Potential Research Challenges for Newly Approved Complex RLDs

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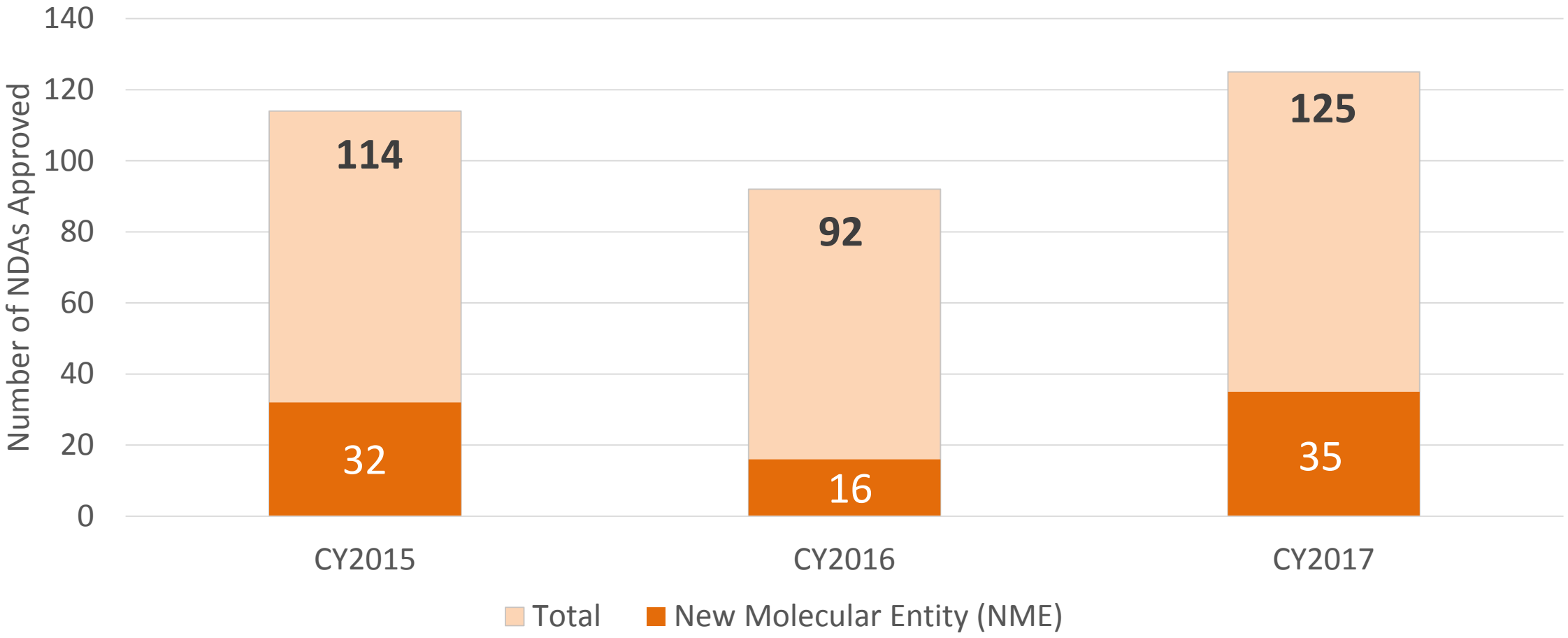
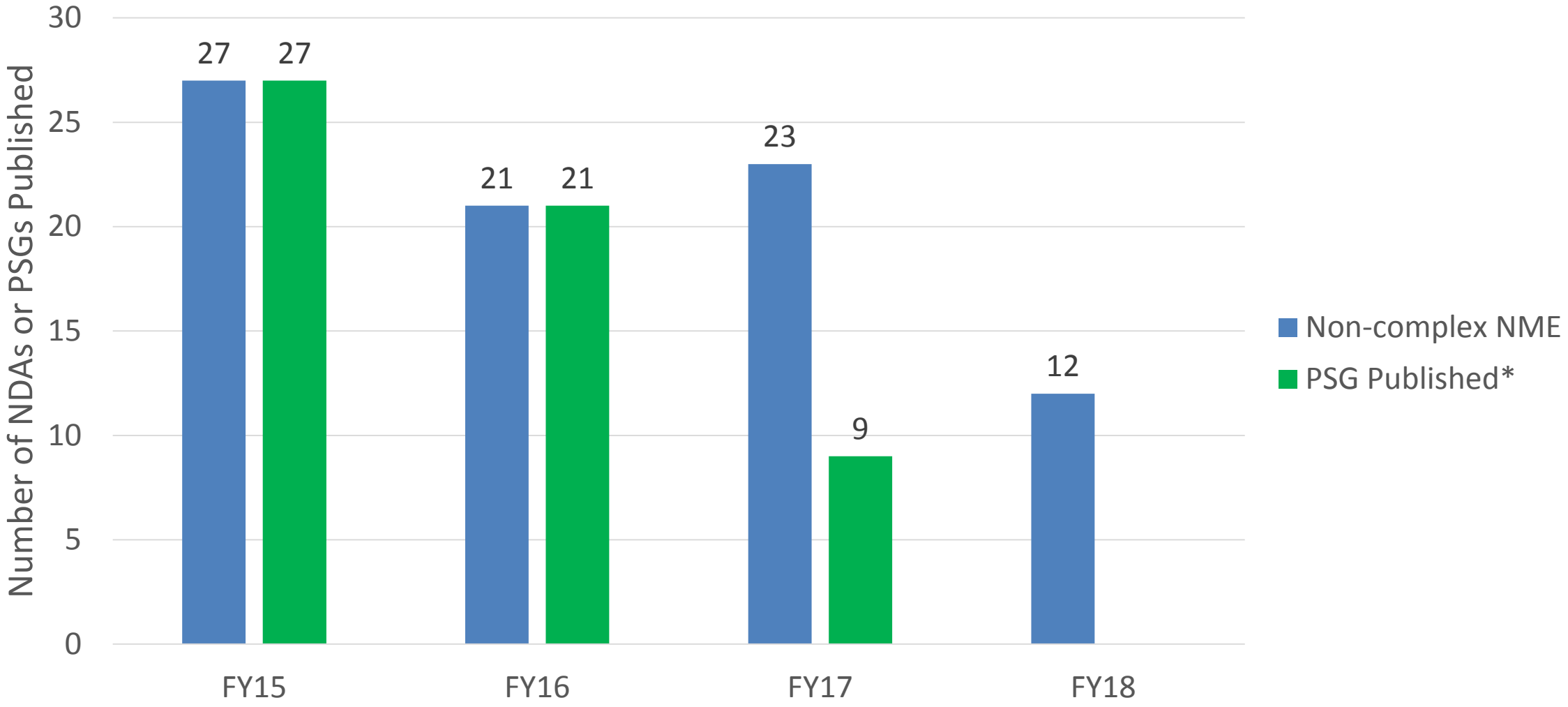
Approved NDAs between 2015-2017



