

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

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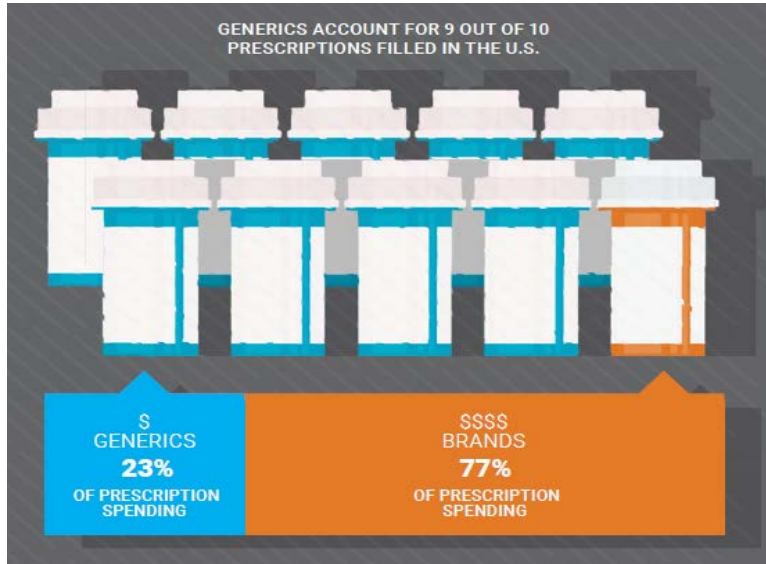
Center for Drug Evaluation and Research, U.S. FDA

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# Generic Drugs in the United States



## Overall Drug Products



### Generic Drugs:

- 90% of prescription
- 23% of spending

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

## However,

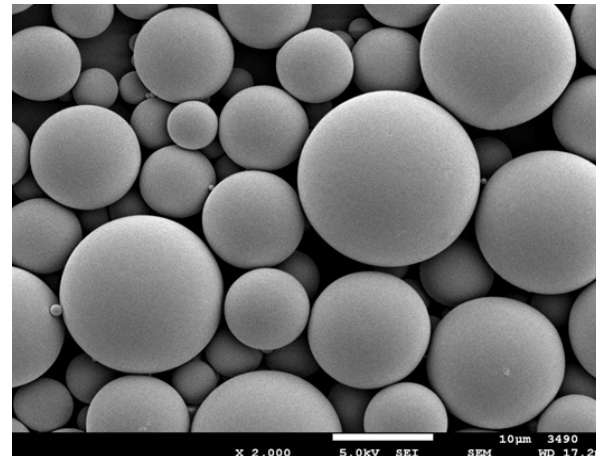
Topical drug products with generics available < 40%  
Ophthalmic products with generics available < 50%

### Orally inhaled drug products



1 Generic

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



No Generics

[https://accessiblemeds.org/sites/default/files/2018\\_aam\\_generic\\_drug\\_access\\_and\\_savings\\_report.pdf](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*

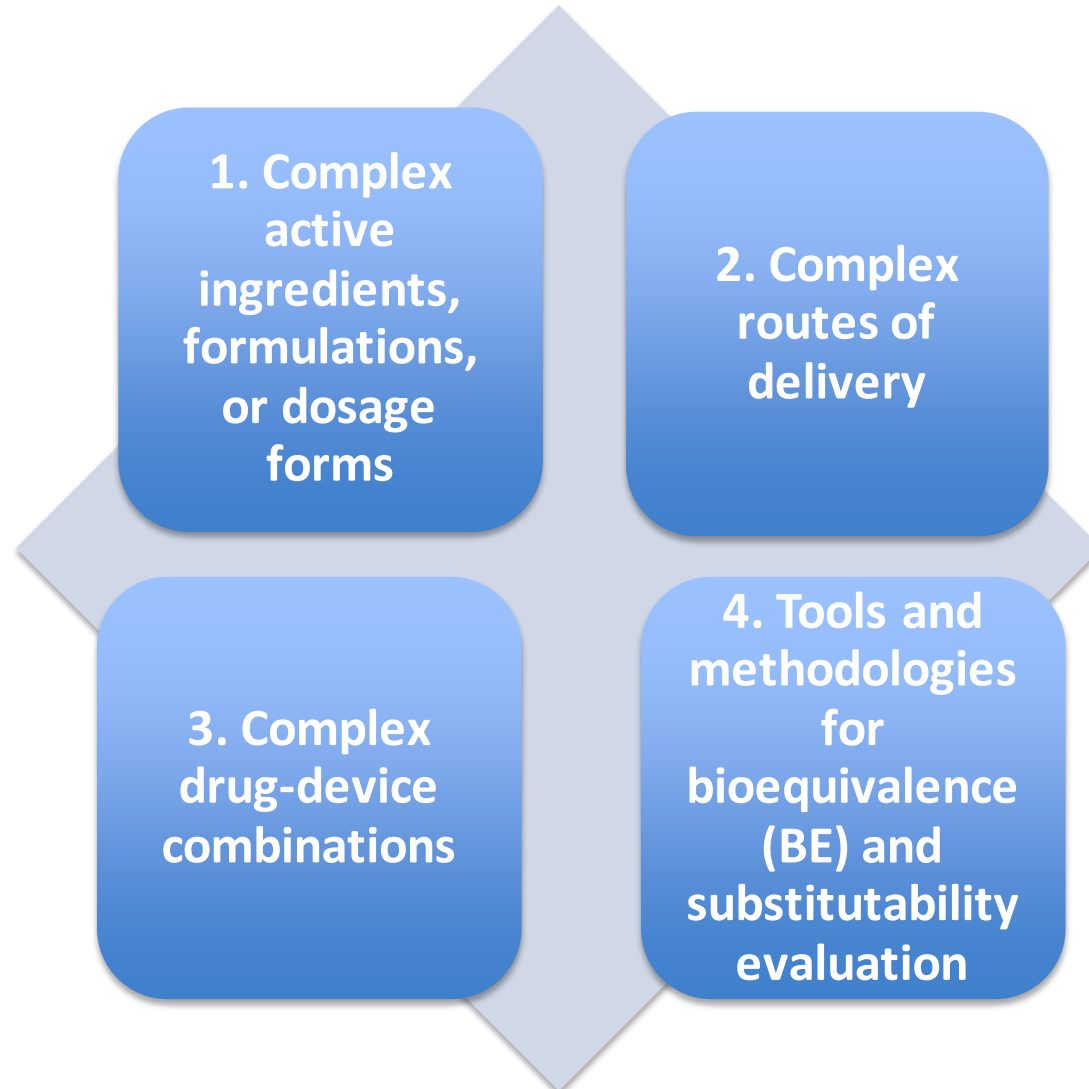
- Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption  
e.g., [Epinephrine Injection \(autoinjector\)](#)

