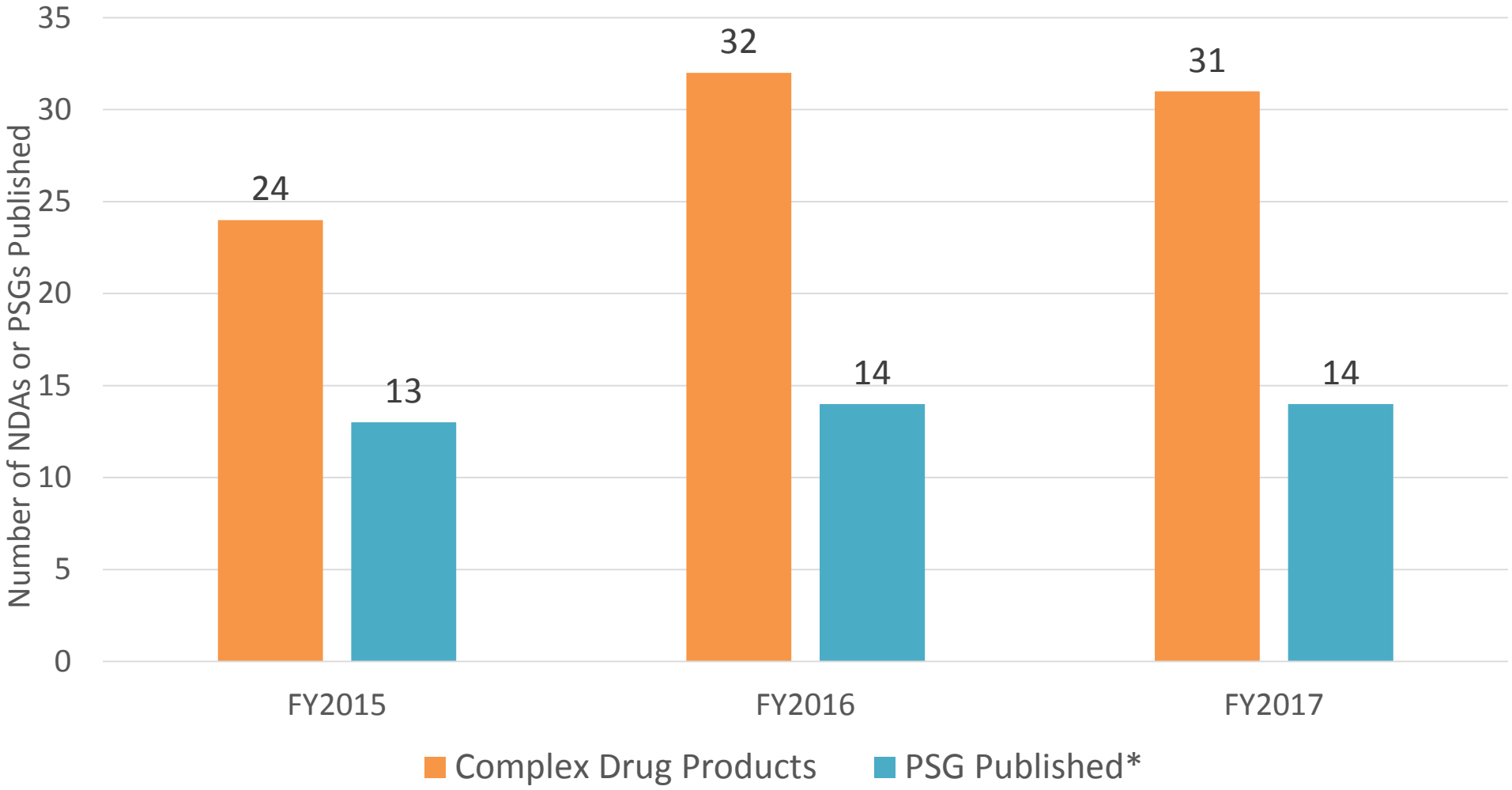
- Nusinersen
- Abaloparatide
- Etelcalcetide