Product Specific Guidance (PSG) Development for Recent Non-complex NMEs



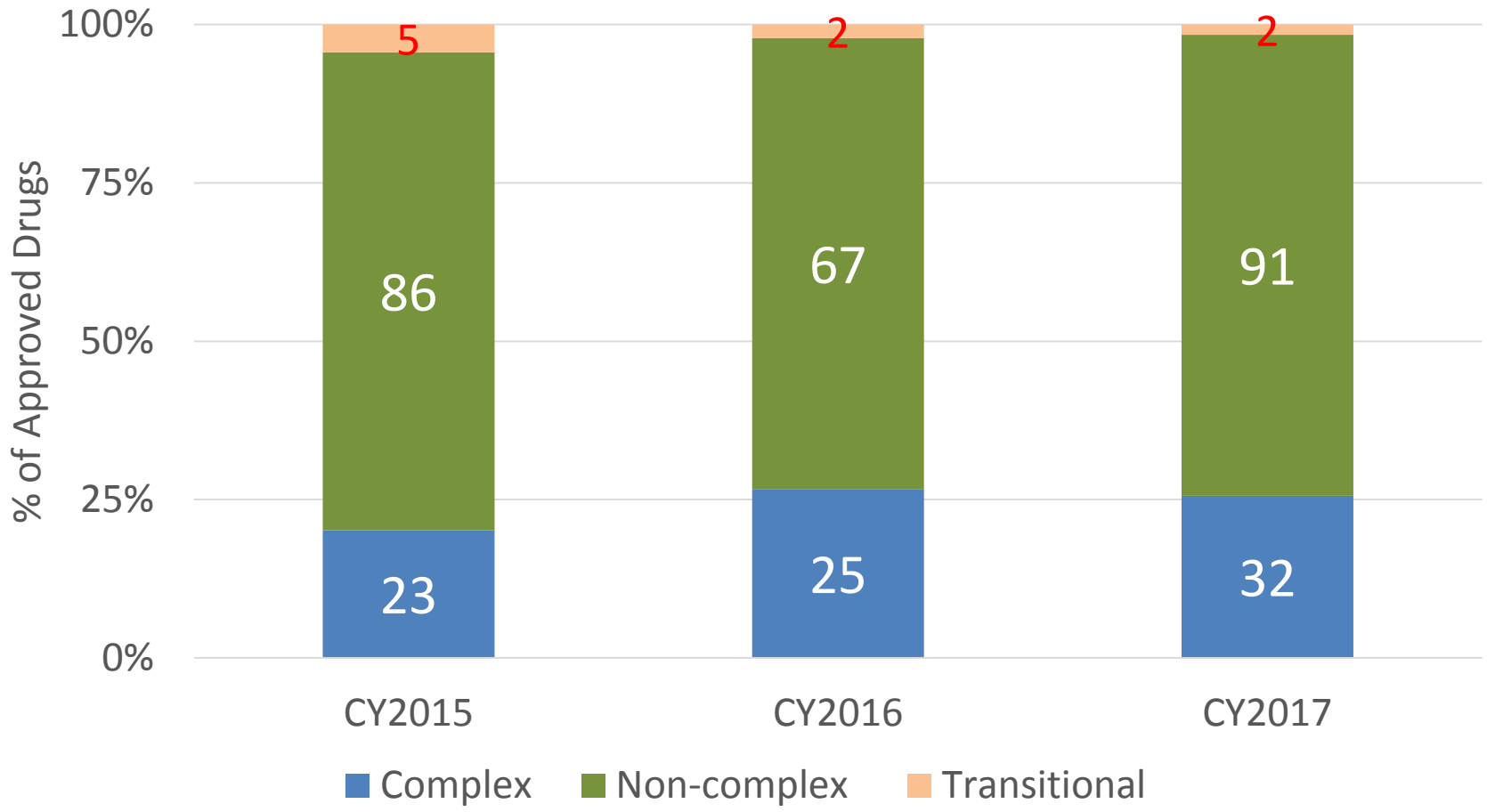
* Number includes PSG published and drug products may be eligible for “biowaiver” under 21 CFR 320.22(b)

Complex Generic Products Outlined in GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

