



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

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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

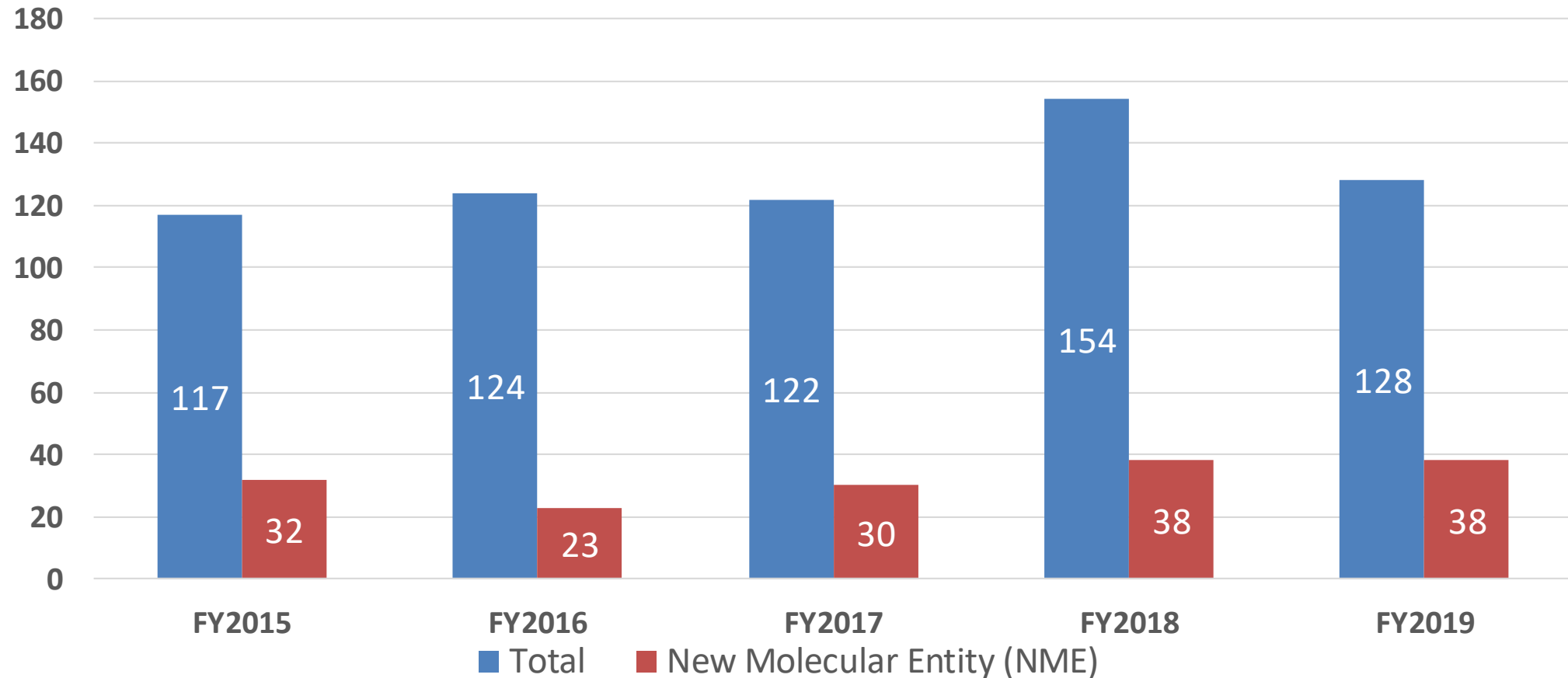
- Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption
e.g., [Epinephrine Injection \(autoinjector\)](#)

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](#)

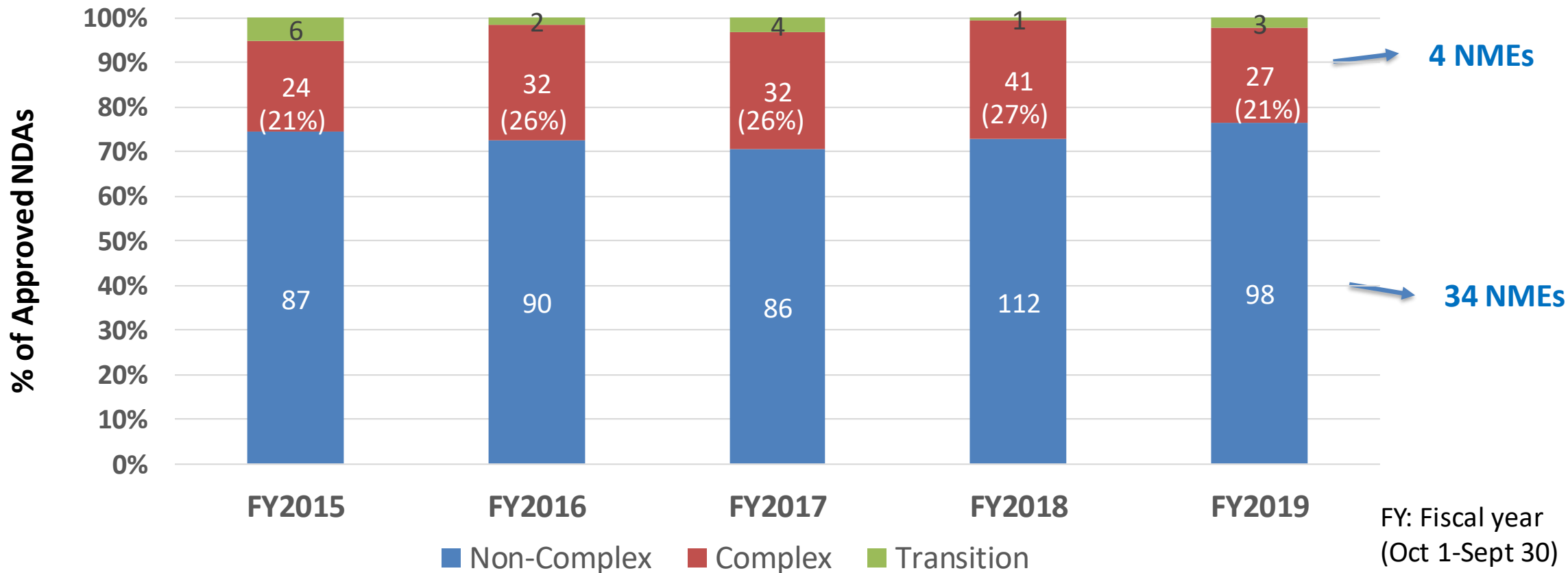
Approved New Drug Applications (NDAs) FY2015-2019