## *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](#)

# FY2019 GDUFA Research Science Priority Areas

15 priority areas under 4 broad categories



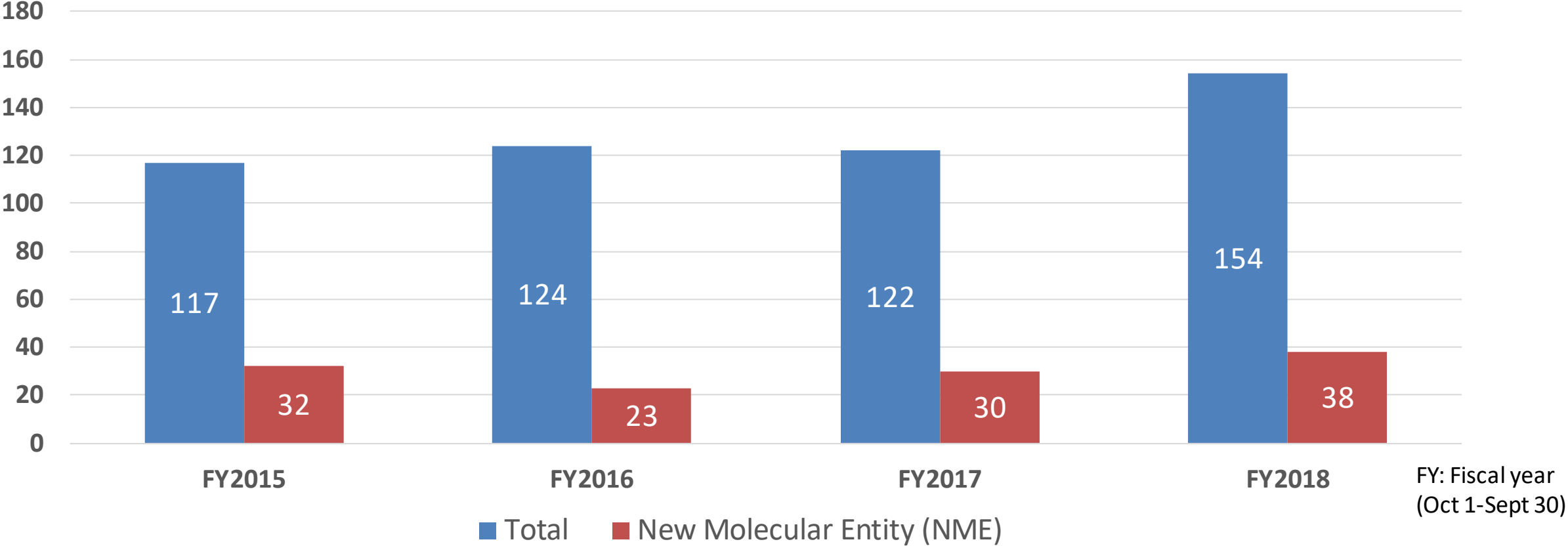
<https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm>

# Questions for the Panel

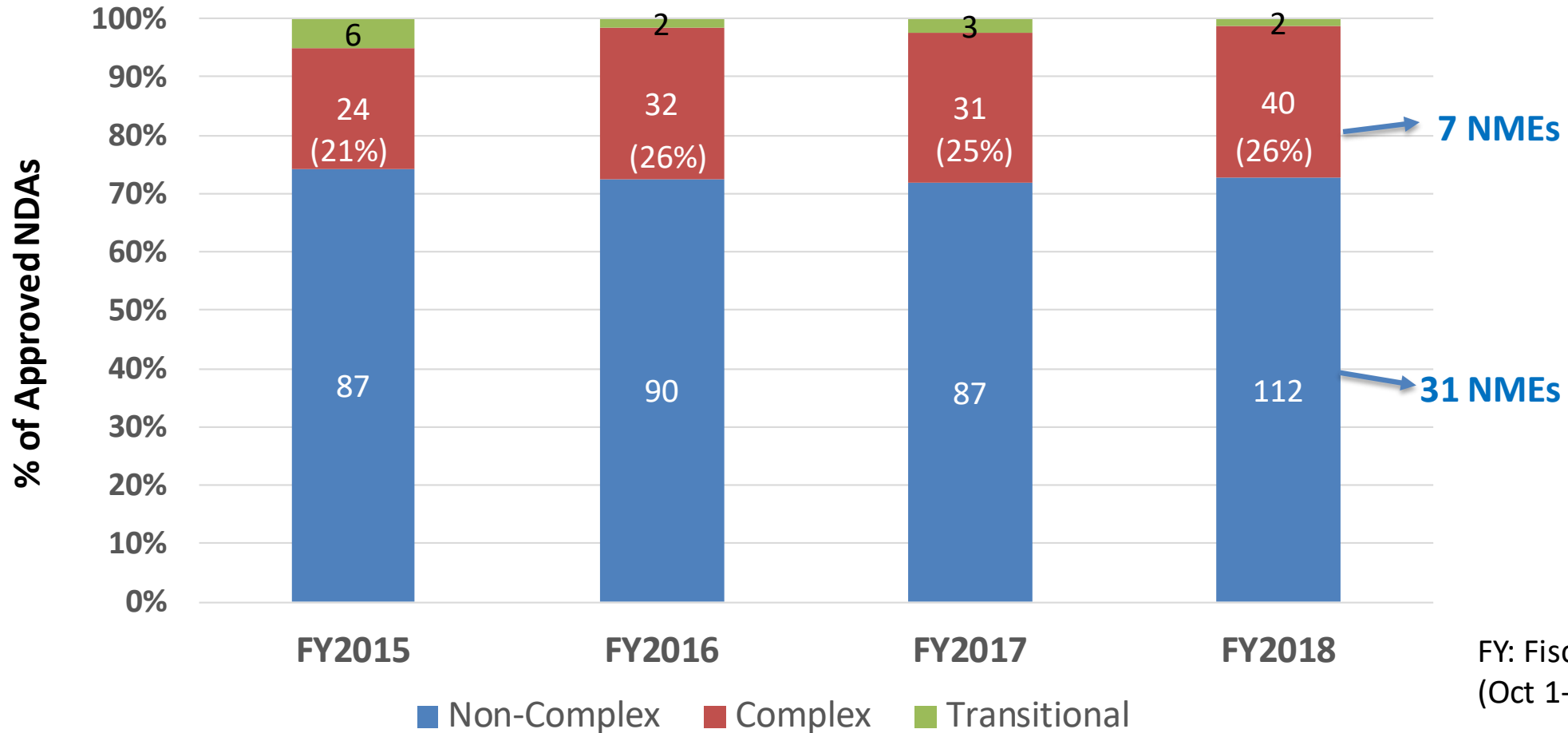
- Do these research priorities address the scientific challenges to developing generics of recently approved complex NDAs (NMEs and Non-NMEs)?
- To aid in this analysis, we will review the landscape.