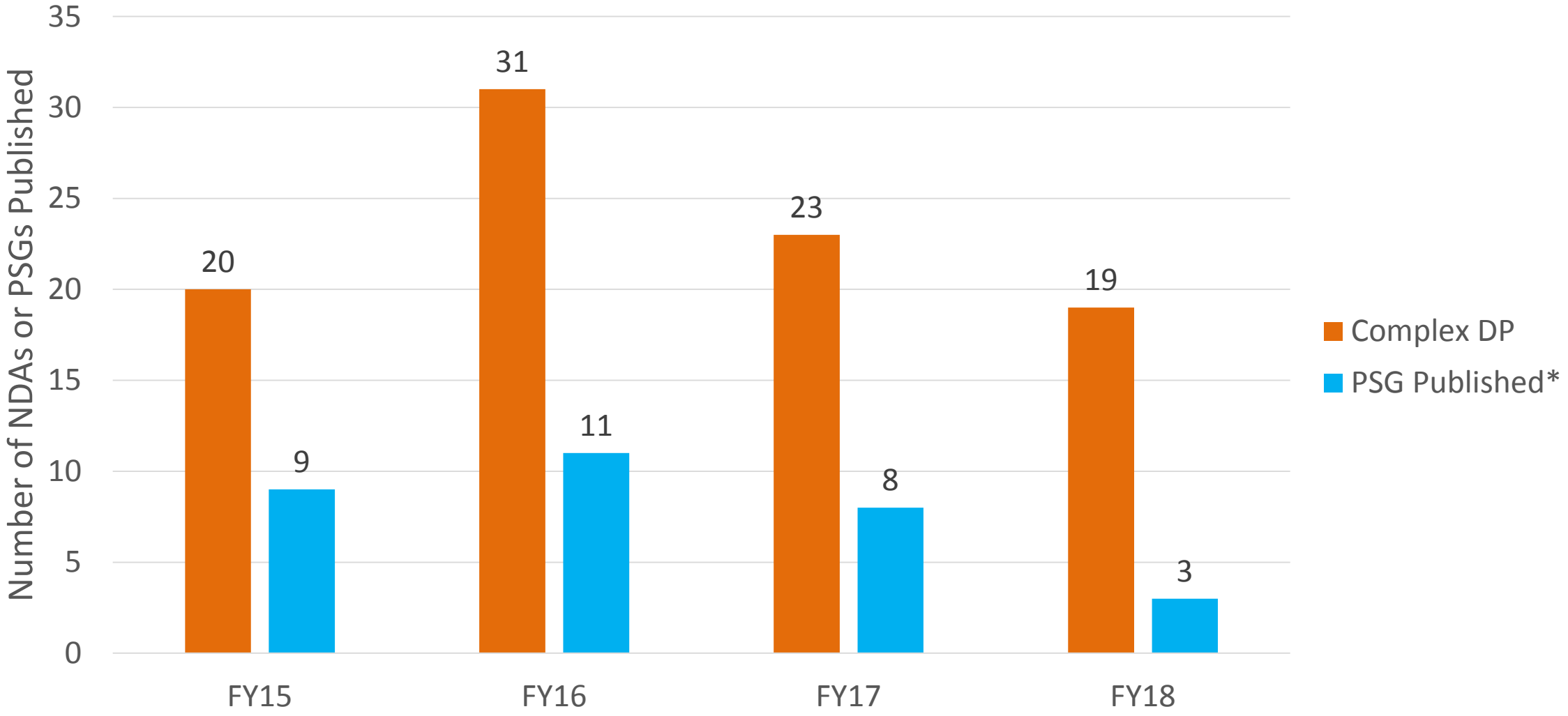
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Drug Products in Approved NDAs 2015-2017



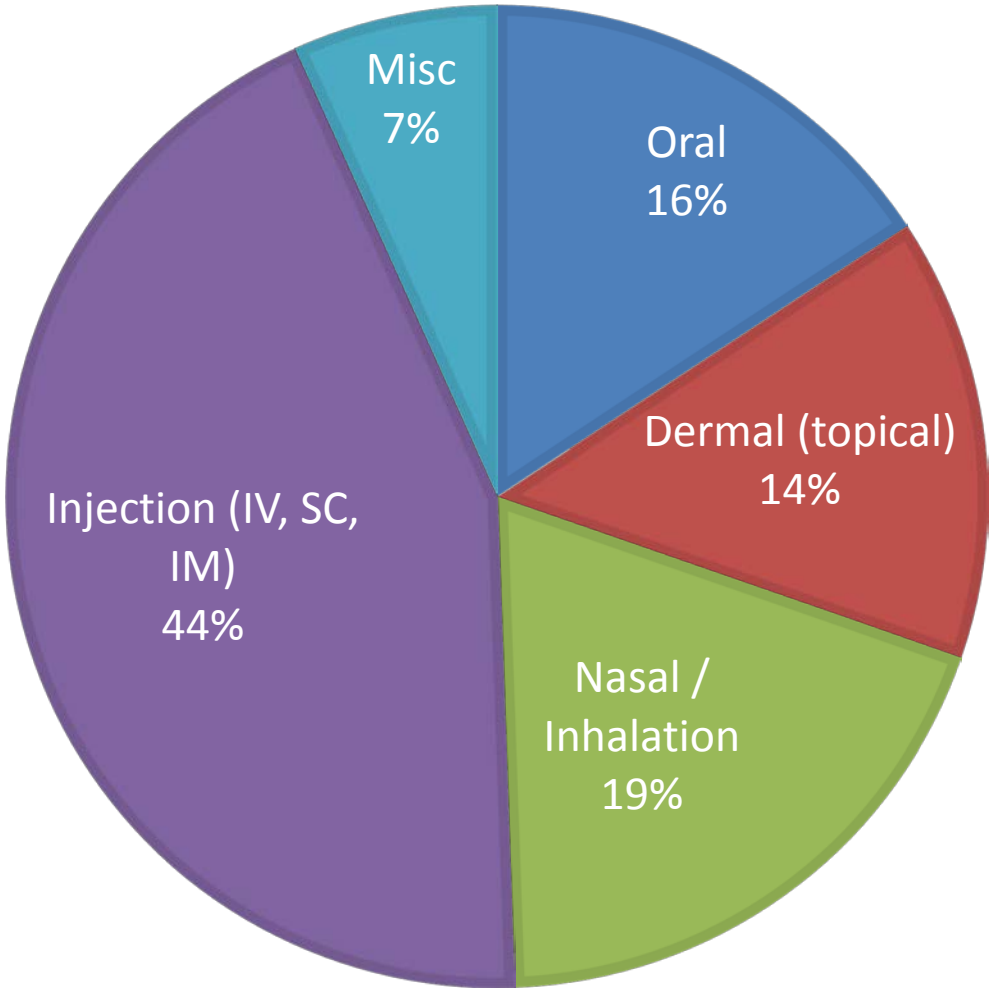
*Numbers noted on the bar graph are the number of approved NDAs, and the height of the graph is normalized