Number of NDAs Approved



FY: Fiscal year
(Oct 1-Sept 30)

Complex Drug Products in Approved NDAs FY2015-2019



*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 (PSGs) Published in FY2019

Total Number of PSGs	New	Revised	Complex	Non-Complex
252	107	145	141 (56%)	111 (44%)
			24 new (17%)	83 new (75%)

FY: Fiscal Year
(Oct 1-Sept 30)

Website to Forecast Upcoming PSGs for Complex Products



Upcoming Product-Specific Guidances for Complex Generic Drug Product Development



Guidances (Drugs)

[Guidance Snapshot Pilot](#)

[Product-Specific Guidances for Generic Drug Development](#)

[Withdrawn Guidances \(Drugs\)](#)

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.

What is a complex generic drug product?

As described in the [GDUFA II Commitment Letter](#), a complex generic drug product generally means the following—

- A product with:
 - a complex active ingredient(s) (e.g., peptides, polymeric compounds, complex

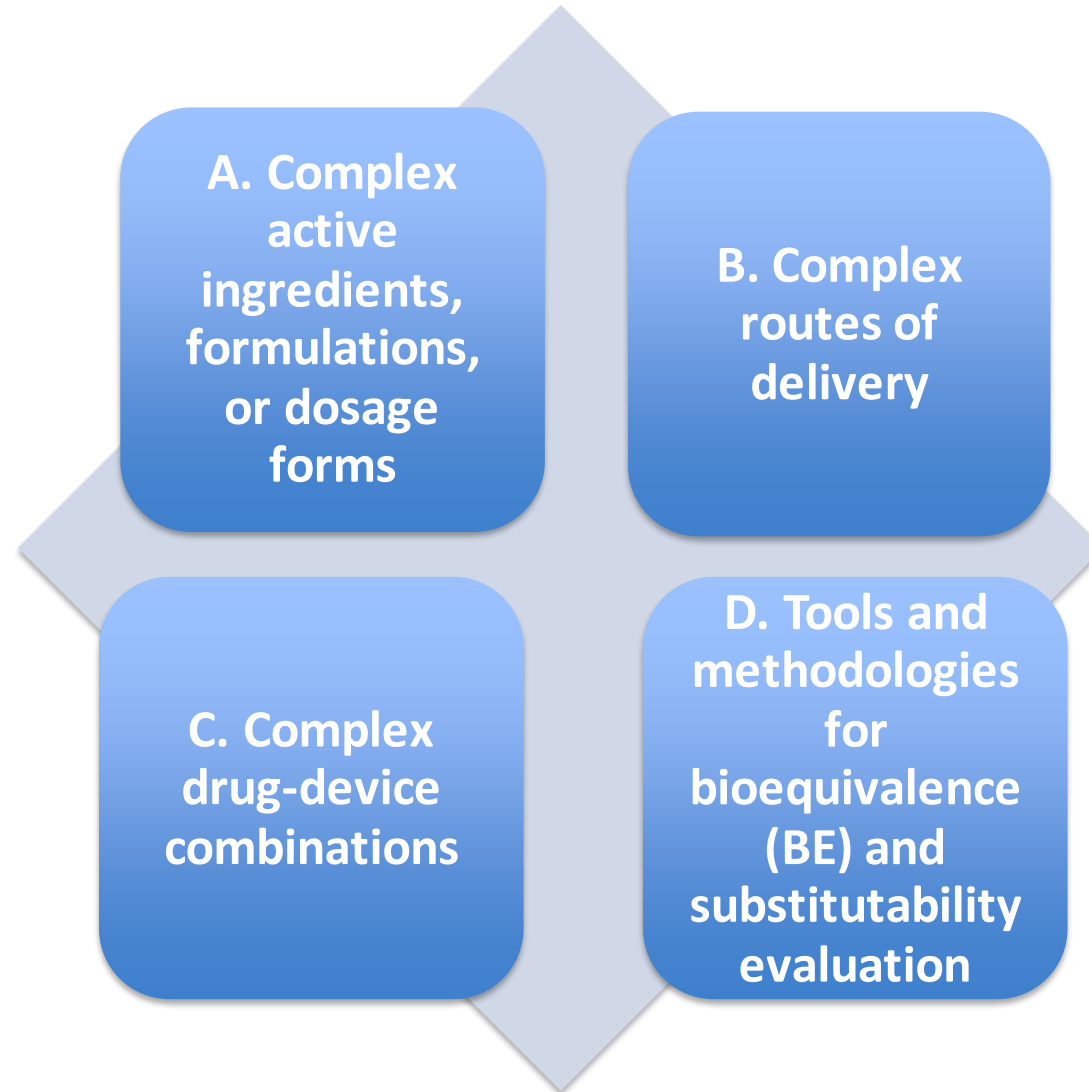
Content current as of:
03/02/2020

Regulated Product(s)
Drugs
Generic Drugs

- Launched in April 2019
- New or revised guidances for complex products that FDA plans to issue in the next 12 months
 - For revision, revision category and a brief description of the reason are provided
 - Timing may be subject to change
- Updated quarterly when a new batch of PSGs is posted

