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

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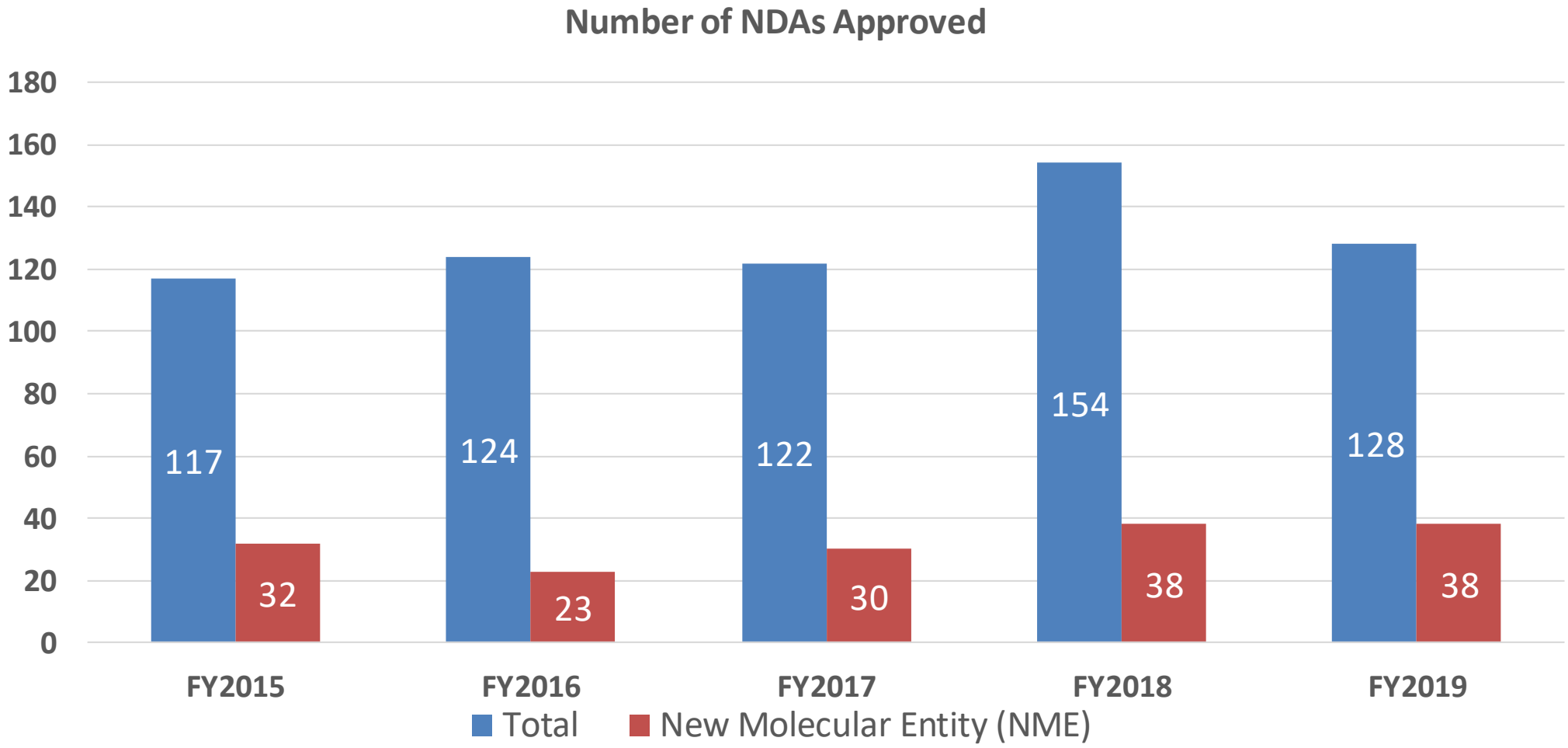
FY2020 Generic Drug Regulatory Science Initiatives Public Workshop

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

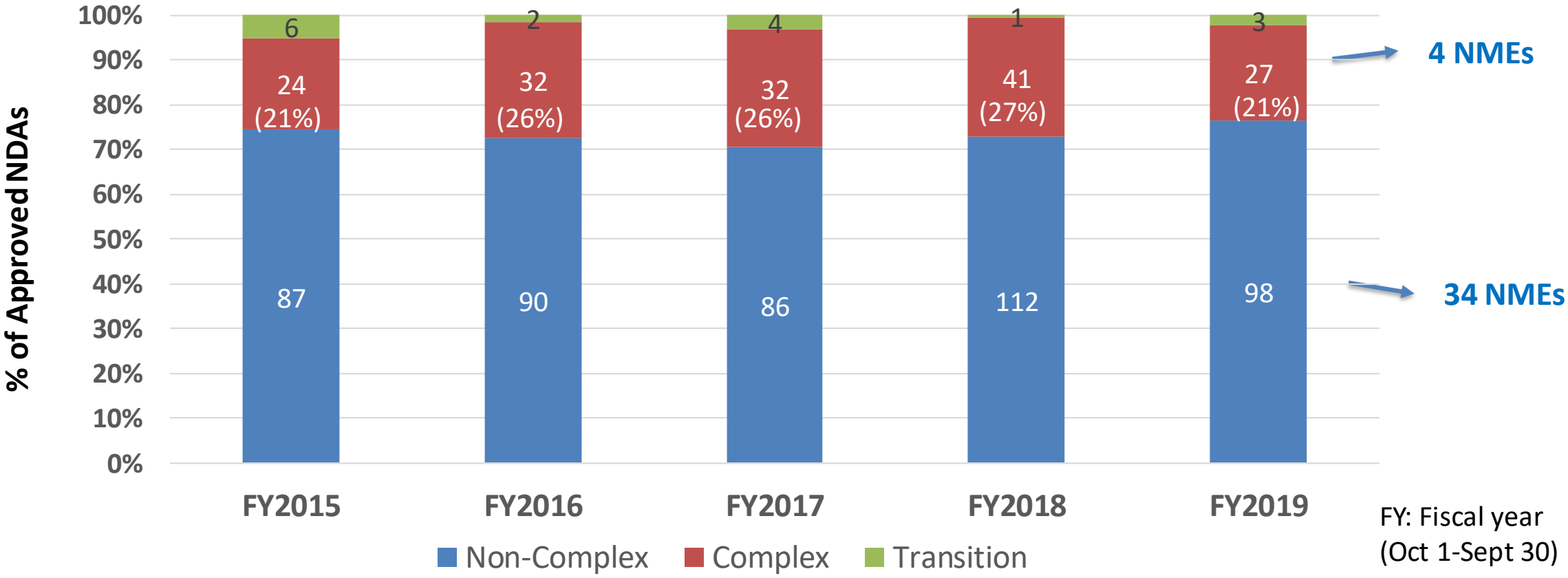
Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, Clinical Pharmacology & Therapeutics (CPT), 2019, Vol.105(4), p.878-885