PSG Development for Recent Complex Drug Products



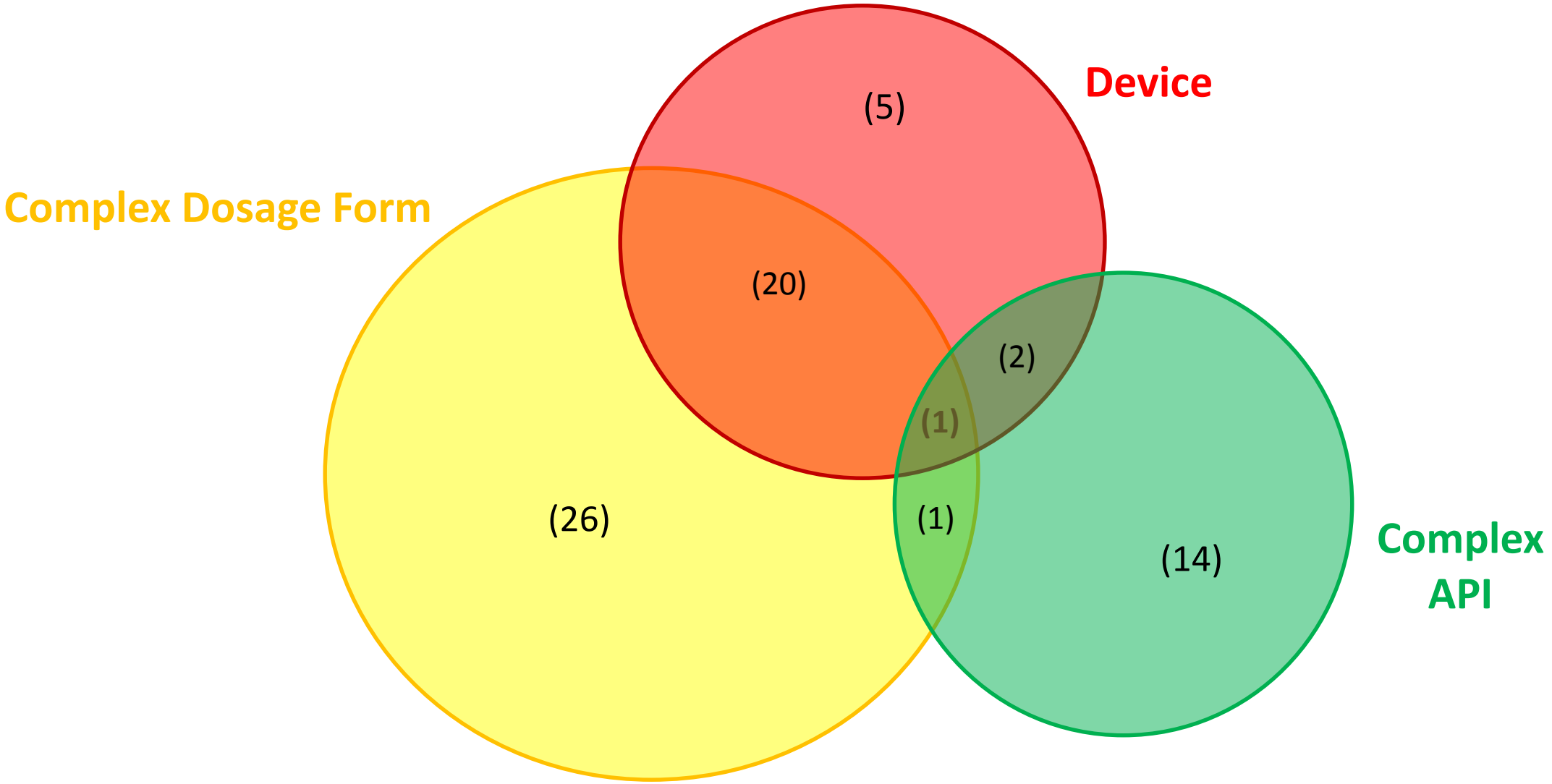
* Number includes PSG published, drug products that are covered under FDA general guidance and may be eligible for "biowaiver" under 21 CFR 320.22(b)

Routes of Delivery of Approved NDA Complex Drug Products 2015-2017



*Drugs under oral route here are locally acting or abuse deterrent formulation products

Intersections of Complex Dosage Form, Drug-Device Combination and Complex API of Complex NDA Drug Products 2015-2017