FY2020 GDUFA Research Science Priority Areas

15 priority areas under 4 broad categories



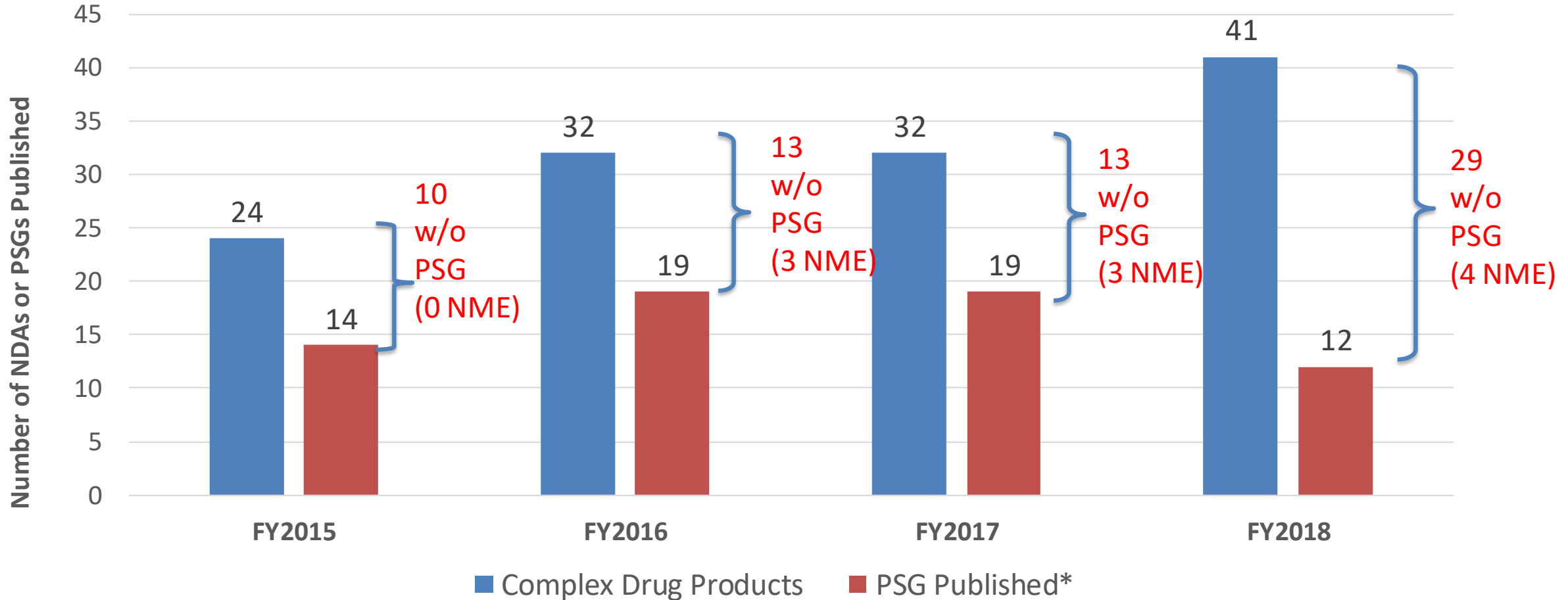
- Do these research priorities address the scientific challenges to developing generics of recently approved complex NDAs (NMEs and Non-NMEs)?
- To aid in this analysis, we will review the landscape and identify possible gaps



FY2015-2018 NDA Approval Cohorts

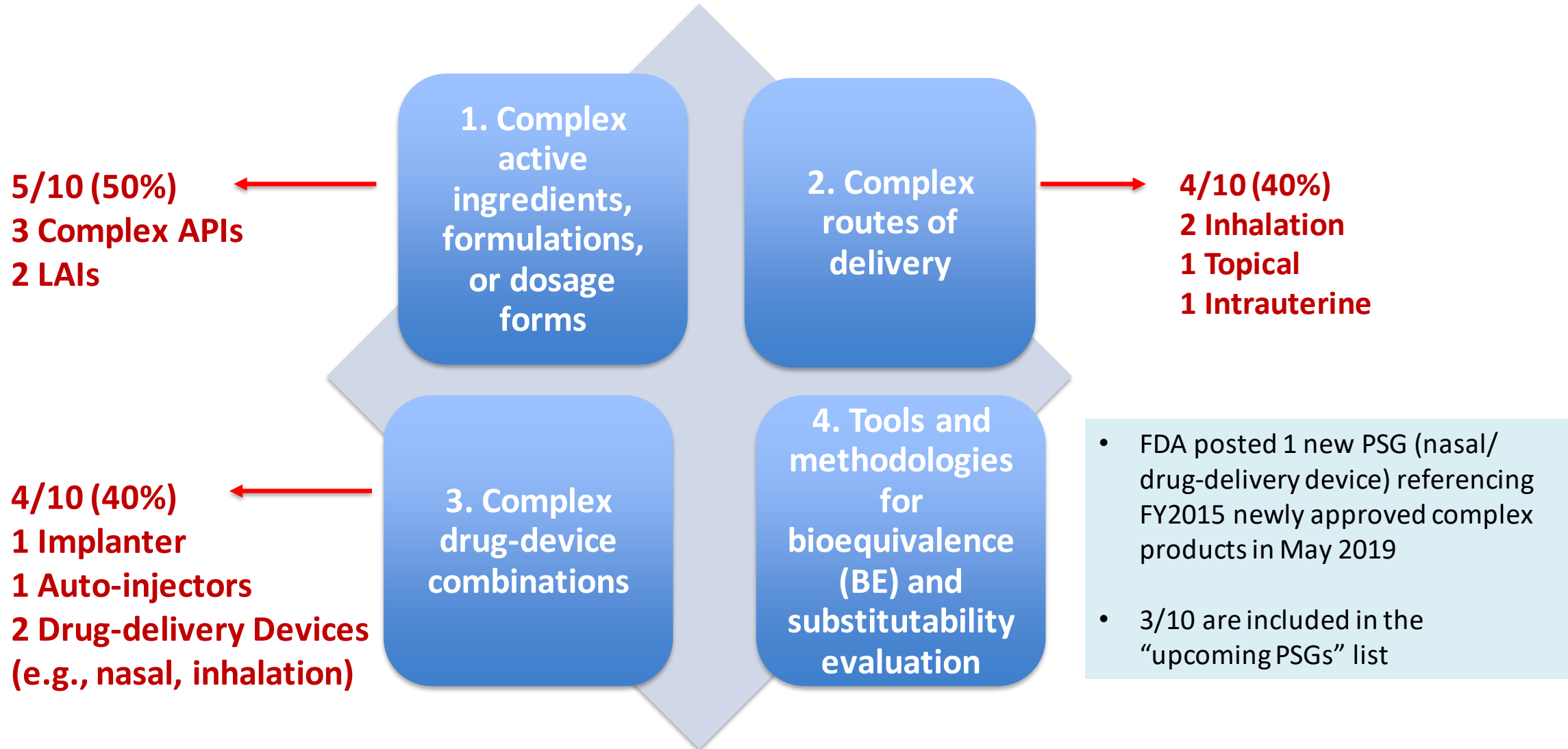
Complex Products

PSG Development for Recent Complex Drug Products (FY2015-2018 NDA Approval Cohorts)