Abaloparatide

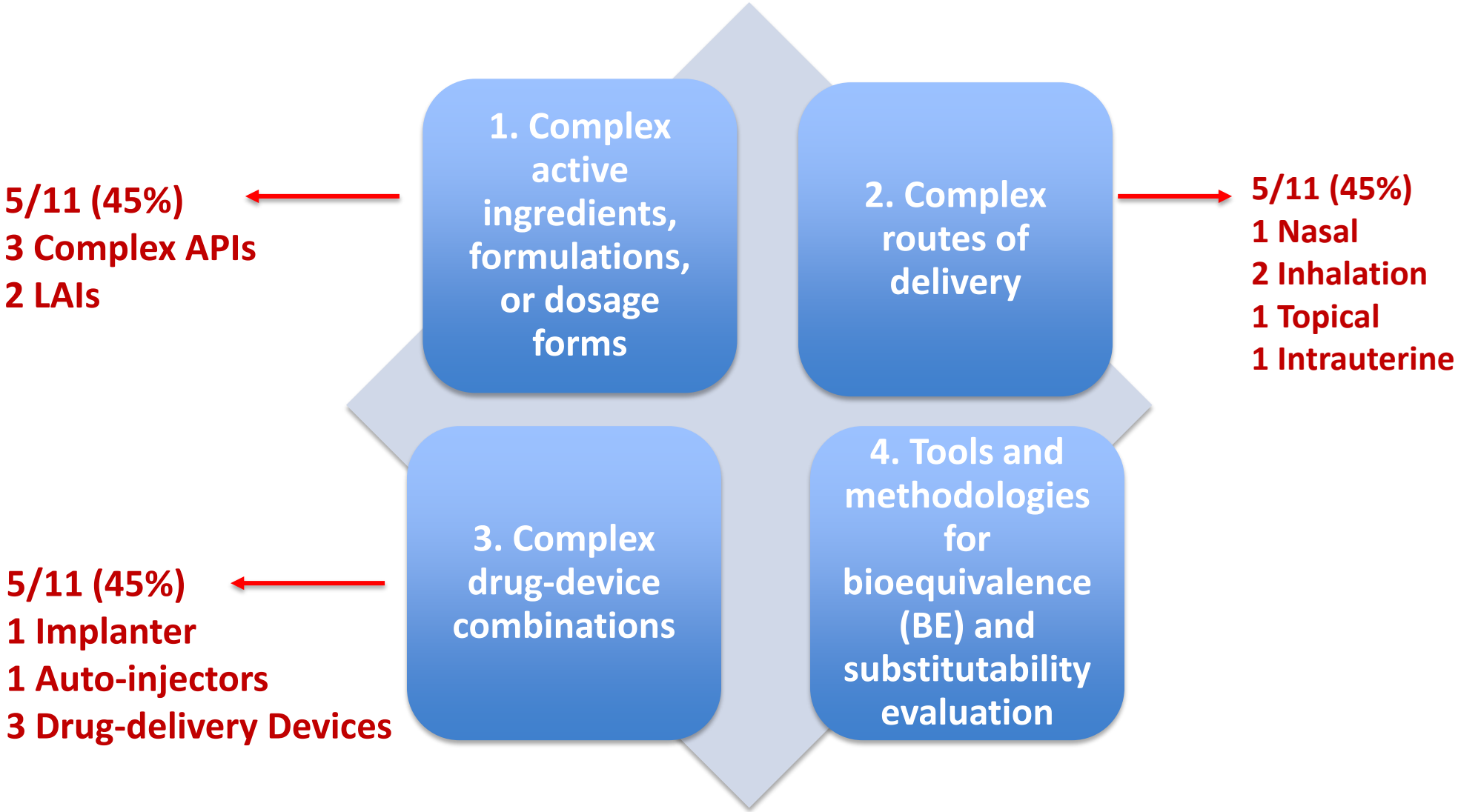
NUSINERSEN SODIUM **(Complex API)**
ABALOPARATIDE **(Complex API; Complex Drug-Device Combination)**
ETELCALCETIDE **(Complex API)**

PSG Development for Recent Complex Drug Products (FY2015-2017 NDA Approval Cohorts)