Approved New Drug Applications (NDAs) FY2015-2019



FY: Fiscal year
(Oct 1-Sept 30)

Complex Drug Products in Approved NDAs FY2015-2019



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 (PSGs) Published in FY2019

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

FY: Fiscal Year
(Oct 1-Sept 30)

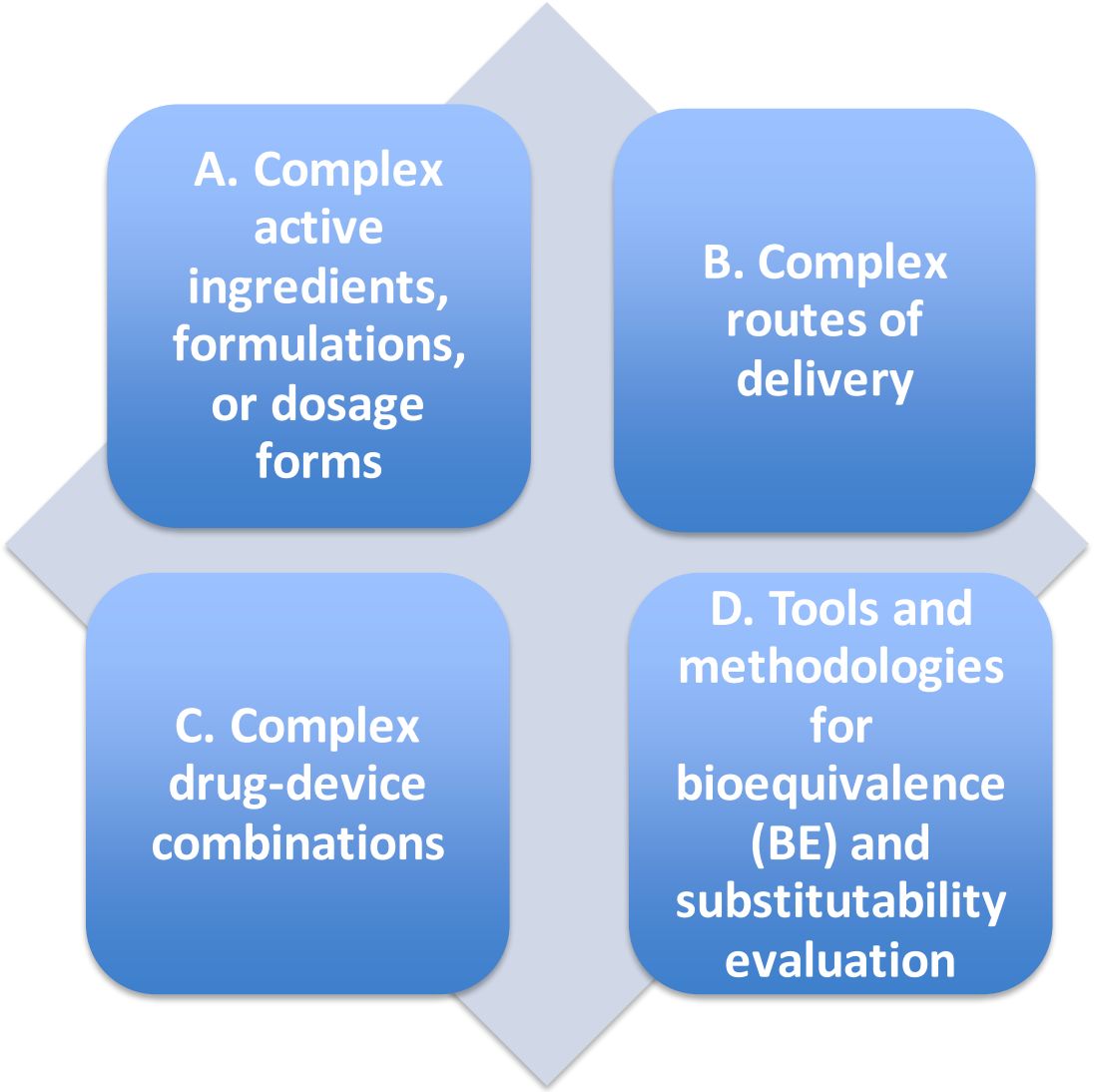
https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Website to Forecast Upcoming PSGs for Complex Products

- 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



https://www.fda.gov/media/132370/download

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

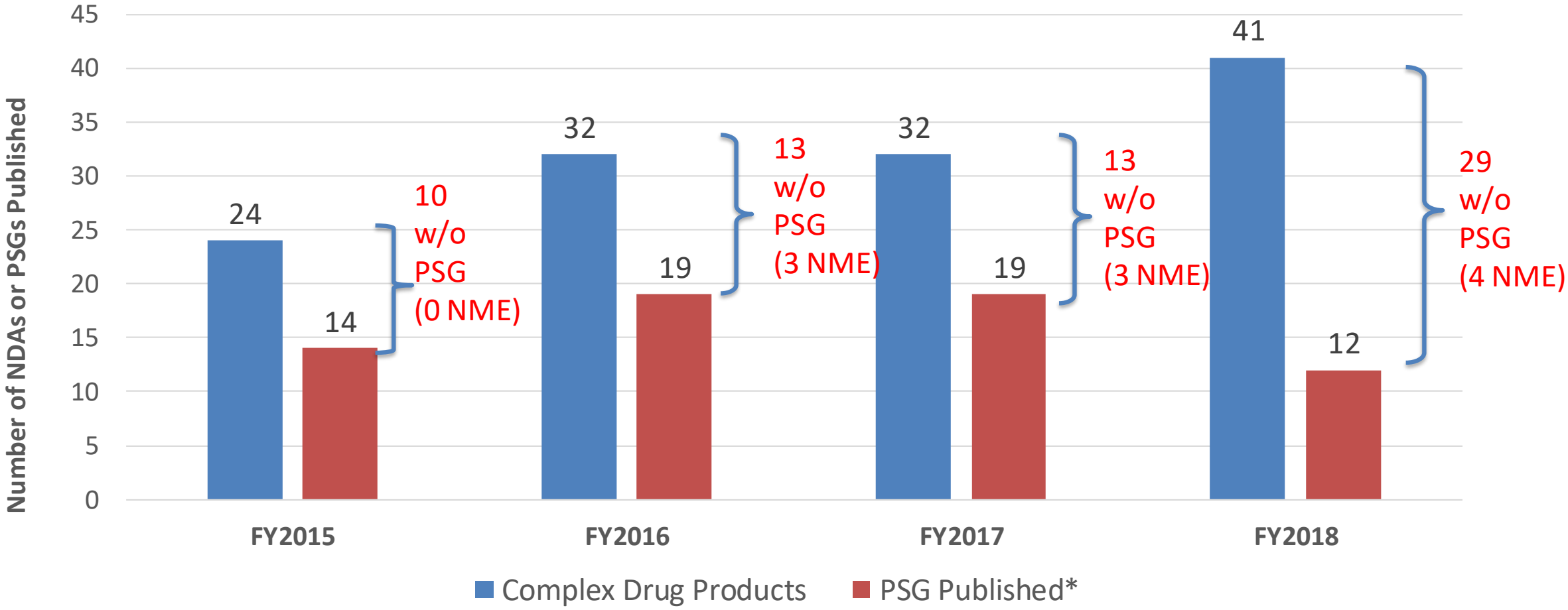
- To aid in this analysis, we will review the landscape and identify possible gaps