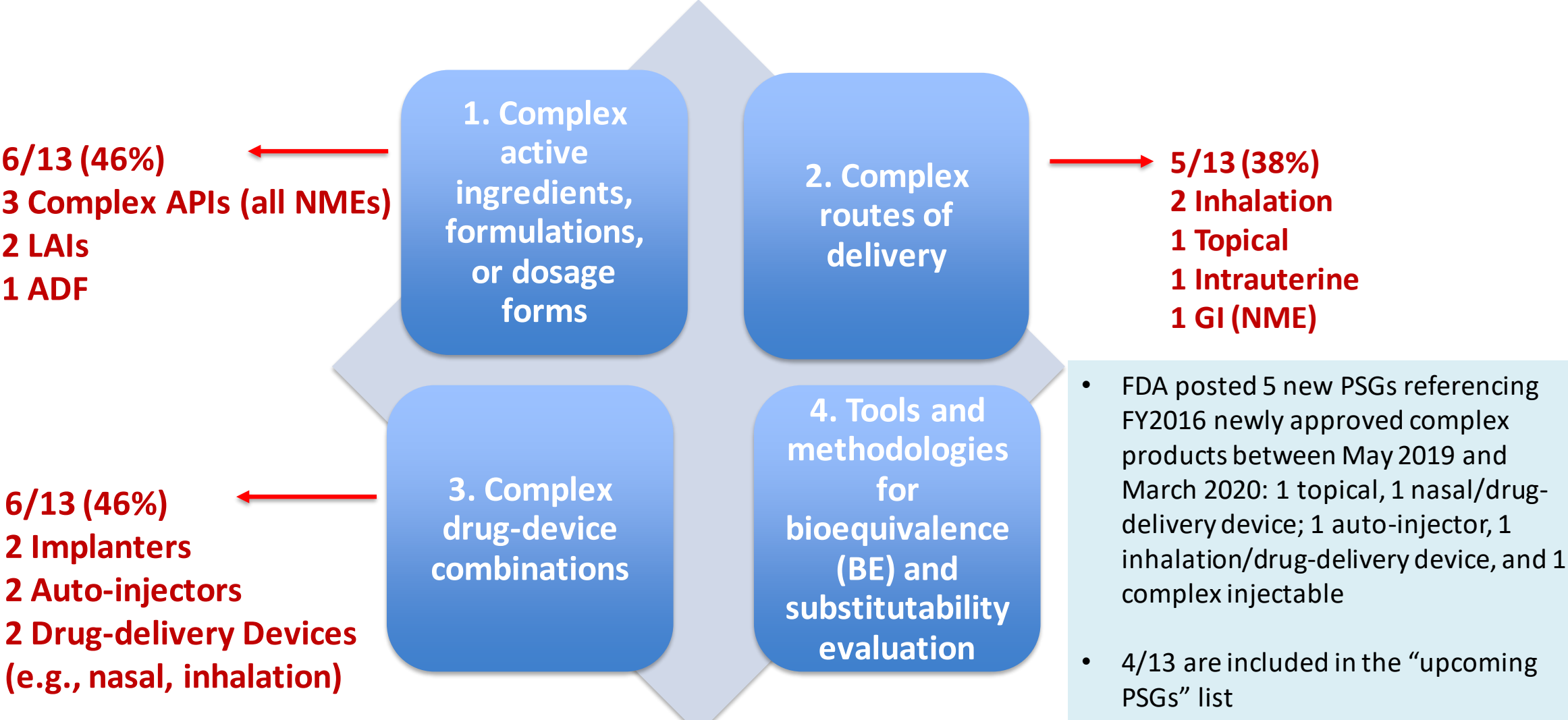


* Number includes PSG published and drug products that may be eligible for “biowaiver” under 21 CFR 320.22(b)
As of March 2020

Recently Approved Complex Drug Products Without PSG FY2015 (N=10, All Non-NME)



Recently Approved Complex Drug Products Without PSG FY2016 (N=13, 3 are NMEs)



Recently Approved Complex Drug Products Without PSG FY2017 (N=13, 3 are NMEs)



10/13 (77%)
5 Complex APIs (1 is LAI, 3 are NMEs)
2 LAIs
3 Complex injectables
1 ADF