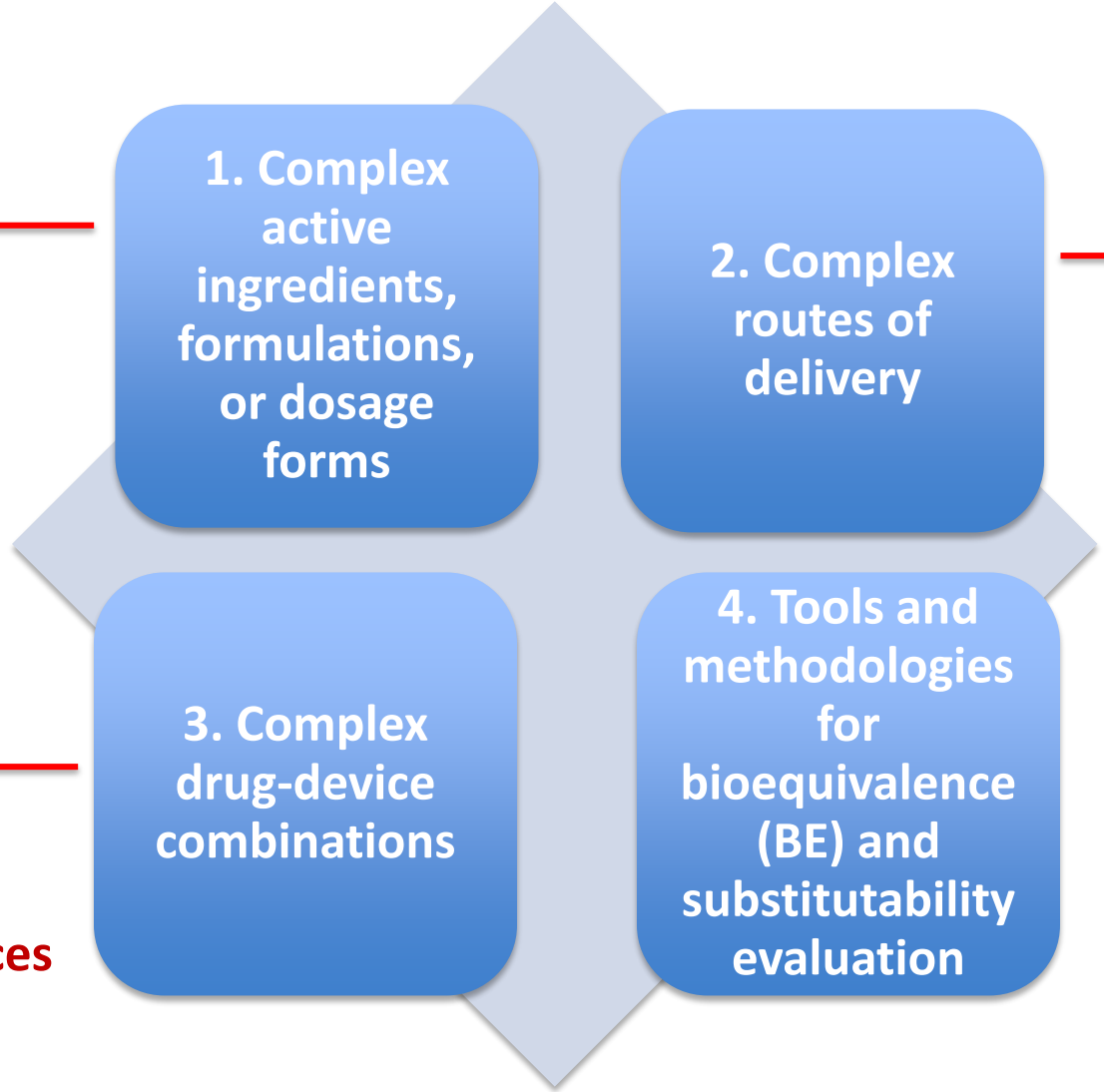
* Number includes PSG published, drug products that are covered under FDA general guidance and may be eligible for "biowaiver" under 21 CFR 320.22(b)