NMEs: New Molecular Entities

FY2015-2018 NDA Approval Cohorts

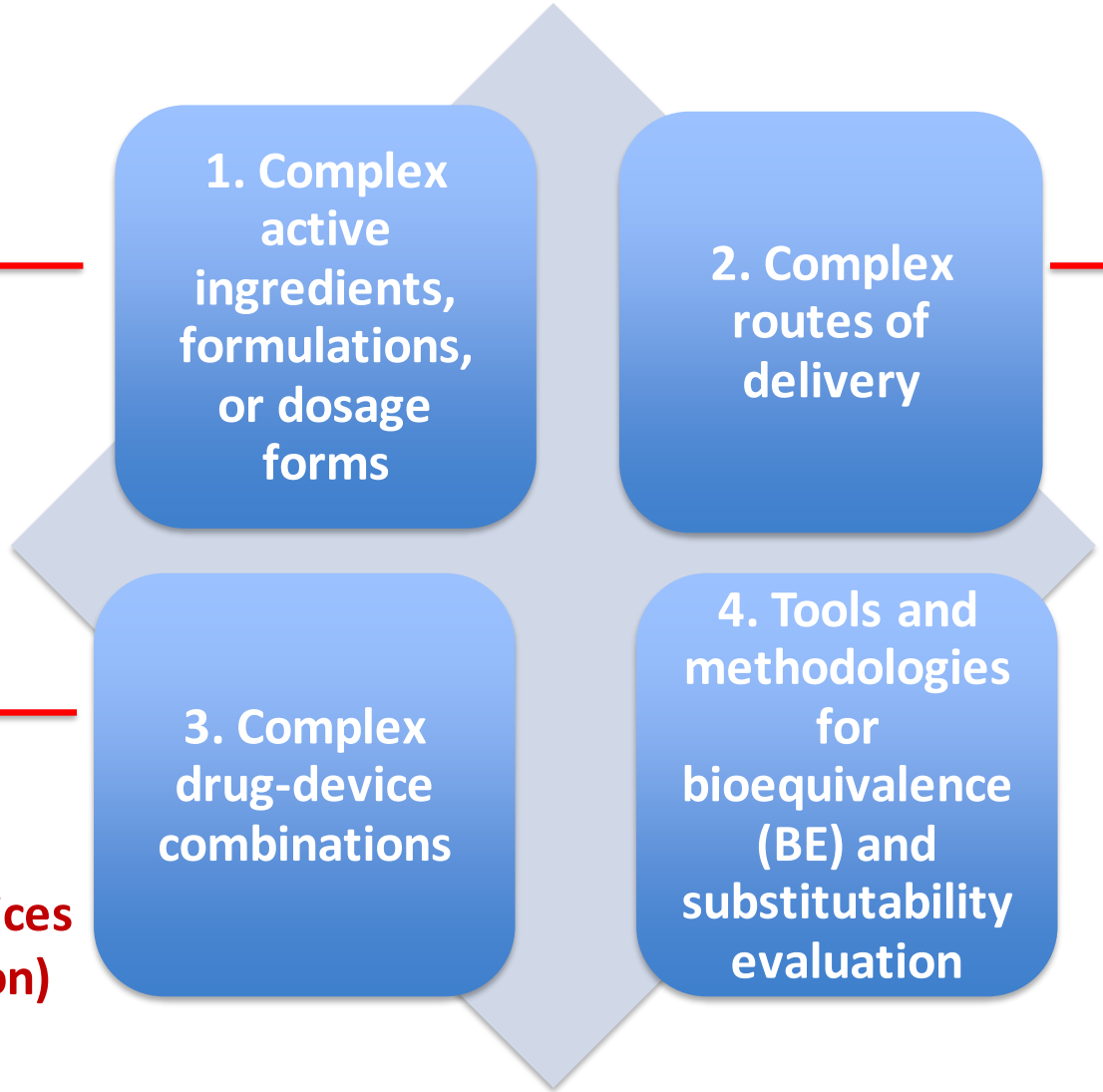
Complex Products

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)