1. Complex active ingredients, formulations, or dosage forms

2. Complex routes of delivery

4/13 (31%)
1 GI
2 Nasal
1 Inhalation

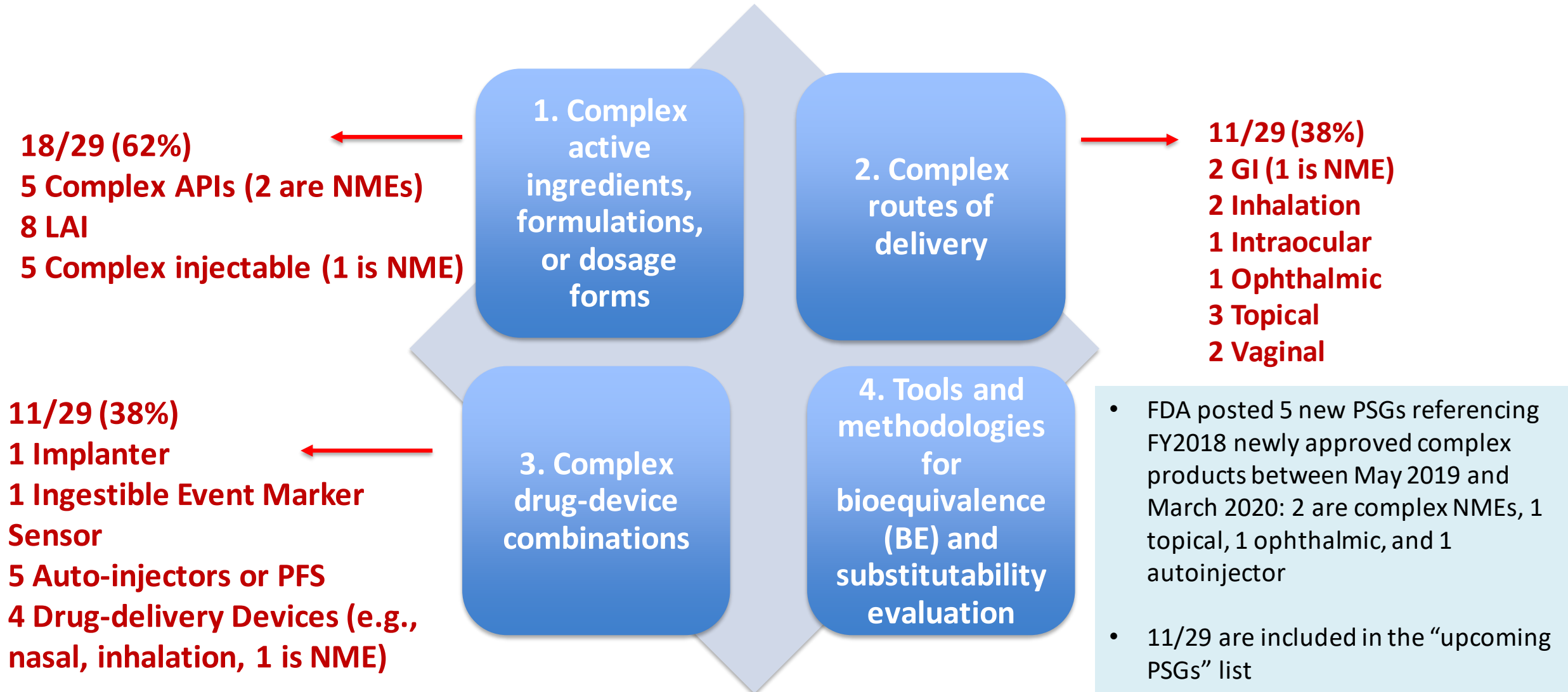
5/13 (38%)
1 Auto-injector (NME)
4 Drug-delivery Devices (e.g., nasal, inhalation)

3. Complex drug-device combinations

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

- FDA posted 4 new PSGs referencing FY2017 newly approved complex products between May 2019 and March 2020: 1 topical and 3 inhalation/drug-delivery device
- 4/13 are included in the “upcoming PSGs” list

Recently Approved Complex Drug Products Without PSG FY2018 (N=29, 4 are NMEs)



FY2018 Approved NMEs that are Complex (N=7)



NDA Number	Active Ingredients	Dosage Form; Route of Administration	Reasons of Complexity
208700	LUTETIUM DOTATATE LU-177	SOLUTION; INTRAVENOUS PSG published in Nov 2019	Complex API
207078	SODIUM ZIRCONIUM CYCLOSILICATE*	FOR SUSPENSION; ORAL	Complex Route of Delivery
209637	SEMAGLUTIDE	SOLUTION; INTRAVENOUS PSG published in March 2020	Complex API; Complex Drug-Device
208945	OZENOXACIN	CREAM; TOPICAL PSG published in Feb 2019	Complex Dosage Form; 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