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



LAI: Long-acting Injectable

Recent Non-NME Complex Drug Products Without PSG FY2016 (N=15)



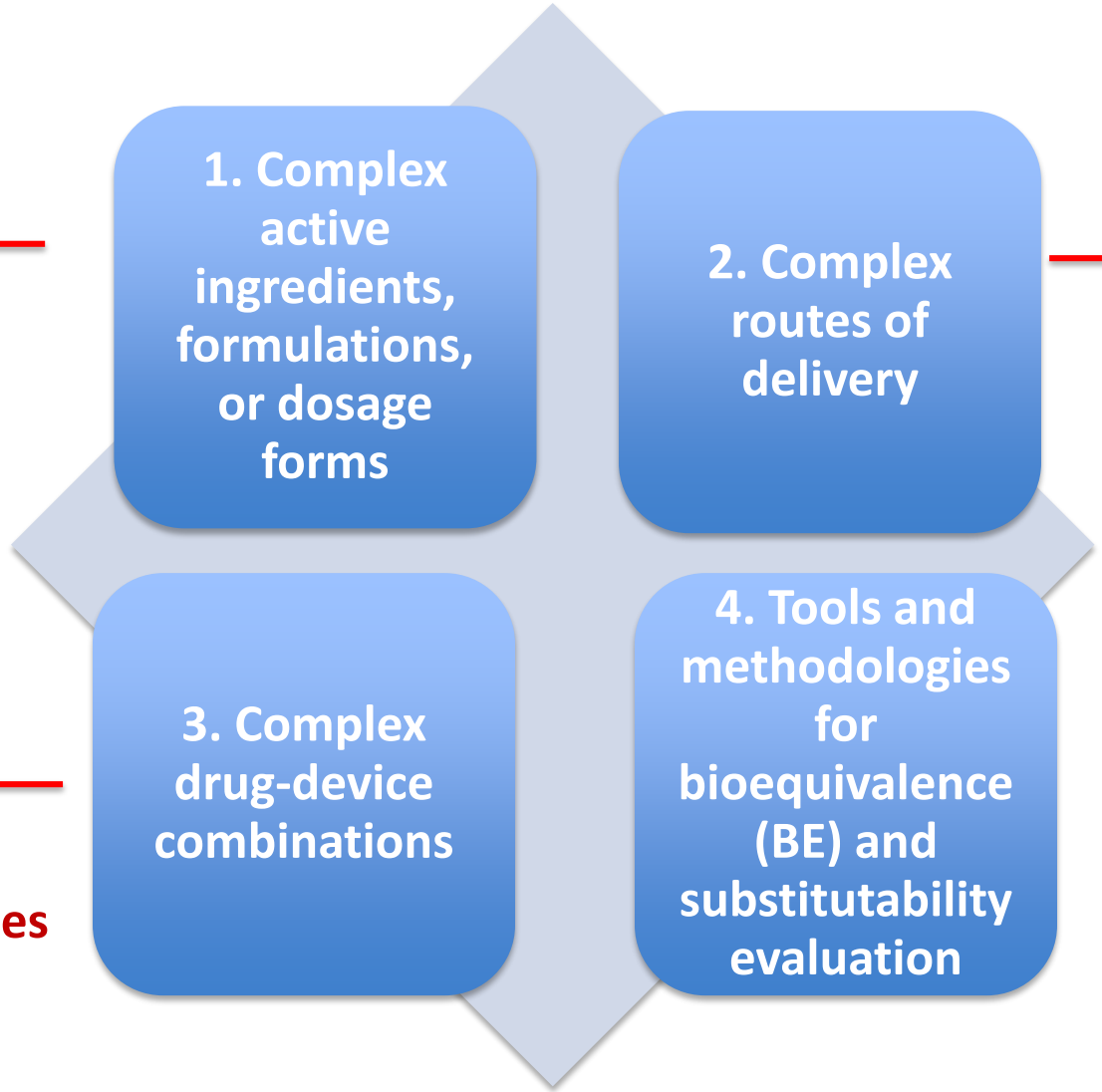
5/15 (33%)
1 Complex APIs
2 LAIs
1 ADF
1 Complex Injectable