5/10 (50%)
3 Complex APIs
2 LAIs

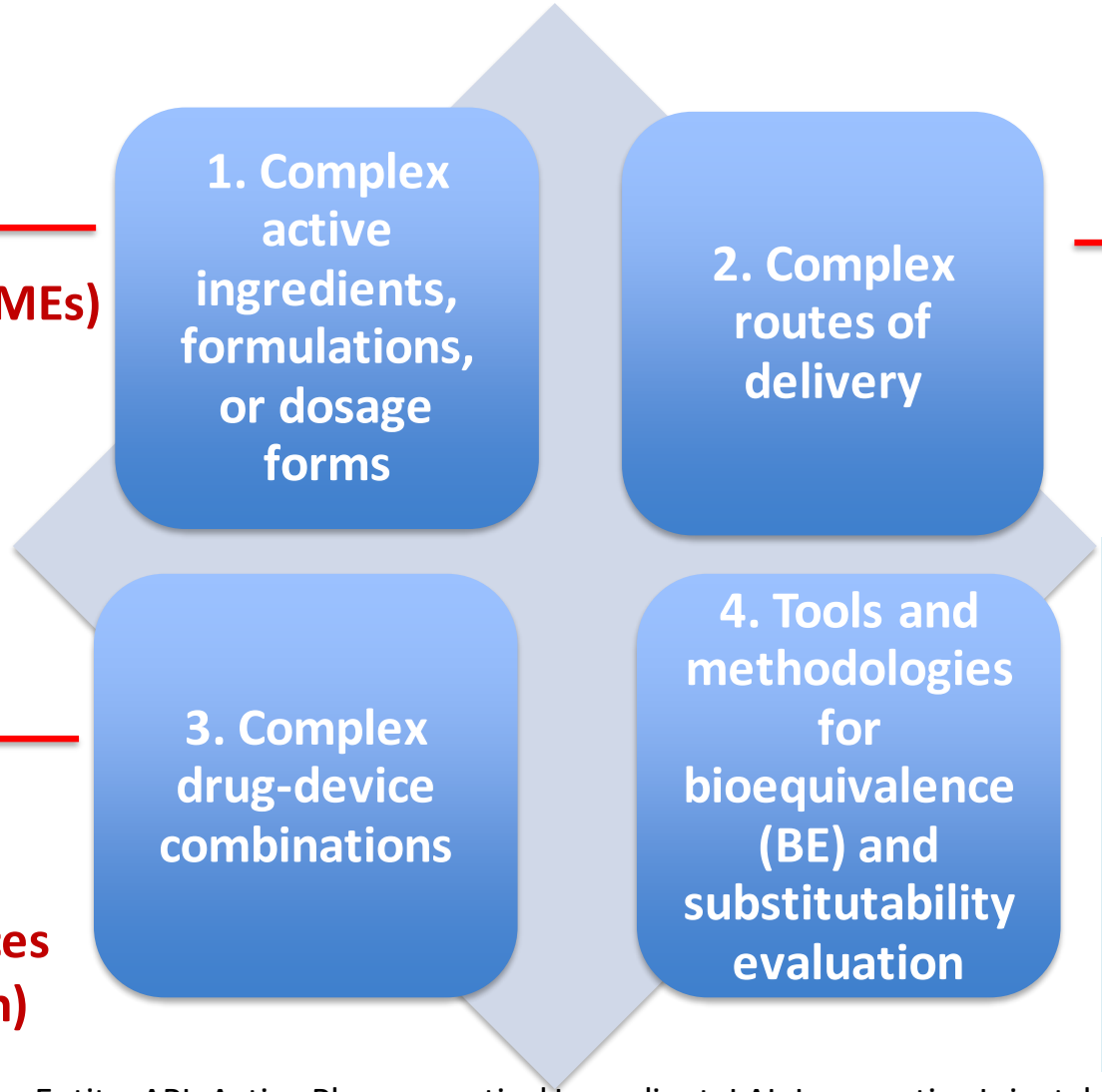
4/10 (40%)
2 Inhalation
1 Topical
1 Intrauterine

4/10 (40%)
1 Implanter
1 Auto-injectors
2 Drug-delivery Devices (e.g., nasal, inhalation)

- FDA posted 1 new PSG (nasal/ drug-delivery device) referencing FY2015 newly approved complex products in May 2019
- 3/10 are included in the "upcoming PSGs" list

NME: New Molecular Entity; API: Active Pharmaceutical Ingredient; LAI: Long-acting Injectable

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



6/13 (46%)
3 Complex APIs (all NMEs)
2 LAIs
1 ADF

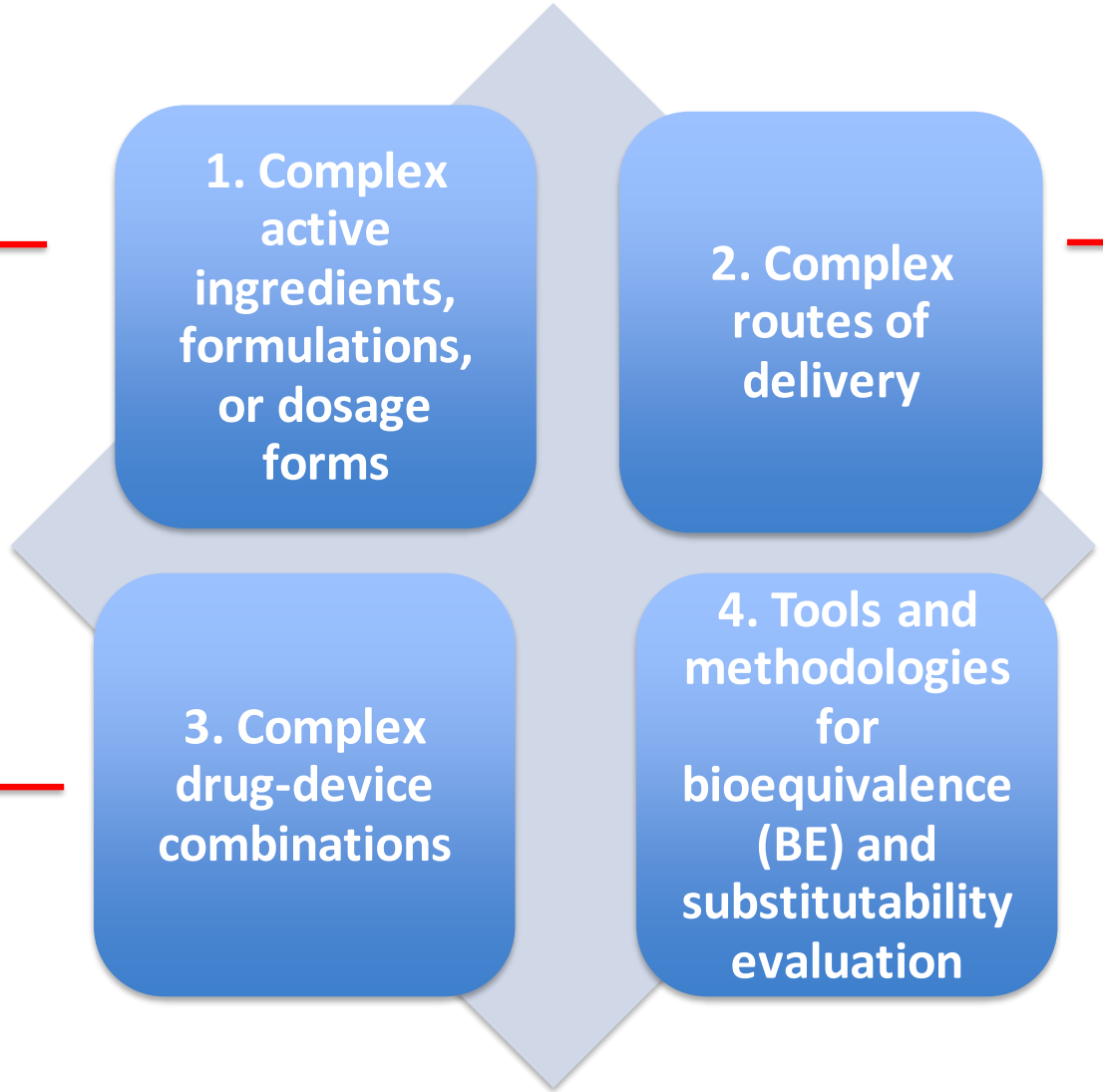
5/13 (38%)
2 Inhalation
1 Topical
1 Intrauterine
1 GI (NME)

6/13 (46%)
2 Implanters
2 Auto-injectors
2 Drug-delivery Devices (e.g., nasal, inhalation)