# Approved New Drug Applications (NDAs) FY2015-2018

## Number of NDAs Approved



# Complex Drug Products in Approved NDAs FY2015-2018



\*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)

- 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

## For Complex Products

- 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

## For Other Products

- Based on requests from the regulated industry and public health priorities



# PSGs Published in FY2018

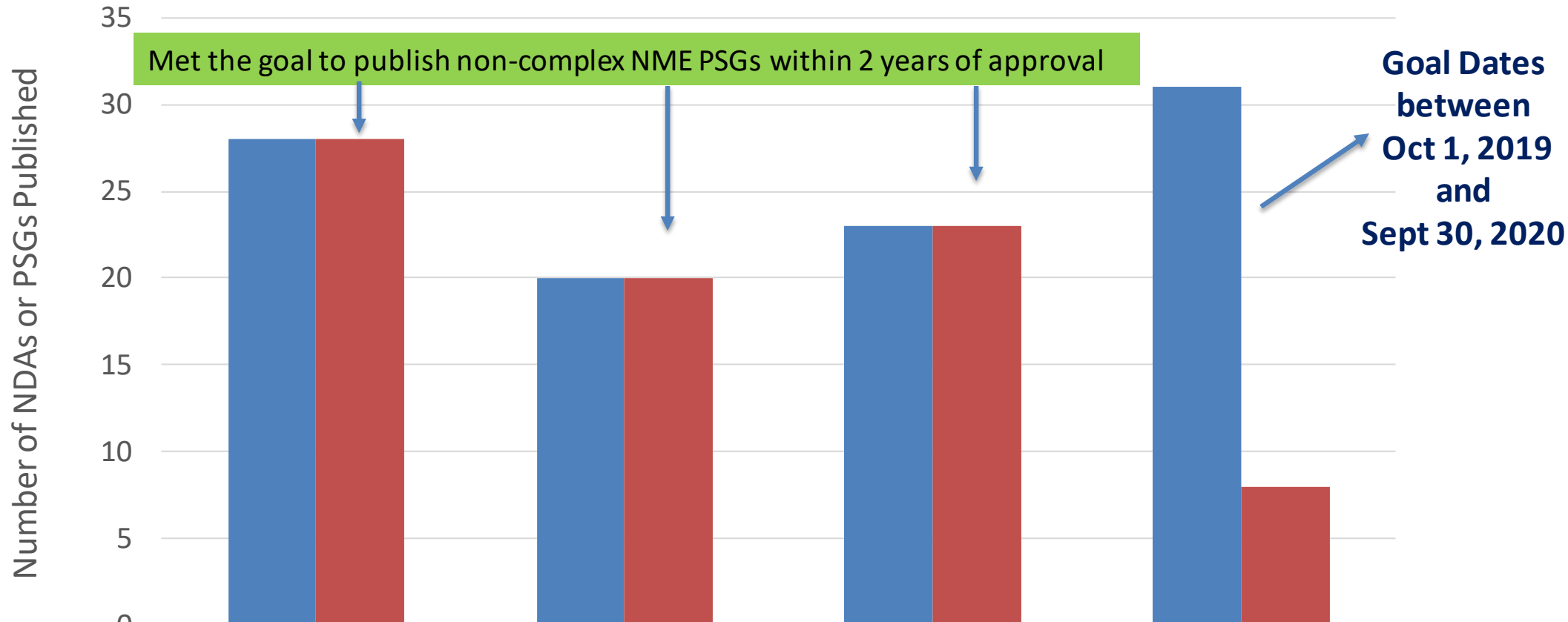
Total Number of PSGs	New	Revised	Complex	Non-Complex
208	136	72	75 (36%)	133 (64%)

FY: Fiscal Year  
(Oct 1-Sept 30)

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



As of Feb 2019



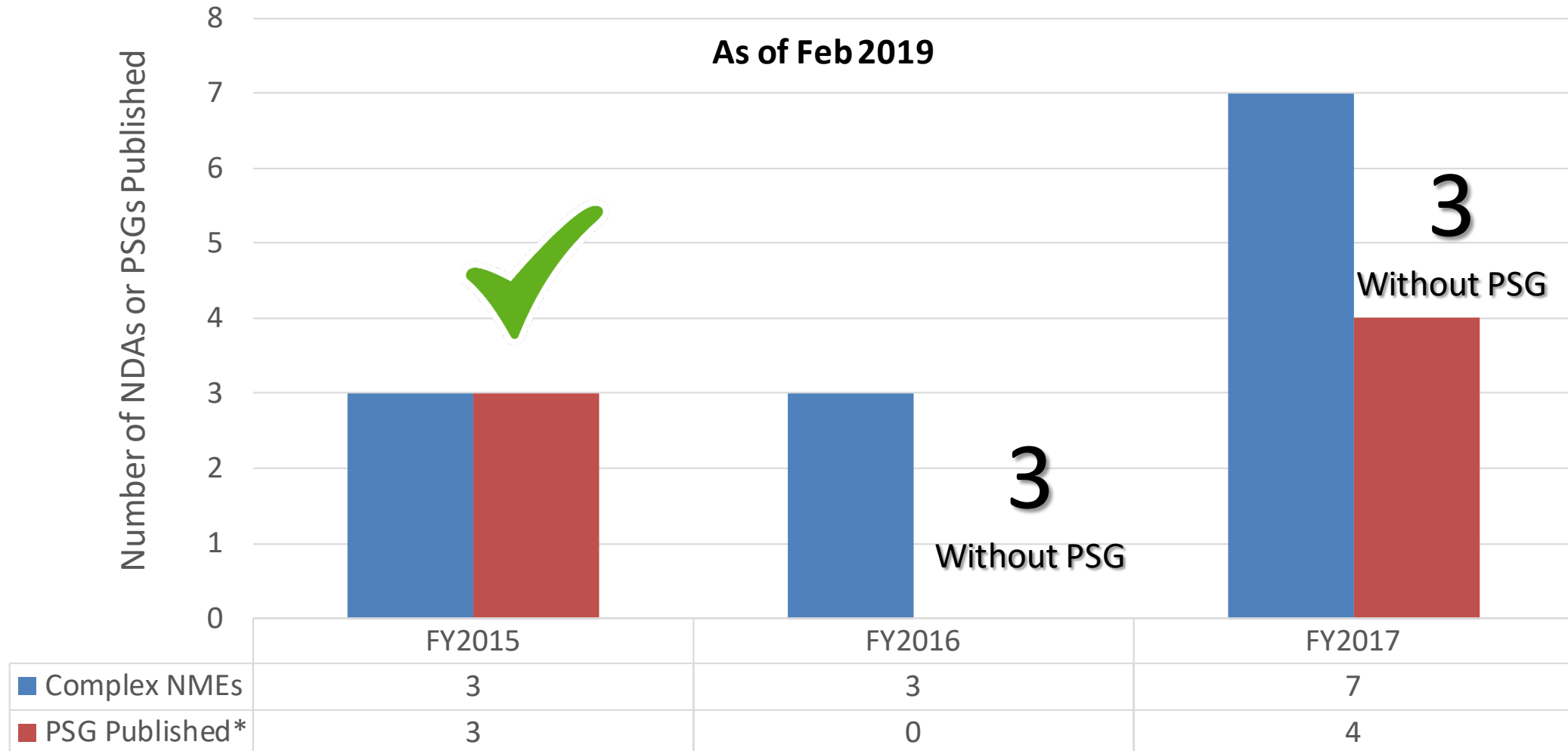
	FY2015	FY2016	FY2017	FY2018	FY: Fiscal Year (Oct 1-Sept 30)
■ Non-complex NMEs	28	20	23	31	
■ PSG Published*	28	20	23	8	