FY2019 NDA Approval Cohort

Complex Products

FY2019 Approved NCEs that are Complex

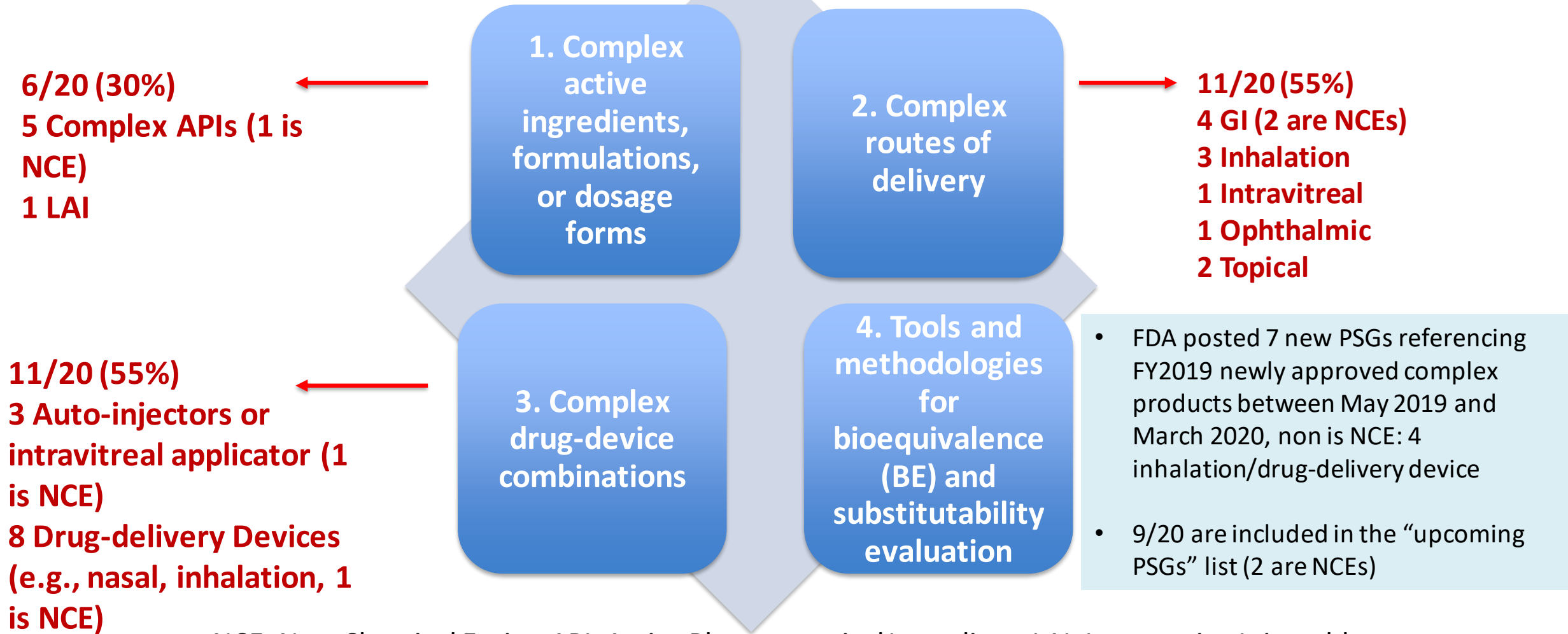


NDA Number	Active Ingredients	Dosage Form; Route of Administration	Reasons of Complexity
210557	BREMELANOTIDE ACETATE*	SOLUTION;SUBCUTANEOUS	Complex Drug-Device
211243	ESKETAMINE HYDROCHLORIDE*	SPRAY;NASAL	Complex Drug-Device
211172	INOTERSEN SODIUM	SOLUTION;SUBCUTANEOUS	Complex API
210910	RIFAMYCIN SODIUM	TABLET, DELAYED RELEASE;ORAL	Complex Route of Delivery
211801	TENAPANOR HYDROCHLORIDE	TABLET;ORAL	Complex Route of Delivery

* Research conducted in previous years has prepared us to develop PSGs for complex products.

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

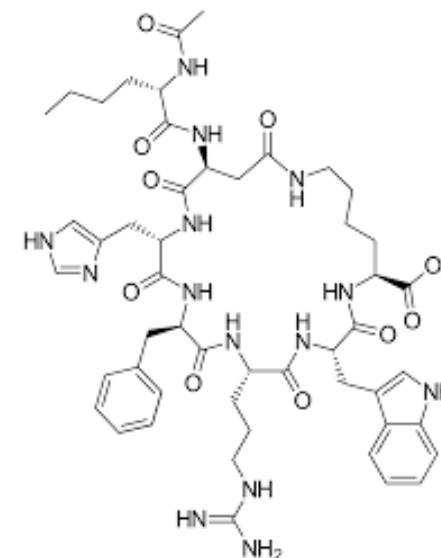
Recently Approved Complex Drug Products Without PSG FY2019 (N=20, 5 are NCEs)



NCE: New Chemical Entity; API: Active Pharmaceutical Ingredient; LAI: Long-acting Injectable; GI: Gastrointestinal

VYLEESI (Bremelanotide Acetate)

- New Molecular Entity
- Approved on 6/21/2019 (NDA 210557)
- **API:** Synthetic, cyclic heptapeptide
- **Dosage Form/Route:** Solution/Subcutaneous
- **Indication:** A melanocortin receptor agonist indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)
- **Complexity:** Complex drug-device combination (autoinjector)

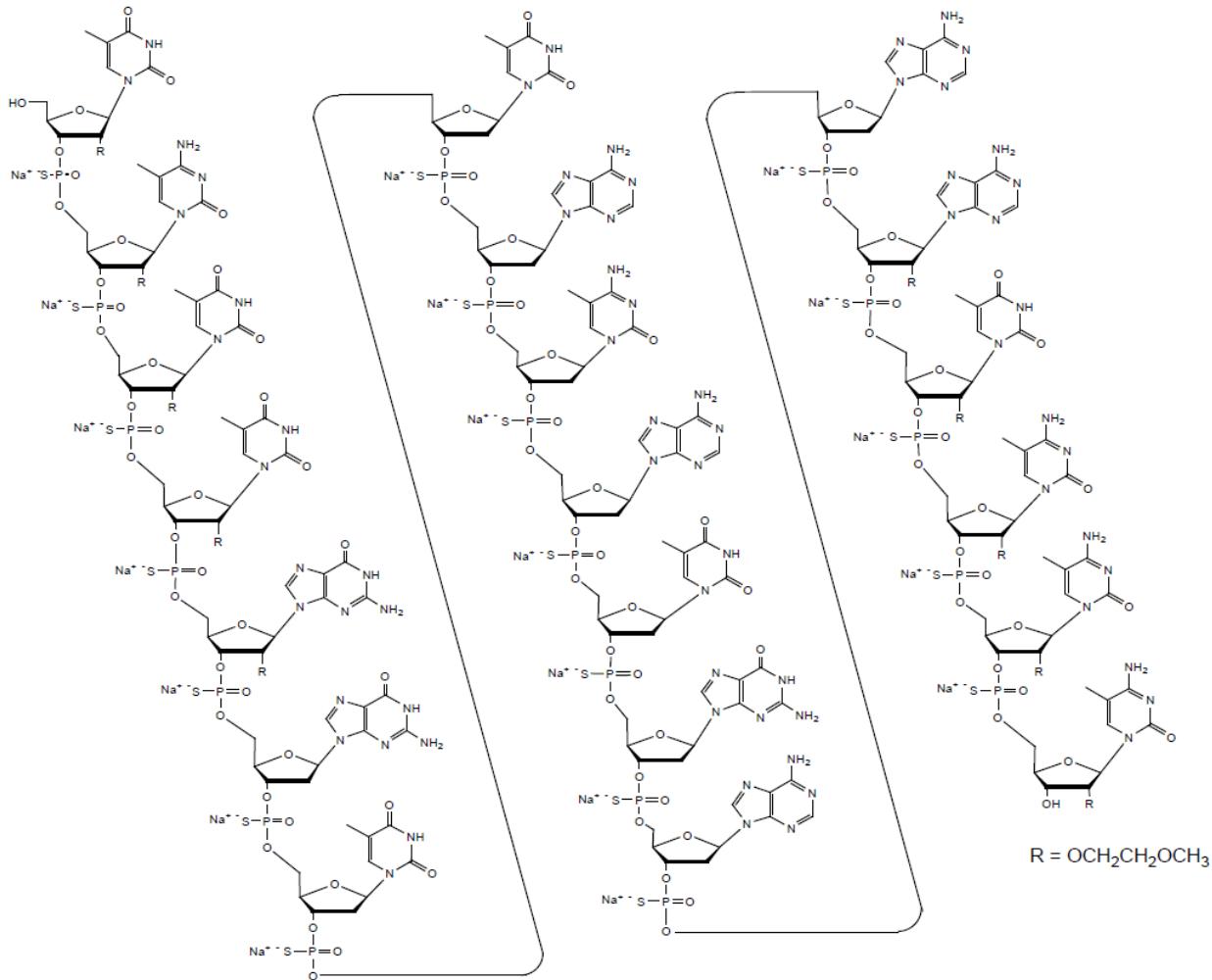


TEGSEDI (Inotersen Sodium)



- New Molecular Entity
- Approved on 10/5/2018 (NDA 211172)
- **API:** An antisense oligonucleotide (ASO)
- **Dosage Form/Route:** Solution/Subcutaneous
- **Indication:** An inhibitor of human transthyretin (TTR) protein synthesis for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- **Complexity:** Complex API

Inotersen Sodium



- Antisense oligonucleotide
- The molecular formula of inotersen sodium is $C_{230}H_{299}N_{69}Na_{19}O_{121}P_{19}S_{19}$
- The molecular weight is 7600.73 Da.