- FDA posted 5 new PSGs referencing FY2016 newly approved complex products between May 2019 and March 2020: 1 topical, 1 nasal/drug-delivery device; 1 auto-injector, 1 inhalation/drug-delivery device, and 1 complex injectable
- 4/13 are included in the "upcoming PSGs" list

NME: New Molecular Entity; API: Active Pharmaceutical Ingredient; LAI: Long-acting Injectable; ADF: Abuse-deterrent Formulation; GI: Gastrointestinal

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

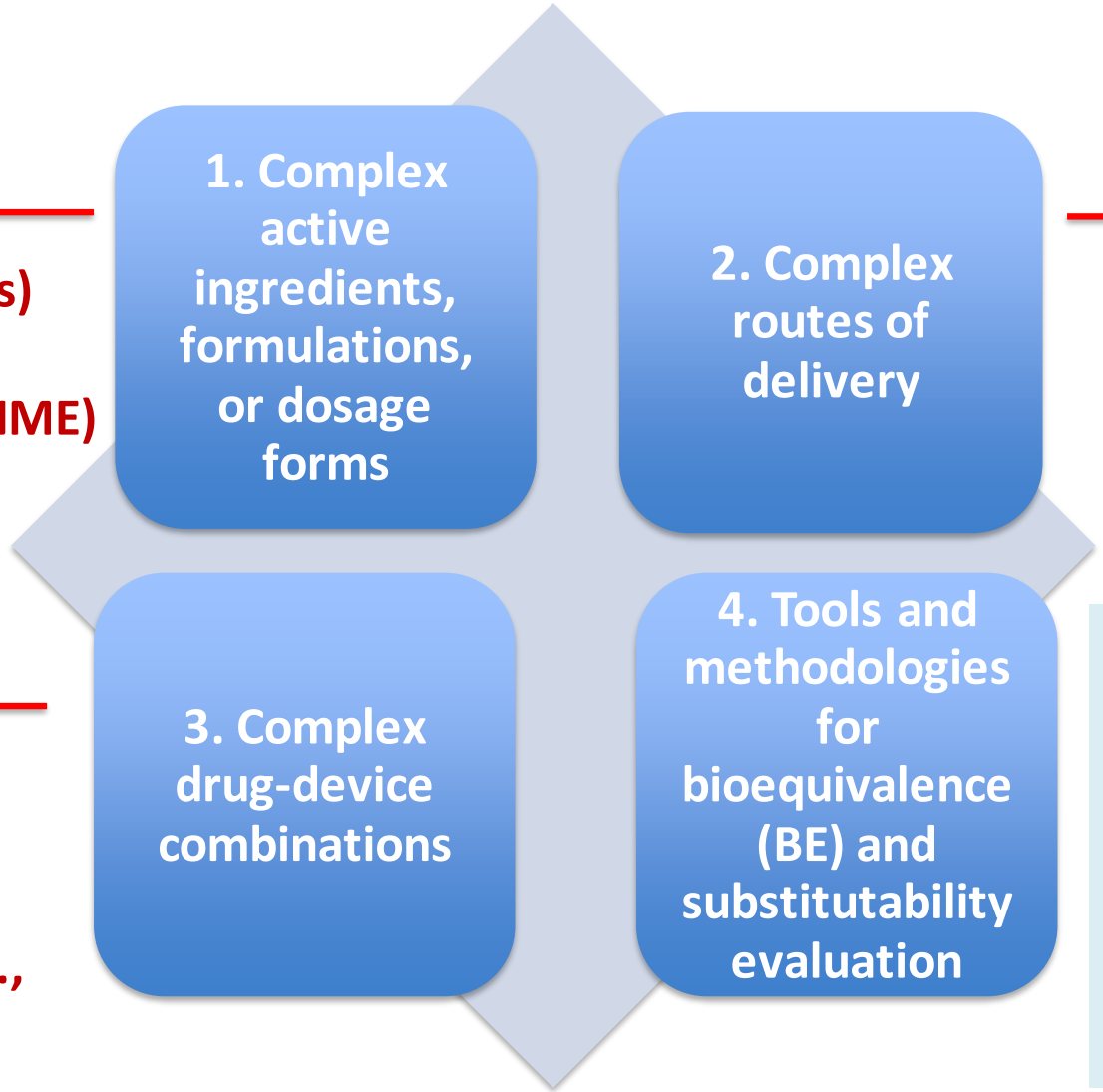
4/13 (31%)
1 GI
2 Nasal
1 Inhalation

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

- 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

NME: New Molecular Entity; API: Active Pharmaceutical Ingredient; LAI: Long-acting Injectable; GI: Gastrointestinal

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



18/29 (62%)
5 Complex APIs (2 are NMEs)
8 LAI
5 Complex injectable (1 is NME)

11/29 (38%)
2 GI (1 is NME)
2 Inhalation
1 Intraocular
1 Ophthalmic
3 Topical
2 Vaginal

11/29 (38%)
1 Implanter
1 Ingestible Event Marker Sensor
5 Auto-injectors or PFS
4 Drug-delivery Devices (e.g., nasal, inhalation, 1 is NME)

- FDA posted 5 new PSGs referencing FY2018 newly approved complex products between May 2019 and March 2020: 2 are complex NMEs, 1 topical, 1 ophthalmic, and 1 autoinjector
- 11/29 are included in the "upcoming PSGs" list

NME: New Molecular Entity; API: Active Pharmaceutical Ingredient; LAI: Long-acting Injectable; PFS: Pre-filled Syringes; GI: Gastrointestinal

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	SOLUT	**Complex API**
207078	SODIUM ZIRCONIUM CYCLOSILICATE*	FOR SUSPENSION; ORAL	Complex Route of Delivery
209637	SEMAGLUTIDE	SOLU	**Complex API**; Complex Drug-Device
208945	OZENOXACIN	CREAM;TOPICAL	orm; 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**