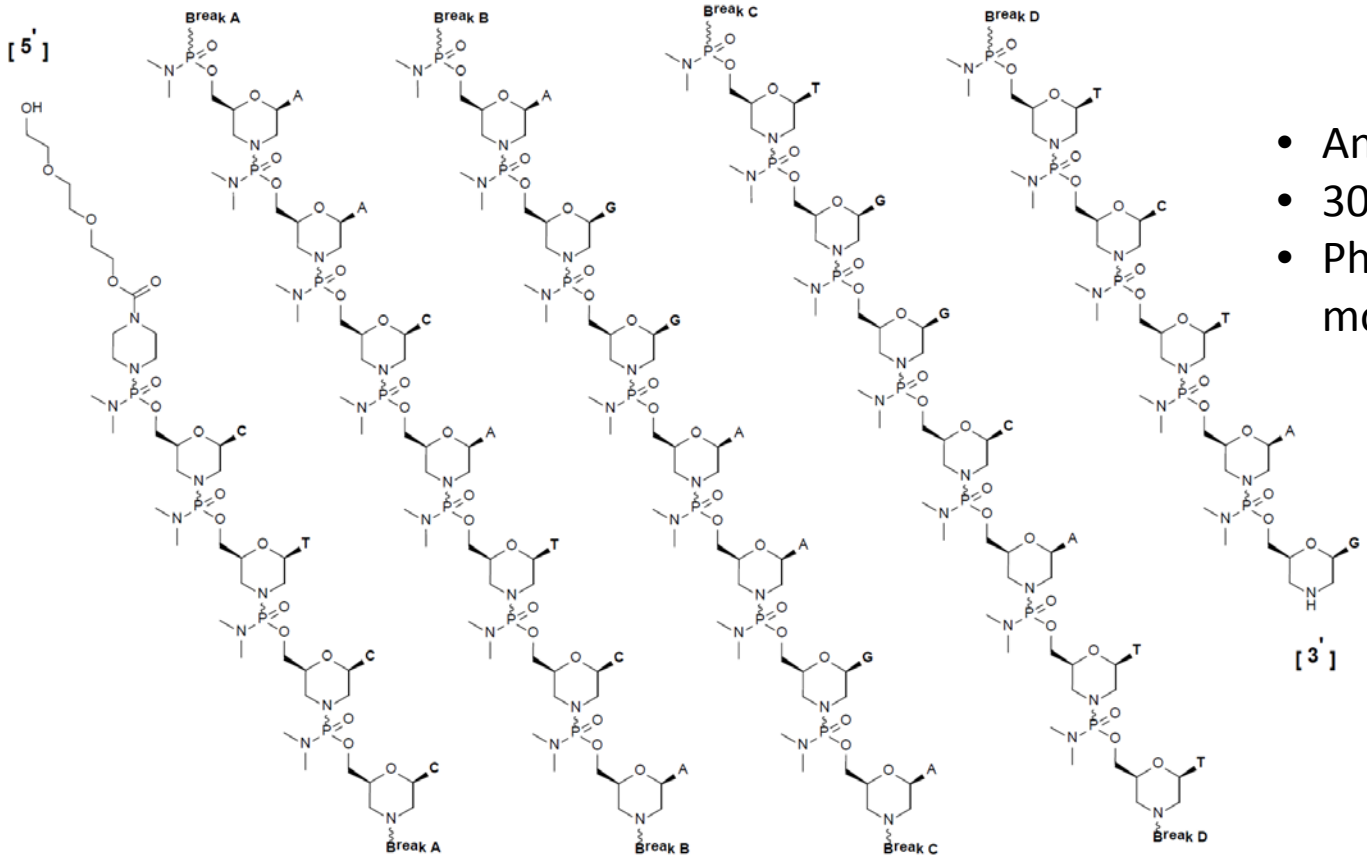
Examples of Complex APIs

- Peptides including lipopeptides
  - Peptide-related impurity analysis
  - Non-clinical immunogenicity assessments on impurities
- Polymeric compounds
  - Sameness assessment
- Oligonucleotides

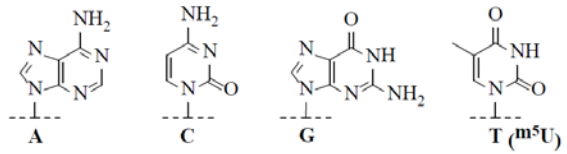
EXONDYS 51 (Eteplirsen)

- Approved 9/19/2016 under NDA 206488, for the treatment of Duchenne muscular dystrophy (DMD)
- IV injection, recommended dose: 30 mg/kg, once weekly