\* 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)

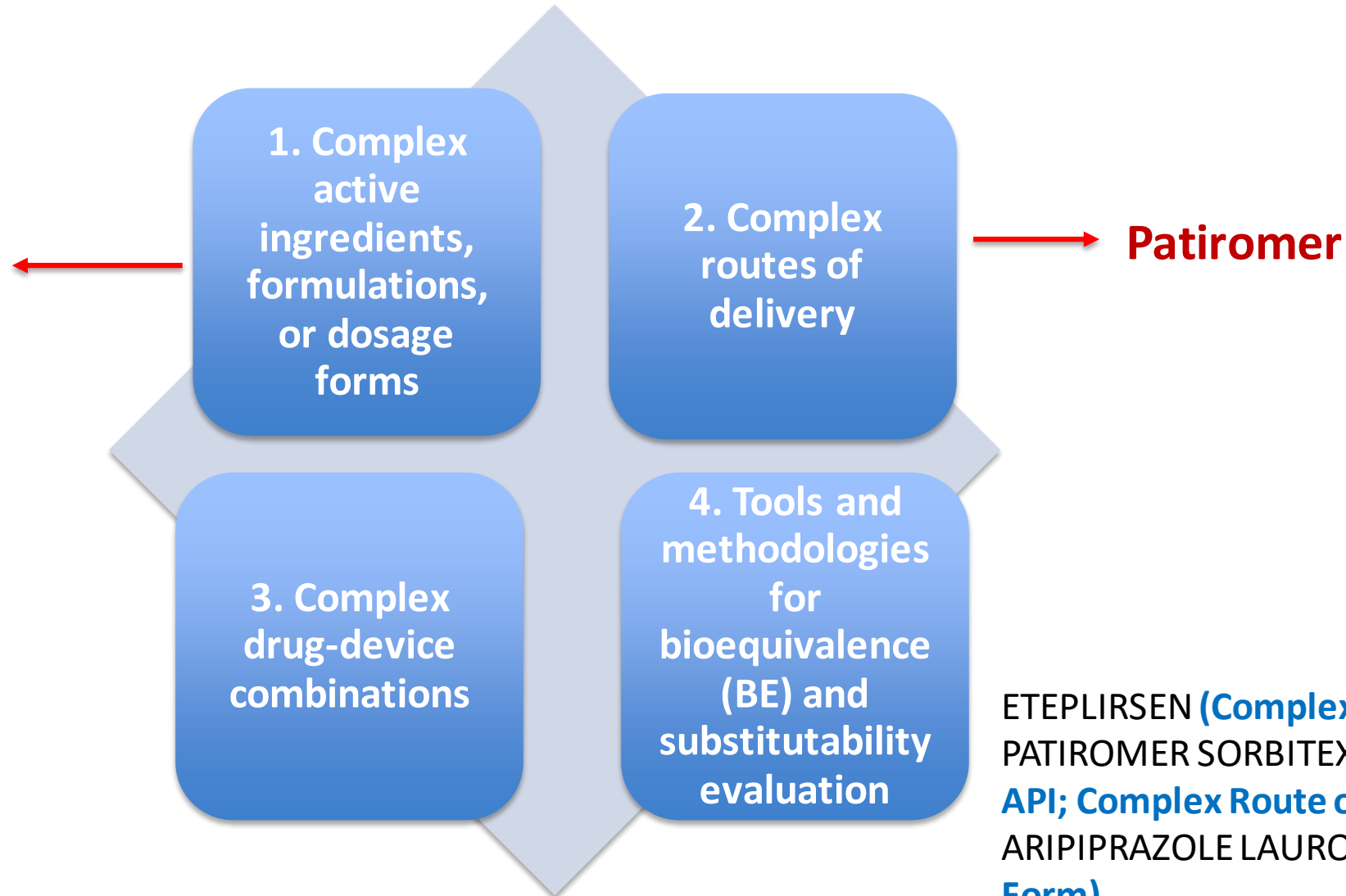


\* Prior to FY18: Number includes PSG published and drug products may be eligible for “biowaiver” under 21 CFR 320.22(b) Starting FY18 (GDUFA II), we will publish PSGs for all non-complex NMEs within 2 years of approval.