PSG published in Nov 2019

PSG published in March 2020

PSG published in Feb 2019

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

FY2019 NDA Approval Cohort

Complex Products

FY2019 Approved NCEs that are Complex

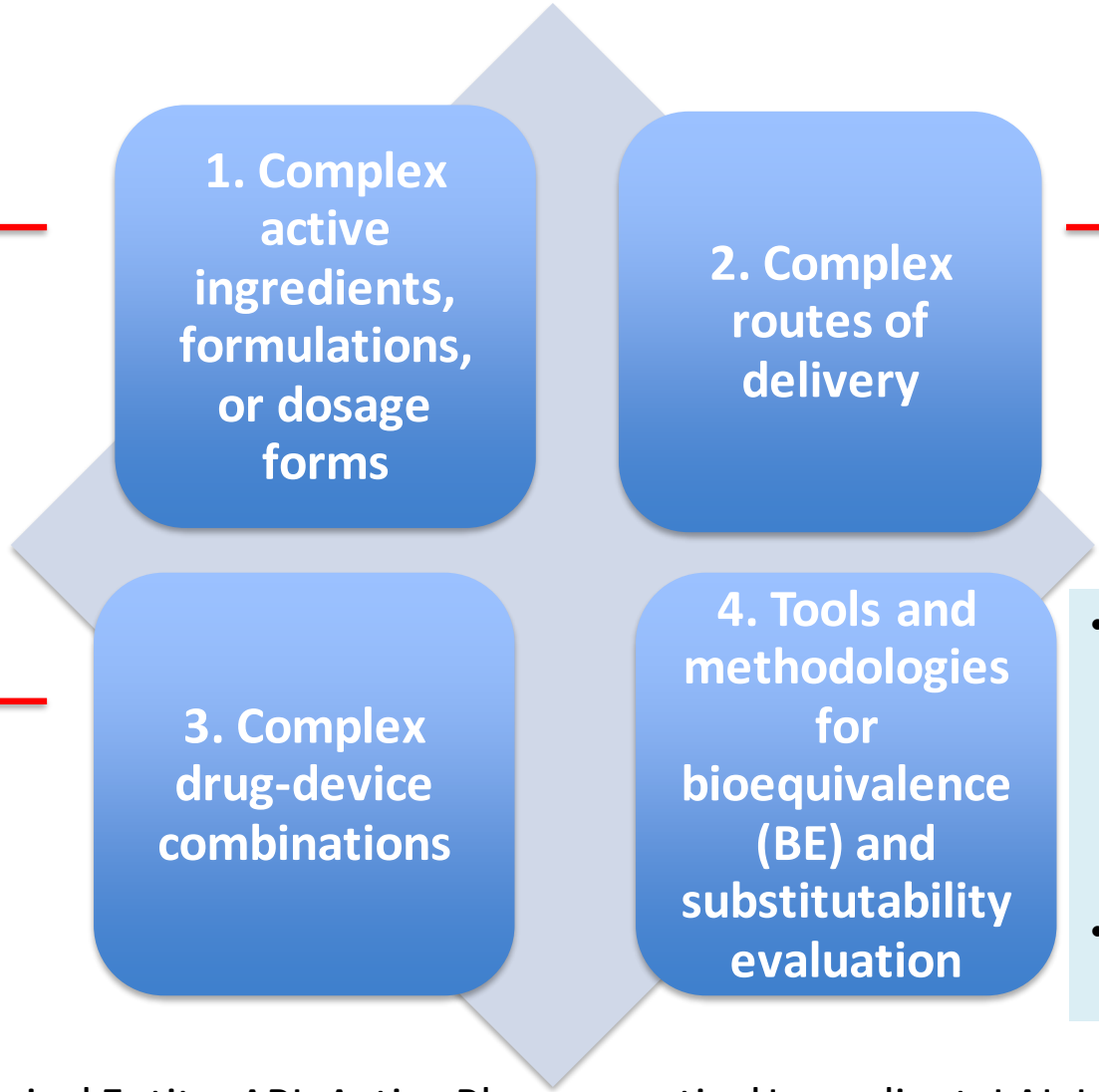
NDA Number	Active Ingredients	Dosage Form; Route of Administration	Reasons of Complexity
210557	BREMELANOTIDE ACETATE*	SOLUTION;SUBCUTANEOUS	Complex Drug-Device
211243	ESKETAMINE HYDROCHLORIDE*	SPRAY;NASAL	Complex Drug-Device
211172	INOTERSEN SODIUM	SOLUTION;SUBCUTANEOUS	Complex API
210910	RIFAMYCIN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

NCE: New Chemical Entity

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



6/20 (30%)
5 Complex APIs (1 is NCE)
1 LAI

11/20 (55%)
4 GI (2 are NCEs)
3 Inhalation
1 Intravitreal
1 Ophthalmic
2 Topical

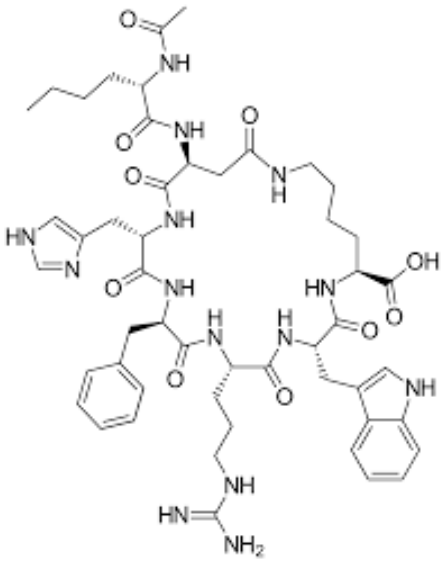
11/20 (55%)
3 Auto-injectors or intravitreal applicator (1 is NCE)
8 Drug-delivery Devices (e.g., nasal, inhalation, 1 is NCE)

- FDA posted 7 new PSGs referencing FY2019 newly approved complex products between May 2019 and March 2020, non is NCE: 4 inhalation/drug-delivery device
- 9/20 are included in the "upcoming PSGs" list (2 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)