- DMD is a X-linked recessive neuromuscular disorder affecting 1 in 3600 boys (1 in 10000 to 14000 males); 13% patients are amenable to skipping exon 51

Eteplirsen



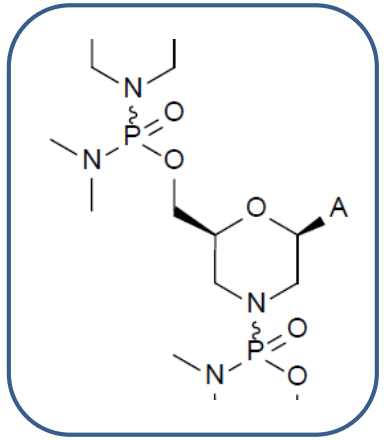
Base:



A C G T (^{m5}U)

The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTTCTAG

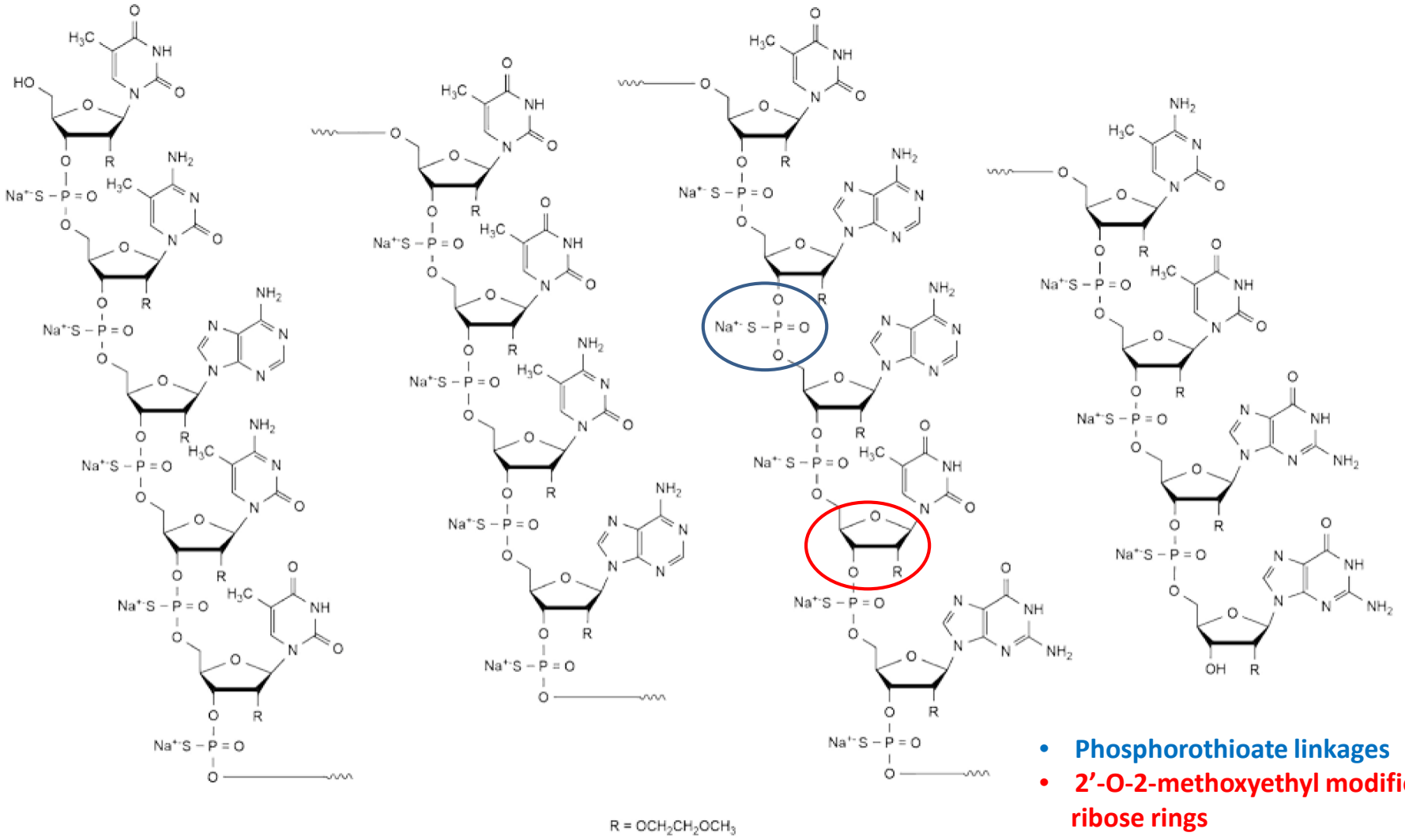
- Antisense oligonucleotide
- 30 linked subunits
- Phosphorodiamidate morpholino oligomer