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



- Eteplirsen
- Patiromer
- Aripiprazole lauroxil



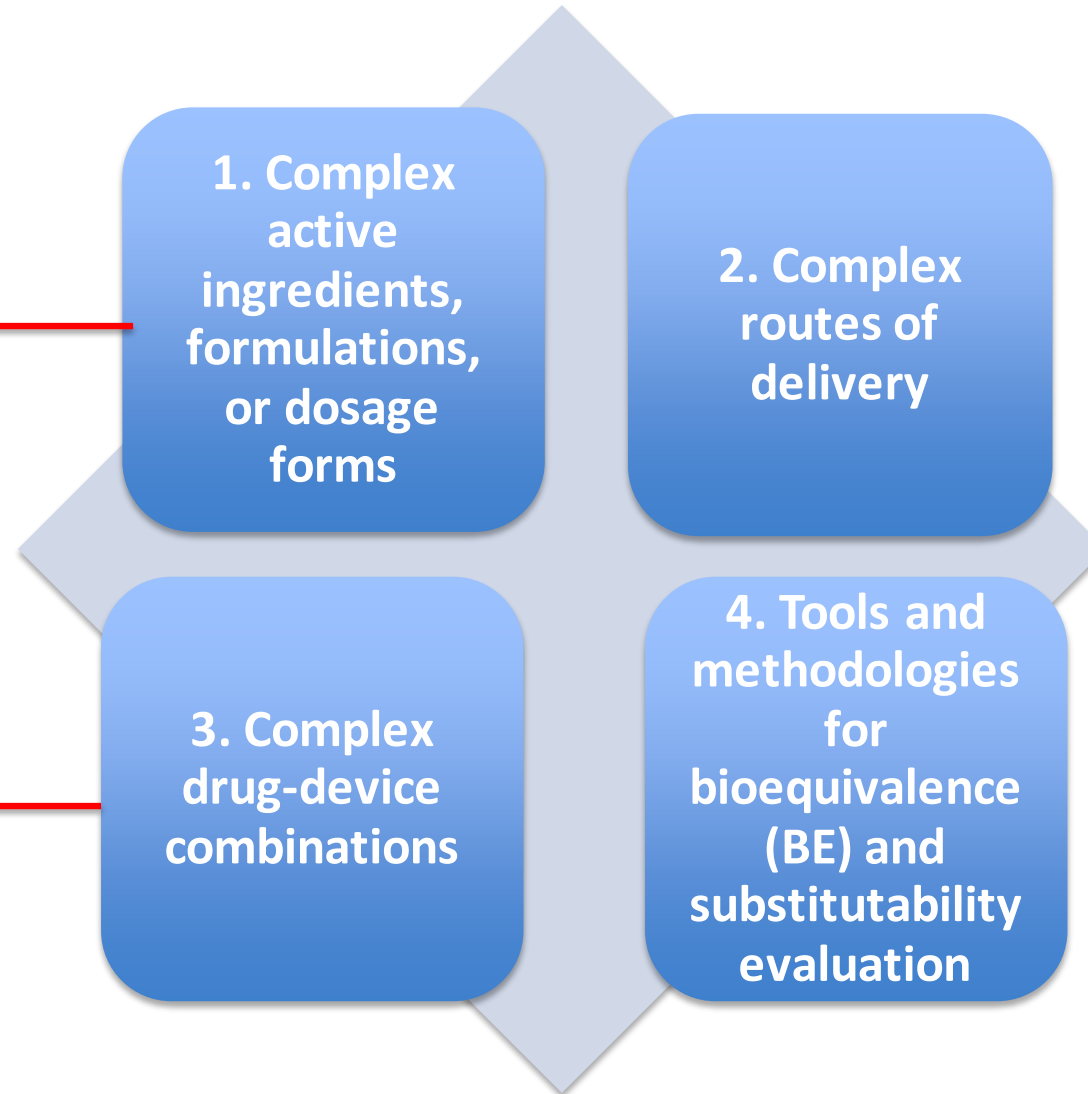
ETEPLIRSEN (**Complex API**)  
PATIROMER SORBITEX CALCIUM (**Complex API; Complex Route of Delivery**)  
ARIPIPRAZOLE LAUROXIL (**Complex Dosage Form**)

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



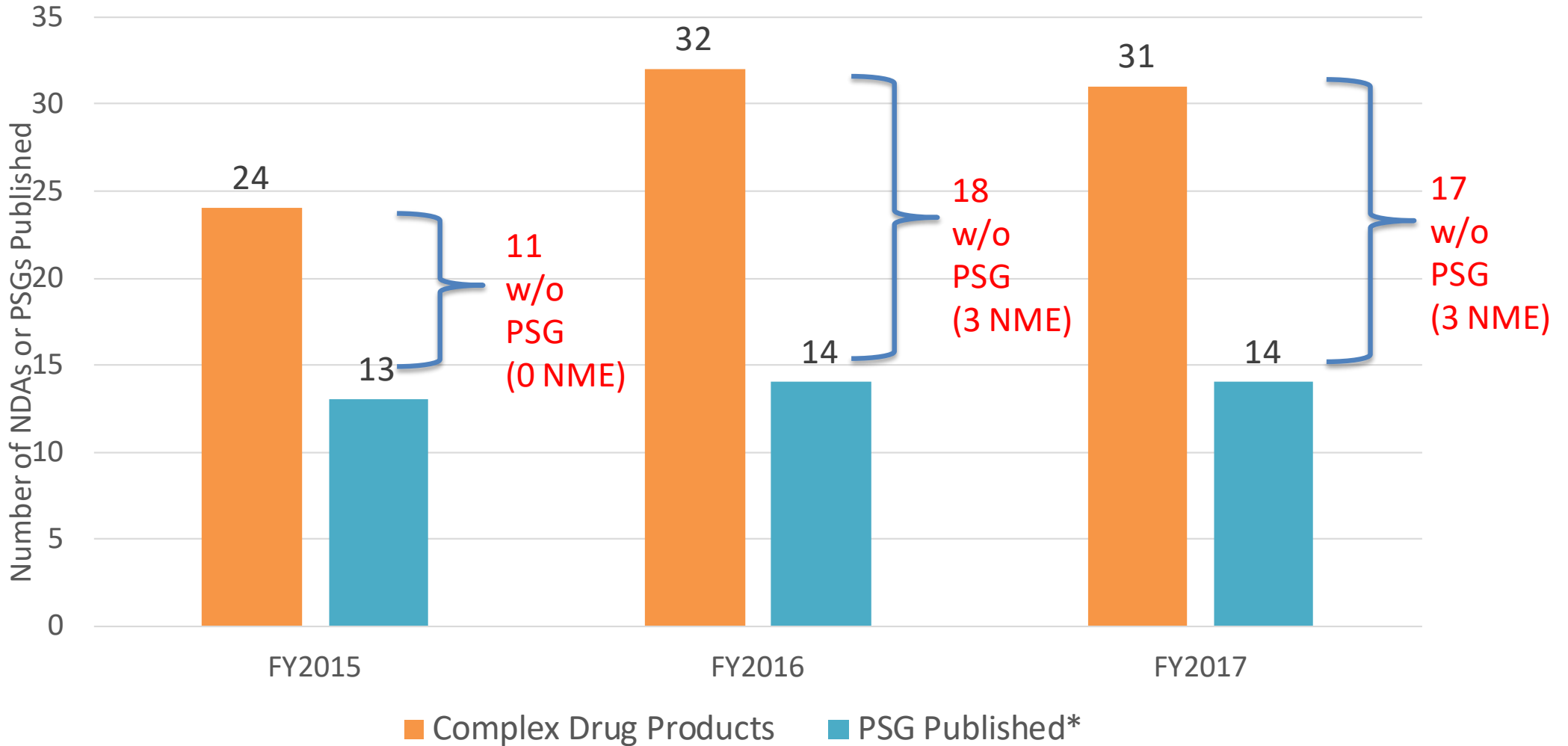
- **Nusinersen**
- **Abaloparatide**
- **Etelcalcetide**