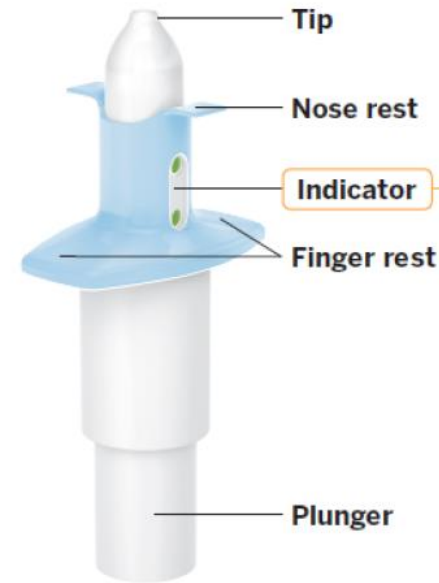
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211172s004lbl.pdf

SPRAVATO™ (Esketamine)



- New Active Ingredient
- Approved on 3/5/2019 (NDA 211243)
- **API:** Esketamine
- **Dosage Form/Route:** Spray/Nasal
- **Indication:** A non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults
 - Schedule III controlled substances/REMS
- **Complexity:** Complex drug-device combination (intranasal device)

Nasal Spray Device

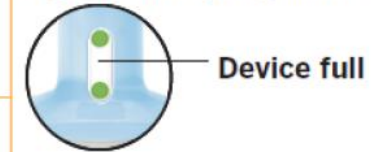


Each device delivers two sprays containing a total of 28 mg of esketamine.

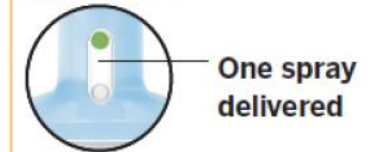
Indicator

One device contains 2 sprays.
(1 spray for each nostril)

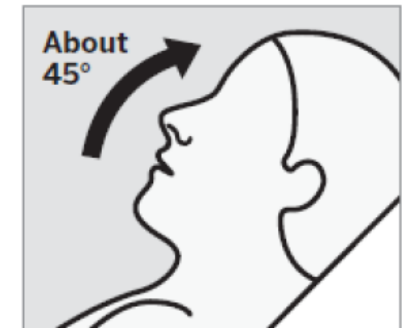
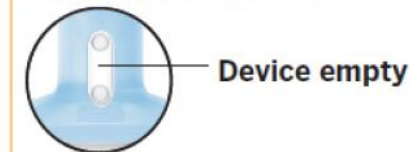
2 green dots (0 mg delivered)



1 green dot



No green dots
Two sprays (28 mg) delivered



YUTIQ™ (Fluocinolone Acetonide)



- New Formulation
- Approved on 10/12/2018 (NDA 210331)
- **API:** Fluocinolone Acetonide
- **Dosage Form/Route:** Implant/Intravitreal Injection
- **Indication:** A corticosteroid for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye
- **Complexity:** Complex Dosage Form (Long-Acting Injectable)/Complex drug-device combination (intravitreal applicator)/Complex route of delivery
 - 36-month sustained-release drug delivery system

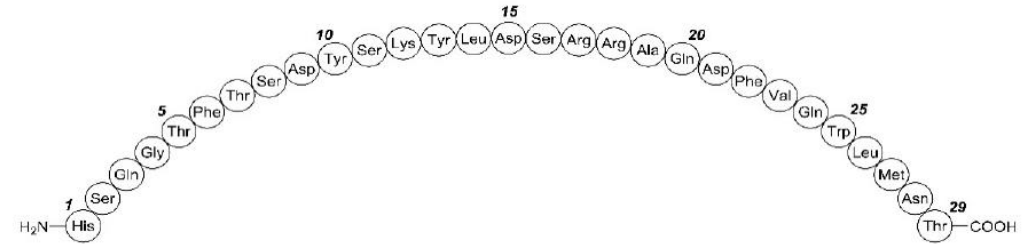


BAQSIMI (Glucagon)

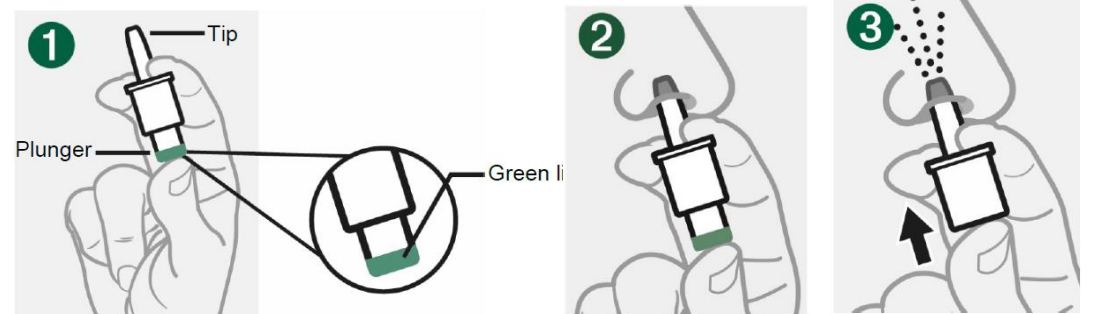
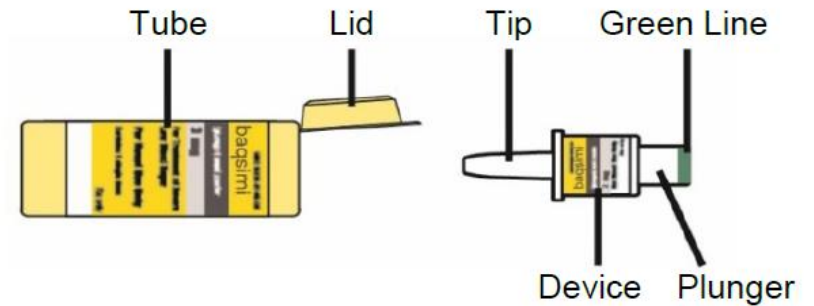