7/15 (47%)
1 Nasal
3 Inhalation
2 Topical
1 Intrauterine

9/15 (60%)
2 Implanters
3 Auto-injectors
4 Drug-delivery Devices

LAI: Long-acting Injectable; ADF: Abuse-deterrent Formulation

Recent Non-NME Complex Drug Products Without PSG FY2017 (N=14)



7/14 (50%)
3 Complex APIs (1 is LAI)
1 LAI
2 Complex injectable
1 ADF

8/14 (57%)
2 Nasal
4 Inhalation
2 Topical
1 GI

7/14 (47%)
1 Auto-injector
6 Drug-delivery Devices

LAI: Long-acting Injectable; GI: Gastrointestinal

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

Questions for the Panel

- FDA believes that the current research priorities address all of the scientific challenges identified for complex product approved in the FY2015 to FY2017 NDA cohorts.
- Does the panel agree?
- Are there specific challenges that should be higher priority?

FY2018 NDA Approval Cohort
Complex Products

FY2018 NDA Approval Cohort
Complex Product Overview

- 40 NDAs are complex products
  - 6 PSGs have already been published as of Feb 2019

- 7 NDAs are NME complex products
  - 1 PSG has been published as of Feb 2019
    - Ozenoxacin Cream

FY2018 Approved NMEs that are Complex

NDA Number	Active Ingredients	Dosage Form; Route of	Reasons of Complexity
208700	LUTETIUM DOTATATE LU-177	SOLUT	
207078	SODIUM ZIRCONIUM CYCLOSILICATE	FOR SU	Delivery
209637	SEMAGLUTIDE	SOLUTI	plex Drug-
208945	OZENOXACIN	CREAM;TOPICAL	rm; Complex Route of Delivery
210589	FISH OIL TRIGLYCERIDES	EMULSION; INTRAVENOUS	**Complex API;** Complex Dosage Form
209627	ETHINYL ESTRADIOL; SEGESTERONE ACETATE	RING; VAGINAL	Complex Dosage Form; Complex Drug-Device
210922	PATISIRAN SODIUM	SOLUTION; INTRAVENOUS	**Complex API**

Research conducted in previous years has prepared us to develop PSGs for complex products. For example, we are developing PSGs for these products and they may be published in the next 12 months.*

PSG published in Feb 2019

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

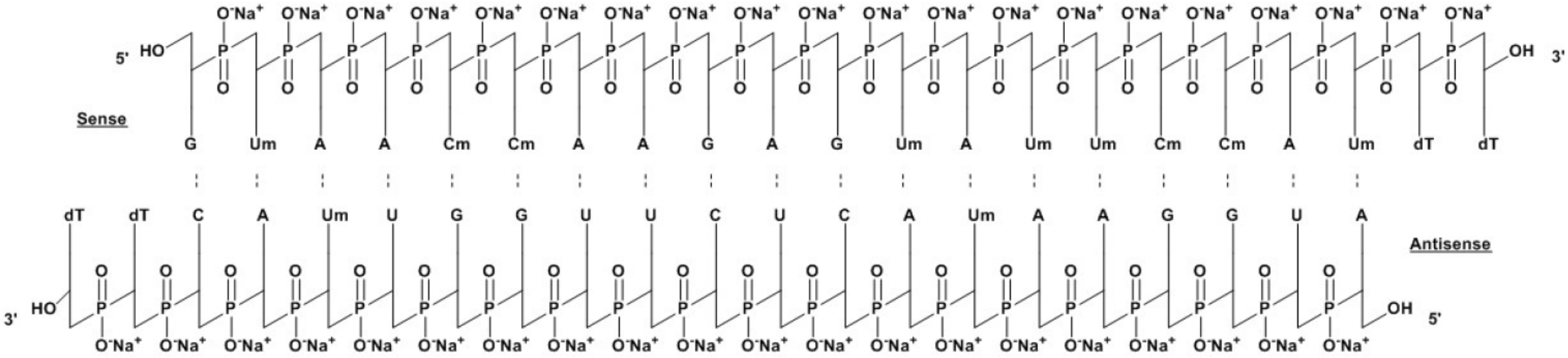
ONPATTRO (Patisiran)