**Abaloparatide**



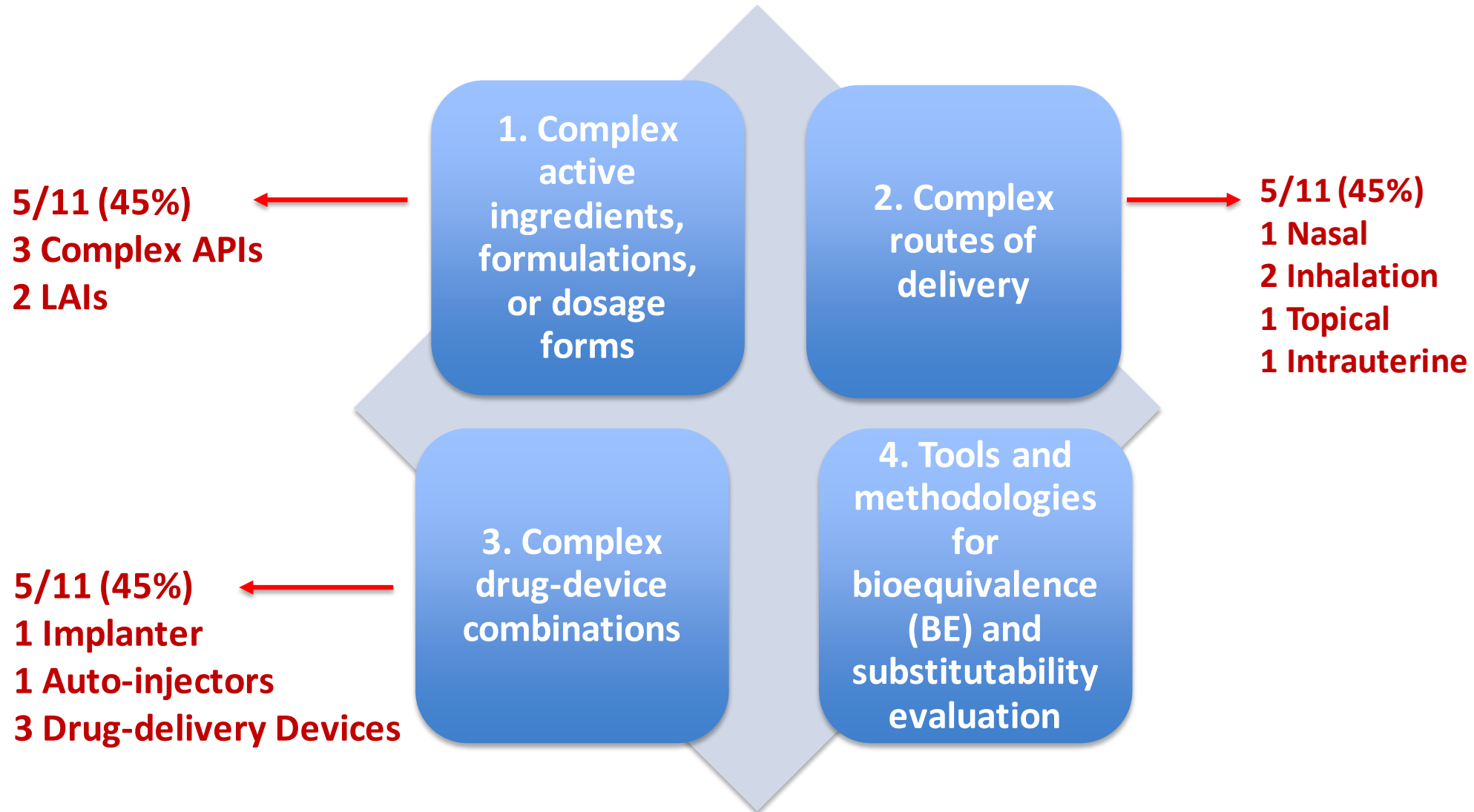
NUSINERSEN SODIUM (**Complex API**)  
ABALOPARATIDE (**Complex API;**  
**Complex Drug-Device Combination**)  
ETELCALCETIDE (**Complex API**)

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



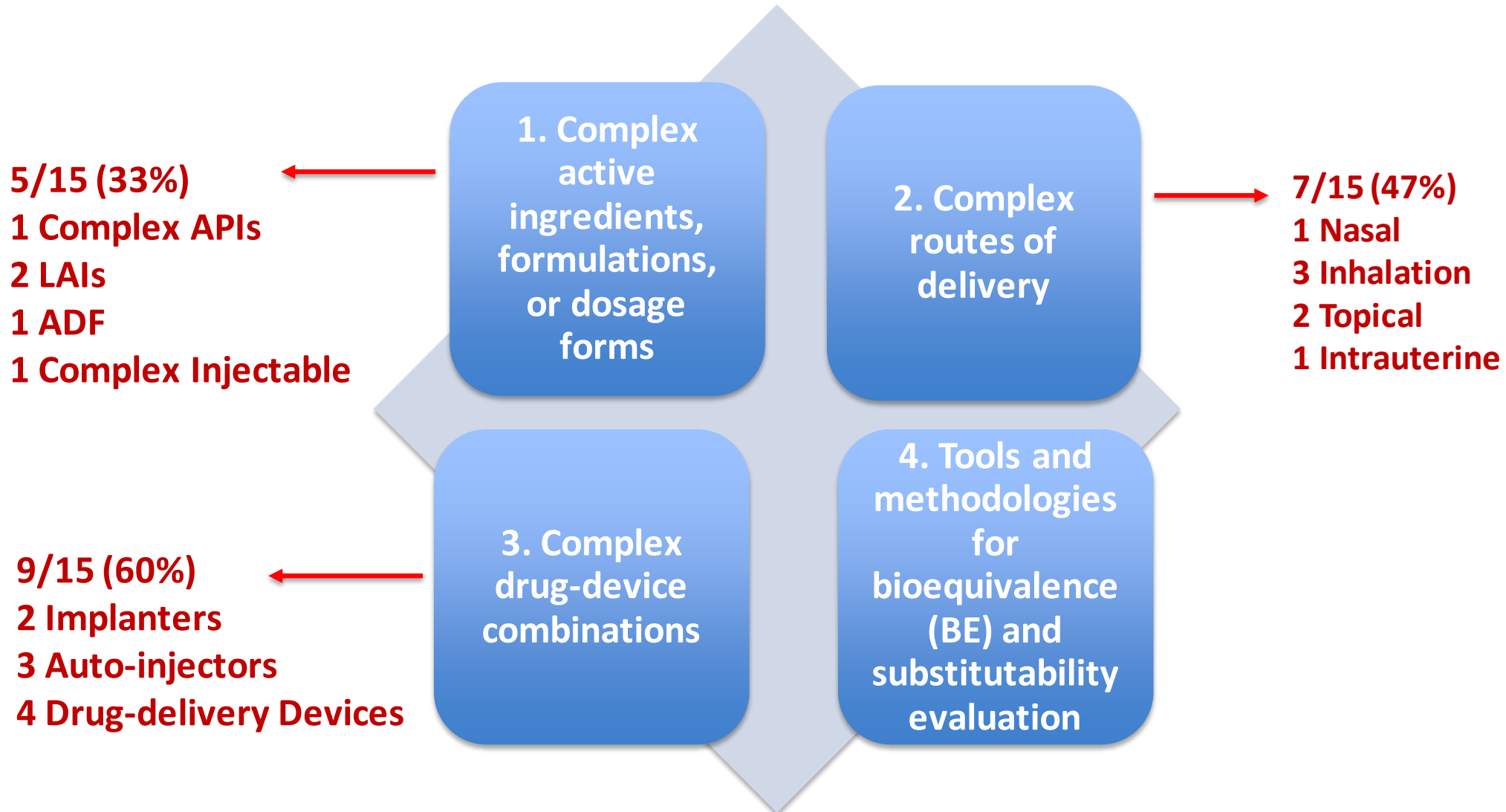
\* Number includes PSG published, drug products that are covered under FDA general guidance and may be eligible for “biowaiver” under 21 CFR 320.22(b)