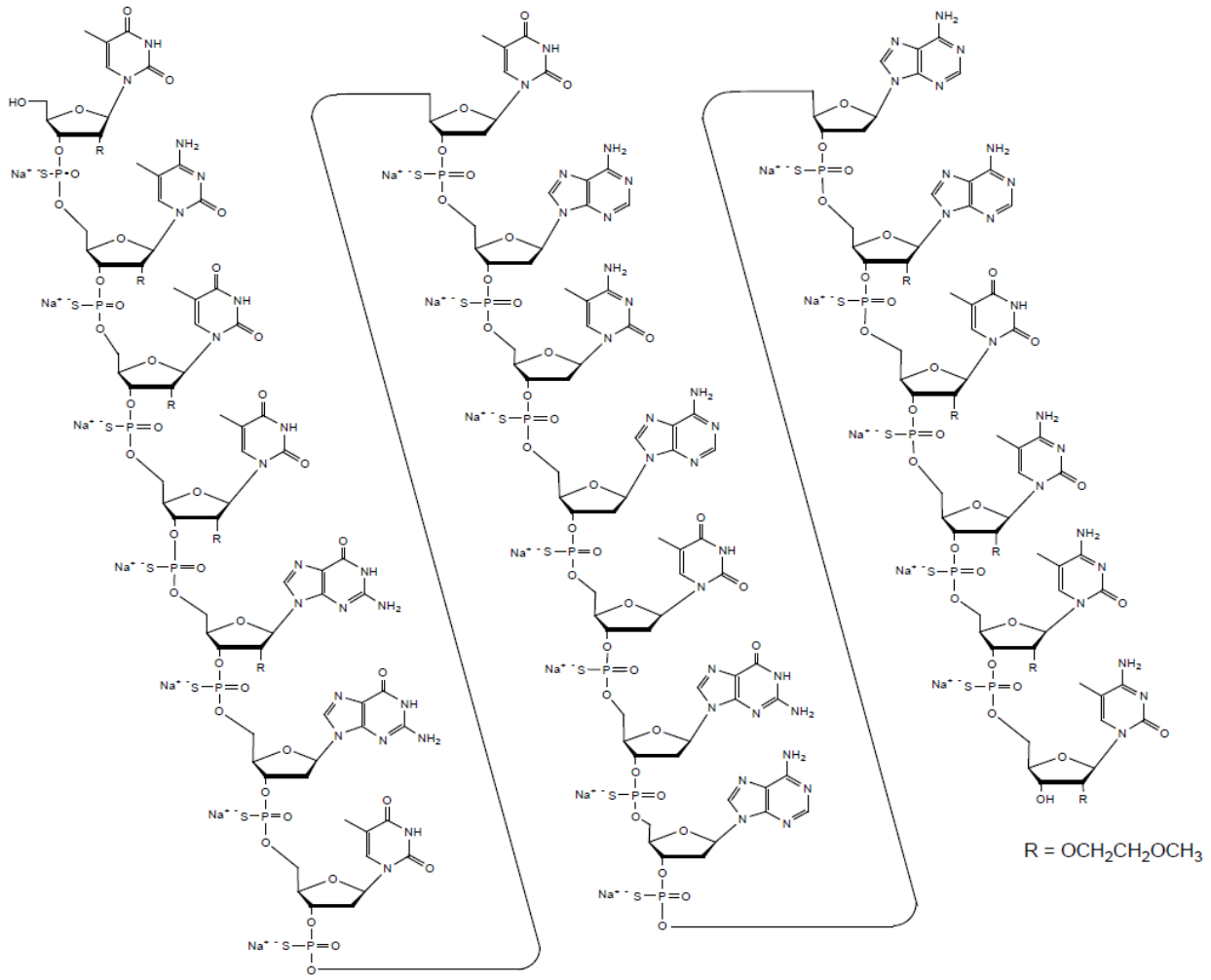


https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210557s000lbl.pdf

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

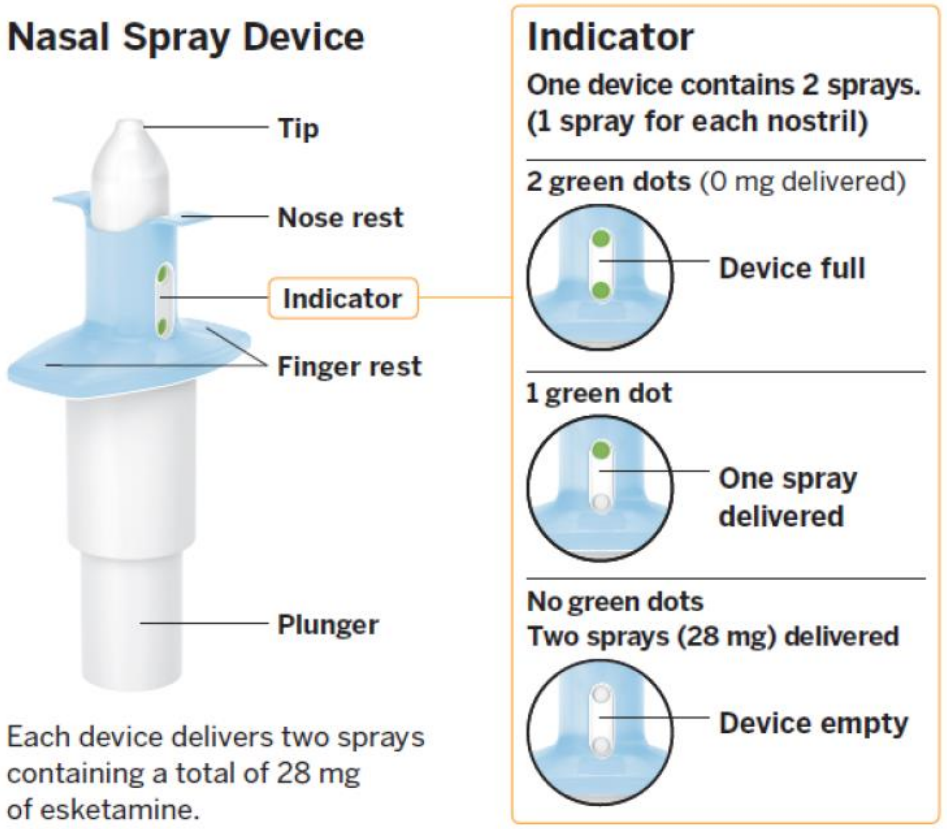


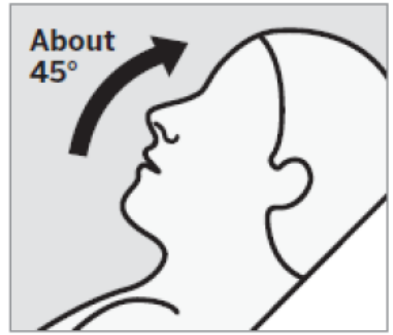
- Antisense oligonucleotide
- The molecular formula of inotersen sodium is $C_{230}H_{299}N_{69}Na_{19}O_{121}P_{19}S_{19}$
- The molecular weight is 7600.73 Da.

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)

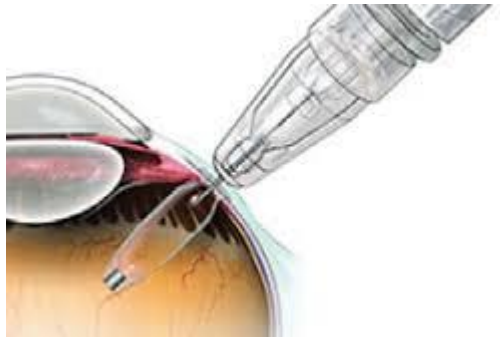




REMS: Risk Evaluation and Mitigation Strategy
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211243s003lbl.pdf