- Approved 8/10/2018 under NDA 210922, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- IV injection
- Complex API
  - Patisiran is a double-stranded small interfering ribonucleic acid (siRNA), formulated as a lipid complex for delivery to hepatocytes
  - Patisiran specifically binds to a genetically conserved sequence in the 3' untranslated region (3'UTR) of mutant and wild-type transthyretin (TTR) messenger RNA (mRNA)

Patisiran

- Antisense oligonucleotide
- 30 linked subunits
- Phosphorodiamidate morpholino oligomer

The structural formula is:

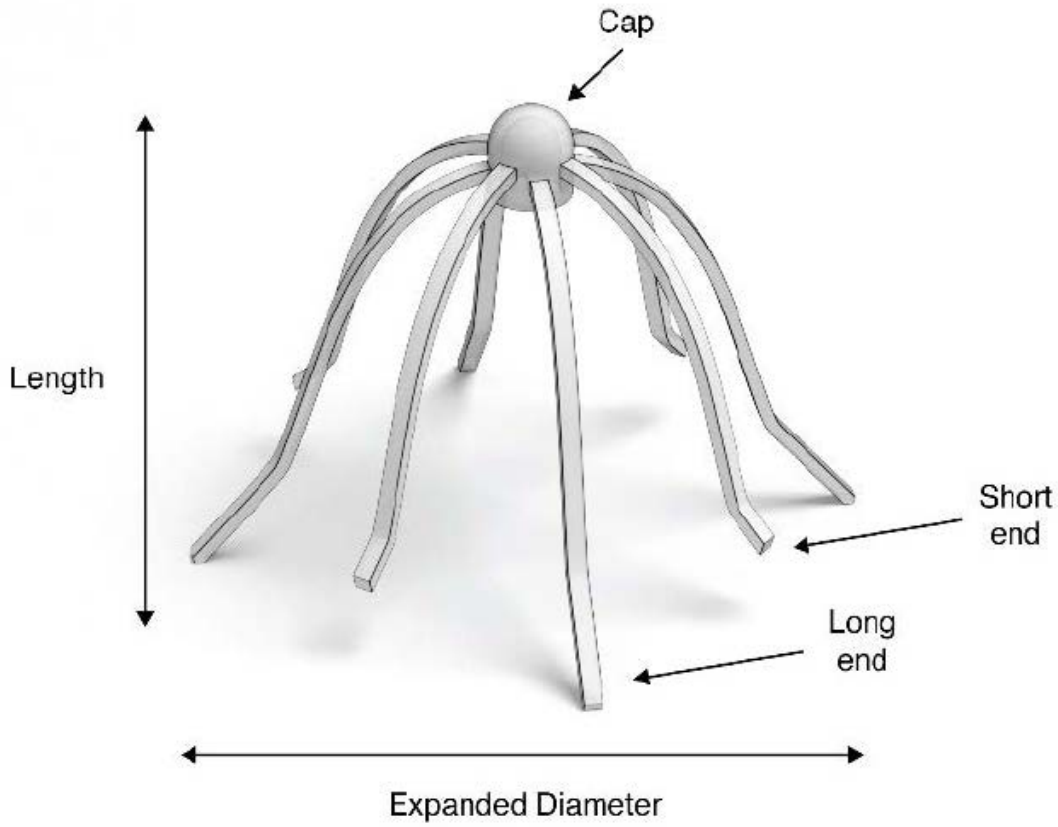


A, adenosine; C, cytidine; G, guanosine; U, uridine; Cm, 2'-*O*-methylcytidine; Um, 2'-*O*-methyluridine; dT, thymidine