SPINRAZA (Nusinersen)

- Approved 12/23/2016 under NDA 209531, for the treatment of spinal muscular atrophy (SMA)
- IV injection, recommended dose: 12 mg/each, 4 loading dose (14-day interval x3, then 30 days after), then once every 4 month
- SMA is a neuromuscular disorder occurring 8.5- 10.3 per 100,000 live births

Nusinersen



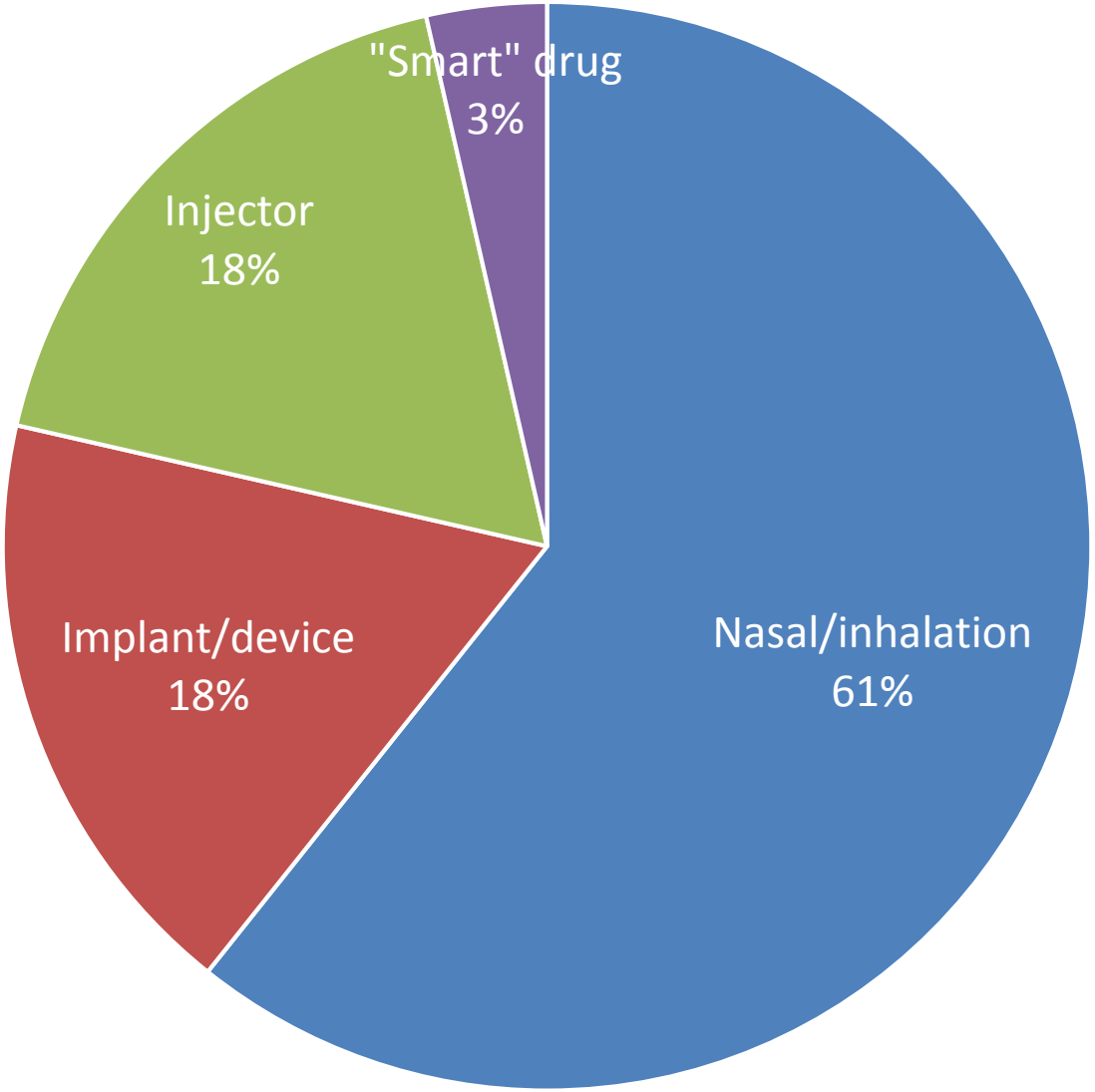
R = $OCH_2CH_2OCH_3$

- **Phosphorothioate linkages**
- **2’-O-2-methoxyethyl modified ribose rings**

Challenges for Generic Synthetic Oligonucleotide

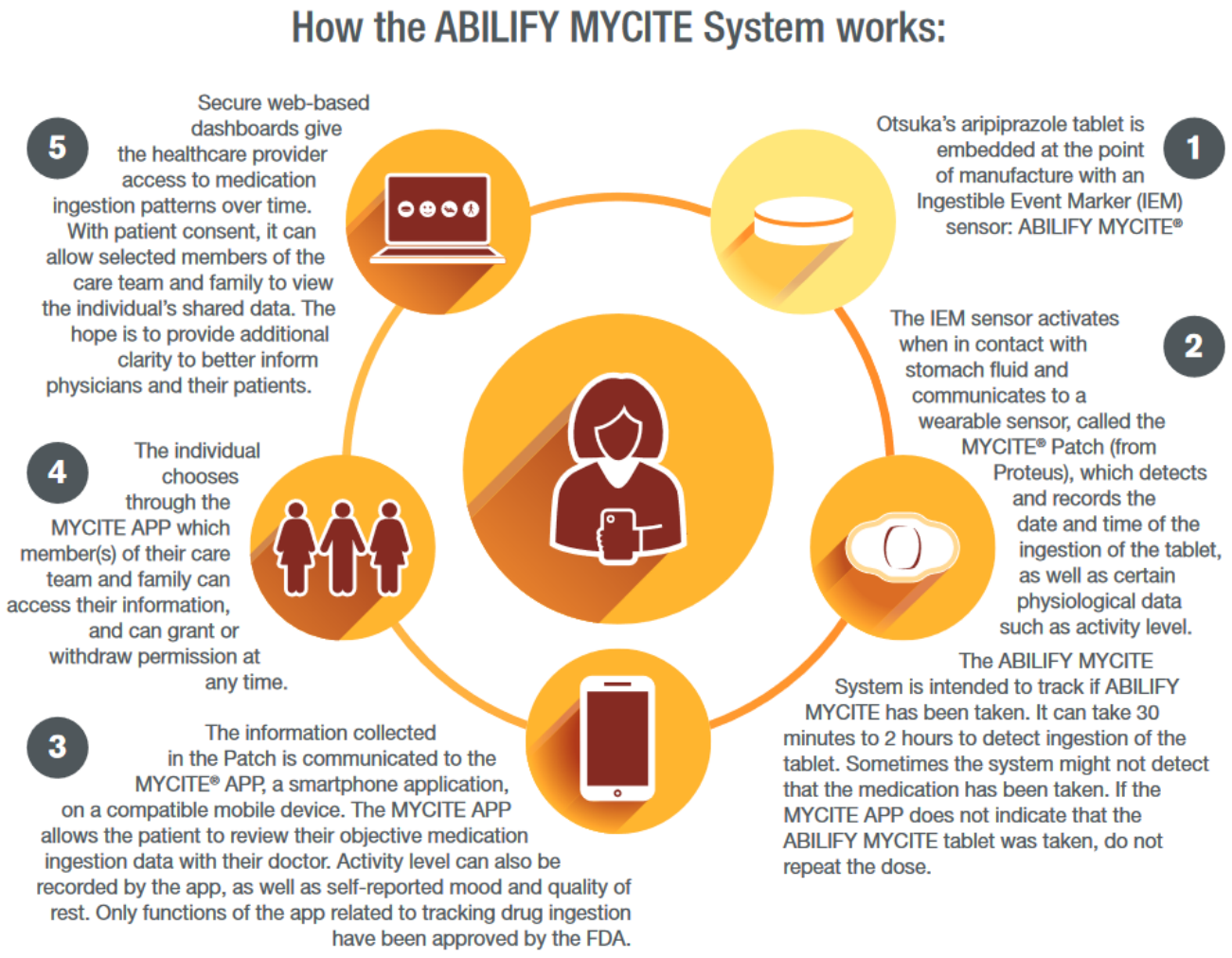
- Characterizations for establishing identity
- Impurity analysis for related-substances

Complex NDA Drug Products with Device Components 2015-2017



Smart Pill ABILIFY MYCITE

- First digital ingestion tracking system approved (NDA 207202) in the U.S.
- Approved: 11/13/2017
- API: ARIPIPRAZOLE
- Dosage Form/Route: TABLET;ORAL
- **Indication:** Treatment of adults with schizophrenia; bipolar I disorder; major depressive disorder
- **Complexity:** Drug-device combination