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

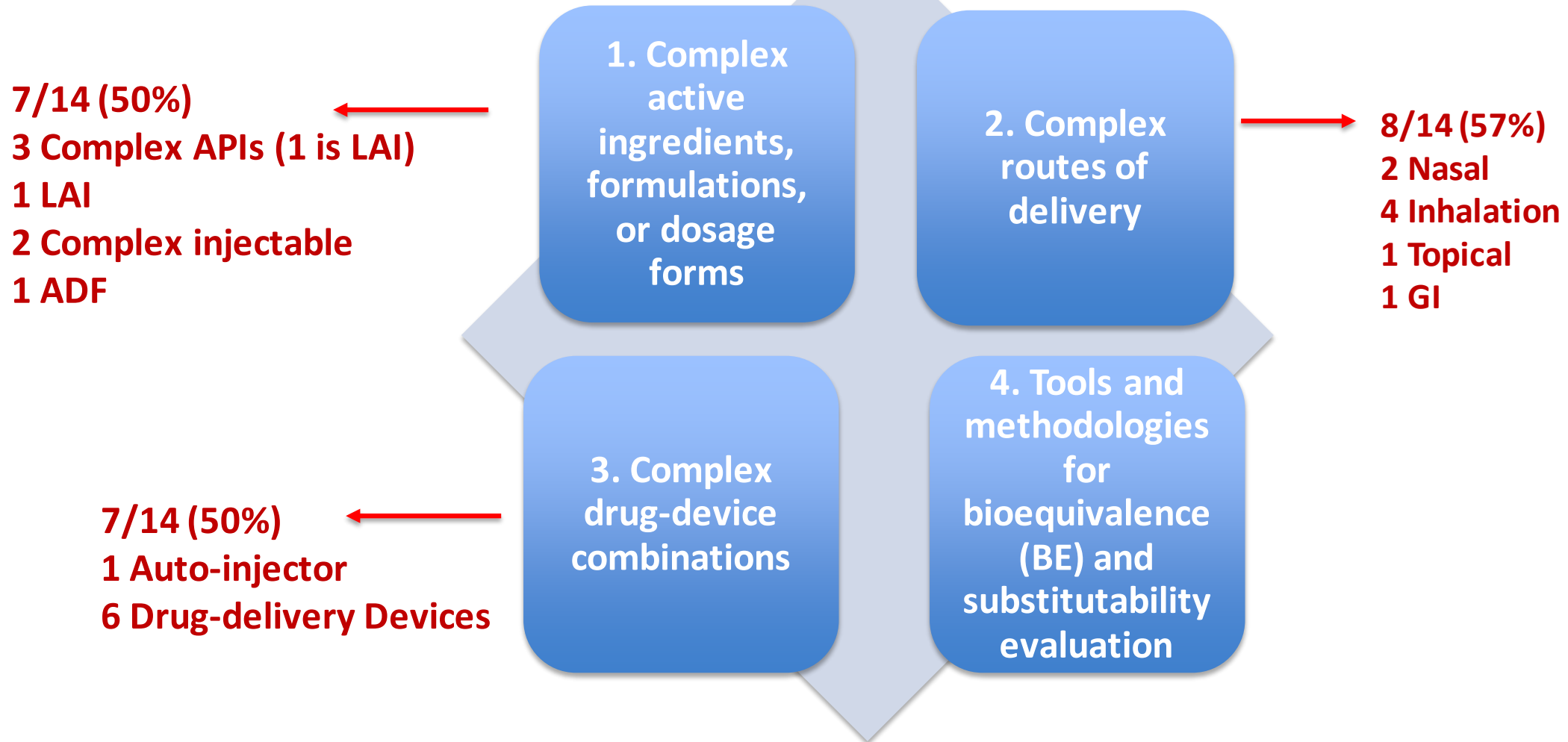




# Recent Non-NME Complex Drug Products Without PSG FY2016 (N=15)



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



# 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 of 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 Administration	Reasons of Complexity
208700	LUTETIUM DOTATATE LU-177	SOLUTION	
207078	SODIUM ZIRCONIUM CYCLOSILICATE	FOR SUBCUTANEOUS INJECTION	Complex Drug-Delivery
209637	SEMAGLUTIDE	SOLUTION	Complex Drug-Delivery
208945	OZENOXACIN	CREAM; TOPICAL	Complex Dosage Form; Delivery PSG published in Feb 2019
210589	FISH OIL TRIGLYCERIDES	EMULSION; INTRAVENOUS	<b>Complex API; Complex Dosage Form</b>
209627	ETHINYL ESTRADIOL; SEGESTERONE ACETATE	RING; VAGINAL	Complex Dosage Form; Complex Drug-Device
210922	PATISIRAN SODIUM	SOLUTION; INTRAVENOUS	<b>Complex API</b>