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf

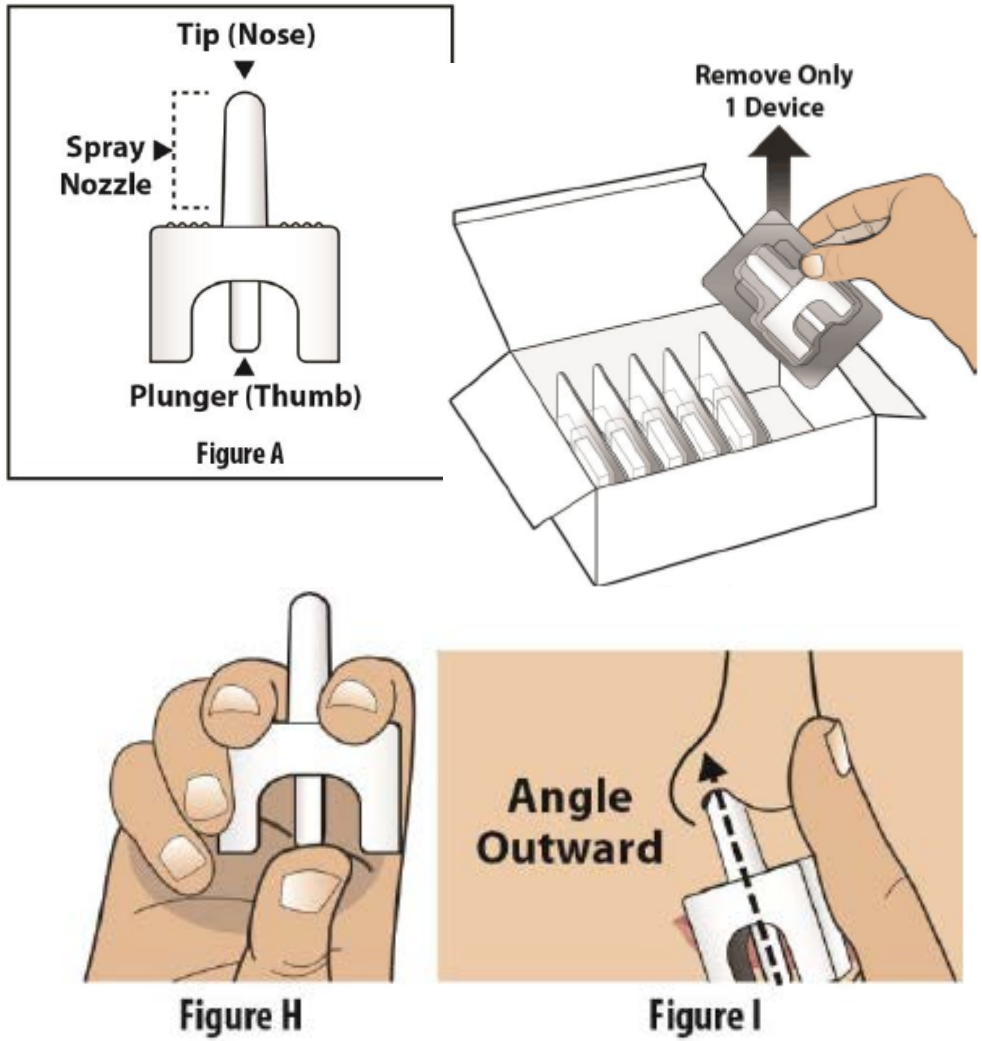
SINUVA (Mometasone furoate)

- 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



TOSYMRA (Sumatriptan) Nasal Spray

- New Dosage Form
  - New way to treat migraine
- Approved: 1/25/2018 (NDA 209310)
- API: Sumatriptan
- Dosage Form/Route: Spray; Nasal
- **Indication: A**cute treatment of migraine with or without aura in adults
- **Complexity**: Complex drug-device combination



Complex NDA Approved in FY2018
Questions for the Panel

- Do these products fit into our existing research priorities?
- Is there a need to adapt our research priorities to the change in the landscape of potential reference listed drugs (RLDs)?

Acknowledgements

- Office of Research and Standards
  - Xiajing (Jean) Gong
  - Meng Hu
  - Wenlei Jiang
  - Xiaohui (Jeff) Jiang
  - Kim Witzmann
  - Darby Kozak
  - Sam Raney
  - Kris Andre
  - Robert Lionberger
- Office of Generic Drugs Staff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