- New Dosage Form
- Approved on 7/24/2019 (NDA 210134)
- **API: Glucagon**
 - A single chain polypeptide containing 29 amino acid residues
 - Recombinant deoxyribonucleic acid (rDNA) origin
- **Dosage Form/Route:** Powder/Nasal
- **Indication:** An antihypoglycemic agent indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and above
- **Complexity:** Complex API/Complex dosage form/Complex drug-device combination (intranasal device)
- General guidance available:
 - “ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA”

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



Tube and Device Parts

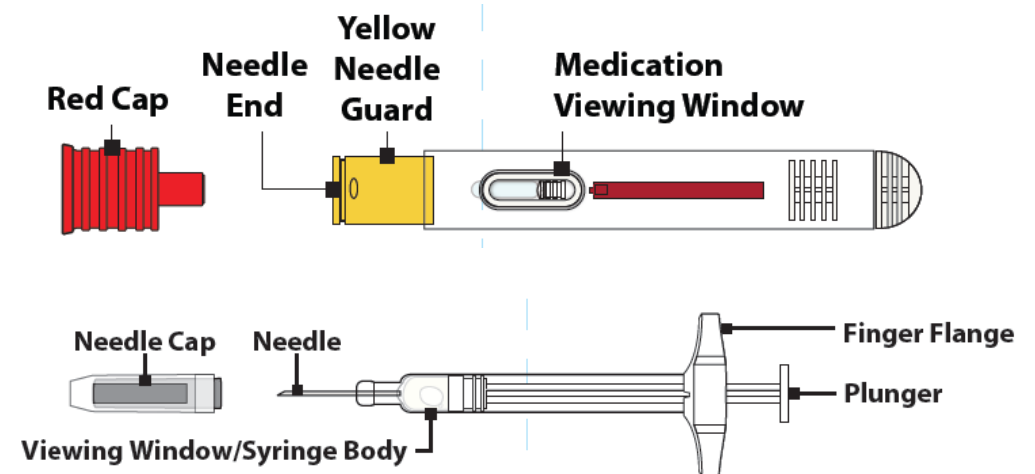


GVOKE (Glucagon)



- New Dosage Form
- Approved on 9/10/2019 (NDA 212097)
- **API:** Glucagon
 - A single chain polypeptide containing 29 amino acid residues
 - Synthetic
- **Dosage Form/Route:** Solution/Subcutaneous
- **Indication:** An antihypoglycemic agent indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above
- **Complexity:** Complex API/Complex drug-device combination (autoinjector)

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



Complex NDA Approved in FY2019



Question for Discussion

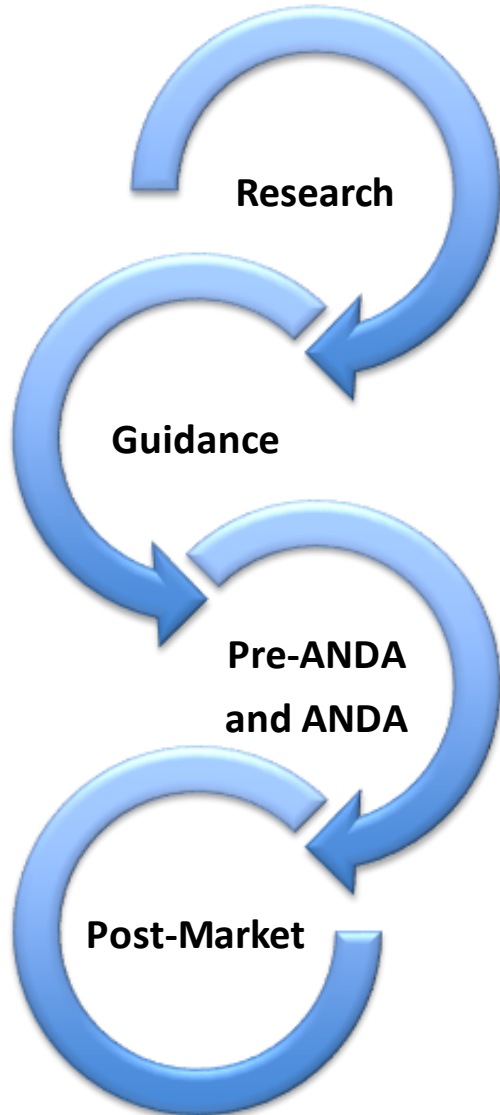
- FDA believes that the scientific challenges identified for complex products approved in the FY2015 to FY2019 NDA cohorts fit into our current 15 research priorities
- Further discussions will be held in the four breakout sessions in the afternoon
 - Post-Market Surveillance of Generic Drugs
 - Drug-Device Combination Products
 - In Vitro Bioequivalence Methods
 - Data Analysis and Model-Based Bioequivalence

Is there a need to adapt our research priorities to the change in the landscape of potential reference listed drugs (RLDs)?

Website: GDUFA Science and Research Outcomes



- FY2018 outcomes: Website launched Oct 1, 2019; yearly update
 - GDUFA research supporting the development of generic drug products
 - GDUFA research supporting the generation of evidence needed to support efficient review and timely approval of ANDAs
 - GDUFA research supporting the evaluation of generic drug equivalence



FY2018 Research Outcome Supporting the Evaluation of Generic Drug Equivalence

Outcome type	Number
Number of pre-ANDA meetings impacted by research	2
Number of PSGs that provided new approaches to equivalence	24
Number of publications, presentations, and external posters that are relevant to this category	45