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

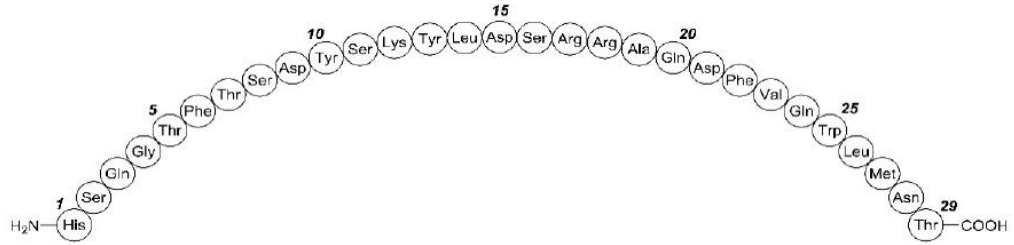


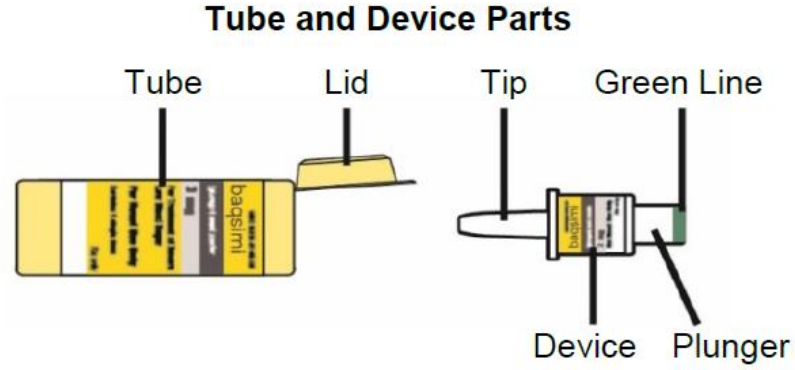
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210331Orig1s000Lbl.pdf

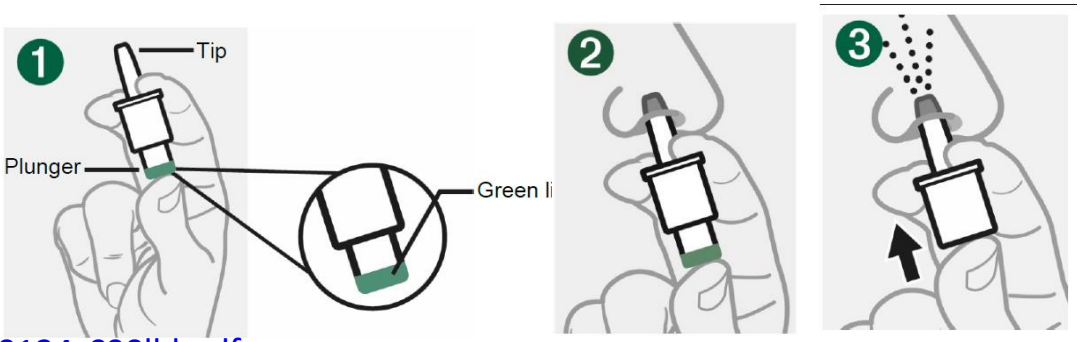
BAQSIMI (Glucagon)

- 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:







https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210134s000lbl.pdf

GVOKE (Glucagon)

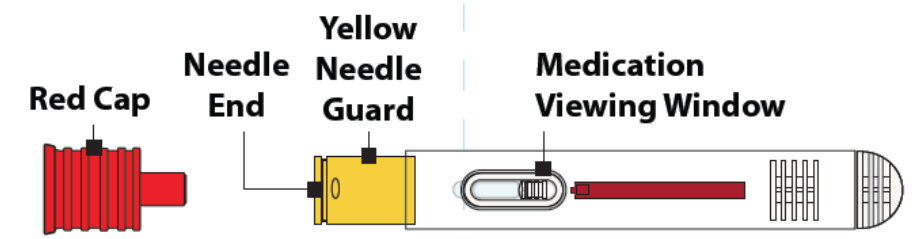
- New Dosage Form
- Approved on 9/10/2019 (NDA 212097)
- **API:** Glucagon
  - A single chain polypeptide containing 29 amino acid residues
  - Synthetic
- **Dosage Form/Route:** Solution/Subcutaneous
- **Indication:** An antihypoglycemic agent indicated for the treatment of severe hypoglycemia in pediatric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

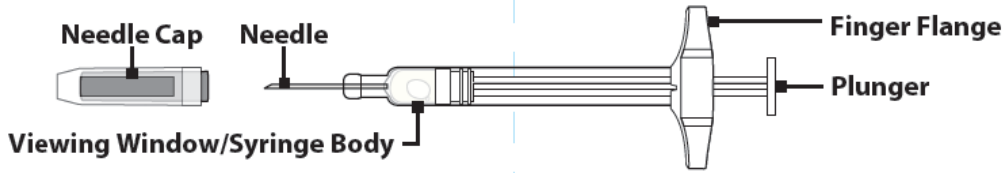
Its molecular formula is $C_{153}H_{225}N_{43}O_{49}S$ with the following structure:

NH_2 - His - Ser - Gln - Gly - Thr - Phe - Thr - Ser - Asp - Tyr - Ser - Lys -
1 2 3 4 5 6 7 8 9 10 11 12

Tyr - Leu - Asp - Ser - Arg - Arg - Ala - Gln - Asp - Phe - Val - Gln - Trp -
13 14 15 16 17 18 19 20 21 22 23 24 25

Leu - Met - Asn - Thr - COOH
26 27 28 29





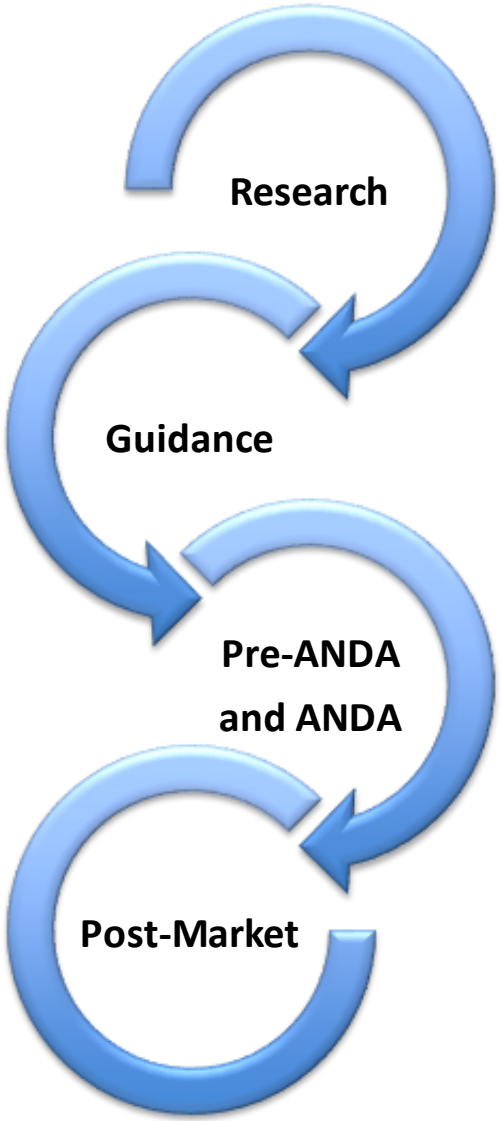
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210134s000lbl.pdf

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

https://www.fda.gov/drugs/generic-drugs/fy-2018-gdufa-science-and-research-outcomes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