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

# 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)

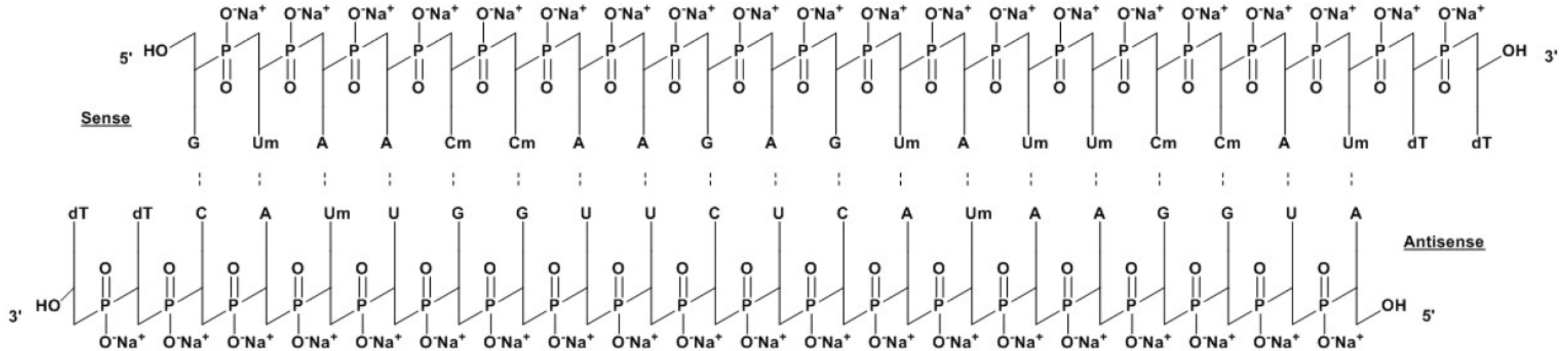


# Patisiran



- Antisense oligonucleotide
- 30 linked subunits
- Phosphorodiamidate morpholino oligomer

The structural formula is:

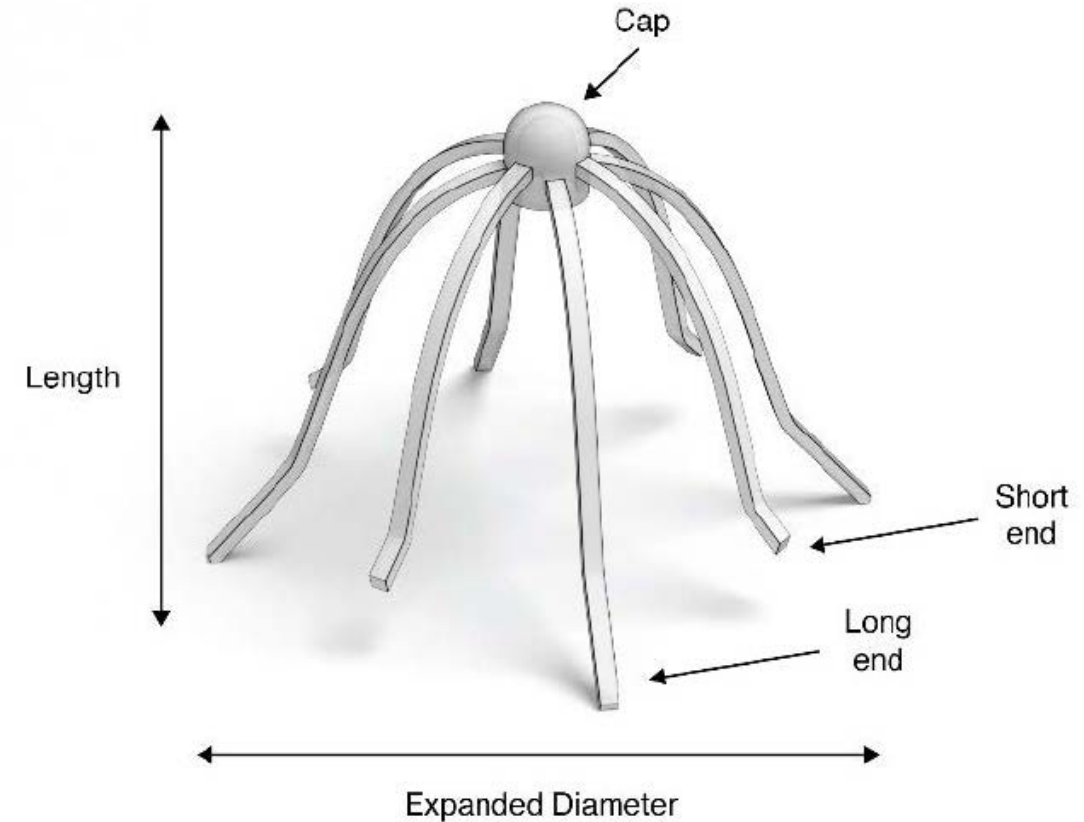


A, adenosine; C, cytidine; G, guanosine; U, uridine; Cm, 2'-O-methylcytidine; Um, 2'-O-methyluridine; dT, thymidine

# 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  $\geq 18$  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:** Acute treatment of migraine with or without aura in adults
- **Complexity:** Complex drug-device combination

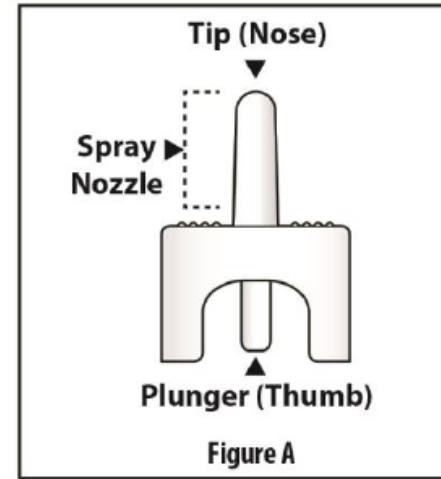


Figure H

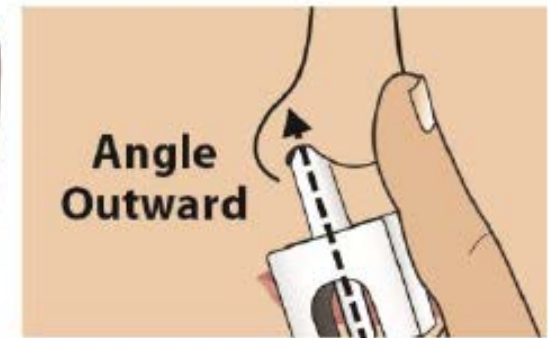


Figure I



# 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

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