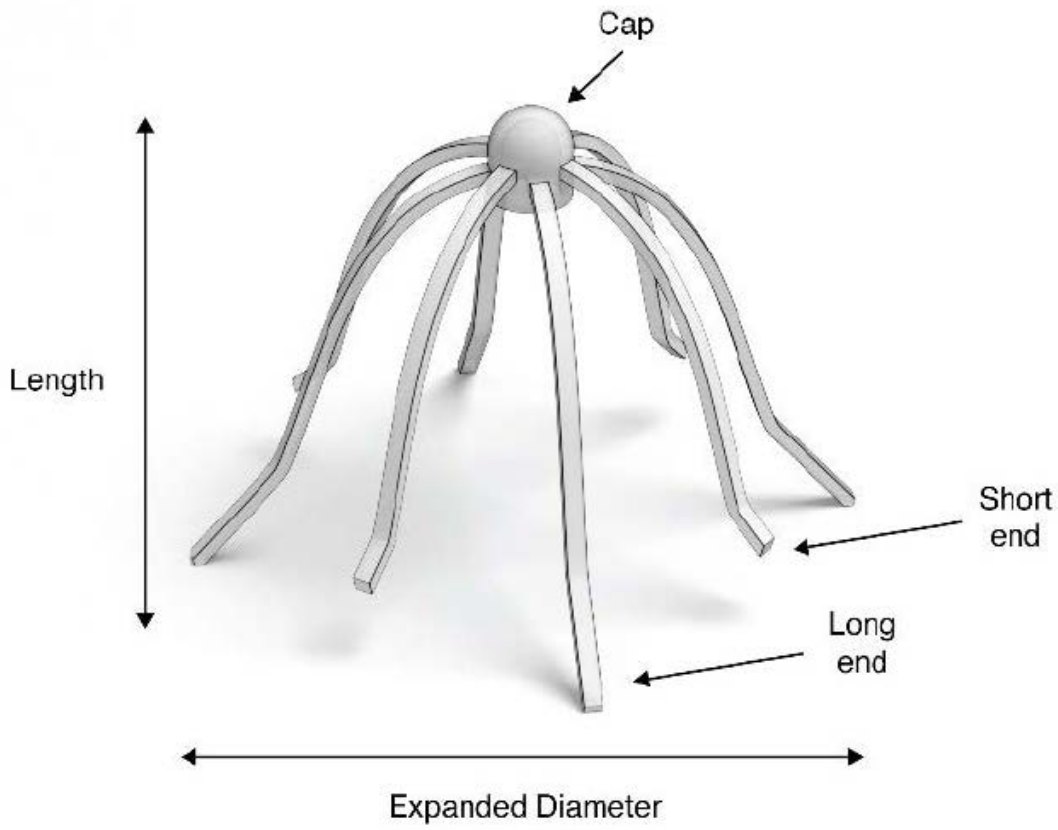


BYDUREON BCISE

- Approved on 10/20/2017 (NDA 209210)
- API: Exenatide (peptide)
- Dosage Form/Route: Suspension, ER; subcutaneous
- **Indication**: is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **Complexity**: Complex API (39 AA peptides); Complex excipient (PLGA microspheres); drug-device combination;

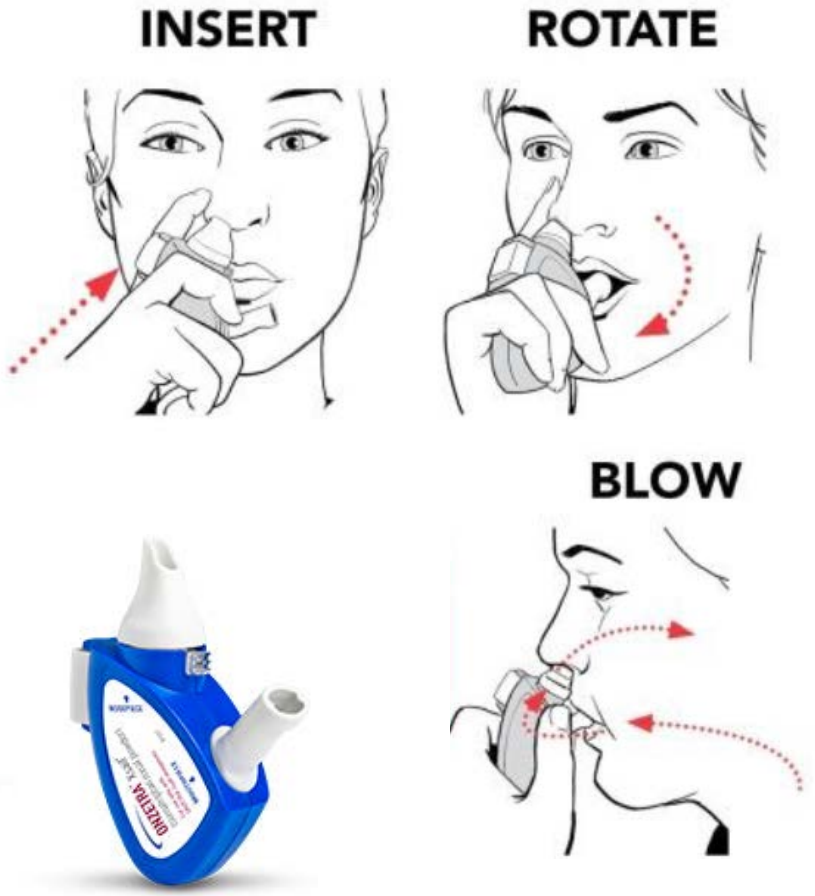
SINUVA

- New Approach to Treating Nasal Polyp Disease
- Approved: 12/08/2017 (NDA 209310)
- API: Mometasone furoate
- Dosage Form/Route: Implant; implantation
- **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



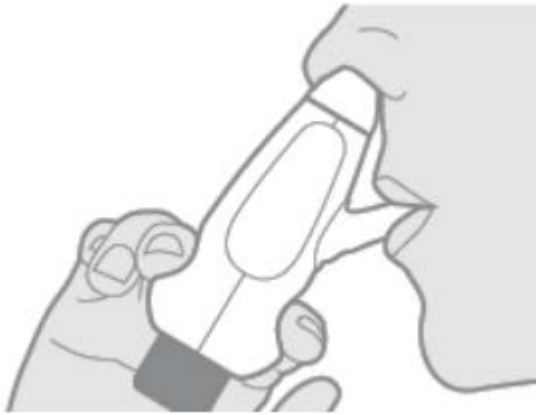
ONZETRA XSAIL

- New approach for the acute treatment of migraine
- Approved: 01/27/2016 (NDA 206099)
- API: Sumatriptan nasal powder
- Dosage Form/Route: nasal powder
- **Complexity**: ONZETRA Xsail is supplied as a disposable nosepiece containing a capsule and a reusable delivery device body. The patient blows forcefully through the mouthpiece to deliver the sumatriptan powder into the nasal cavity.



XHANCE

- New approach to nasal spray
- Approved: 09/18/2017 (NDA 209022)
- API: Fluticasone propionate
- Dosage Form/Route: nasal spray
- **Complexity**: XHANCE is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing (exhaling) into the mouthpiece of the device.



STIOLTO RESPIMAT

- New approach to inhalation spray
- Approved: 05/21/2015 (NDA 206756)
- API: Tiotropium bromide and olodaterol
- Dosage Form/Route: inhalation spray
- **Complexity**: Respimat is a new inhalation drug delivery device and commonly referred to as "Soft Mist Inhaler"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