Fiscal Year (FY) 2021 Generic Drug Science and Research Initiatives

BACKGROUNDER DOCUMENT FOR THE PLENARY PANEL DISCUSSION

FDA is seeking public input about what research on bioequivalence approaches is needed to support the development of prospective generic products referencing the complex products[1] in Table 1.

FDA is also interested in gauging the priority, interest, and/or degree of challenge for generic industry stakeholders for products in Table 1.

Table 1: List of products approved under a new drug application (NDA) during fiscal year (FY) 2020 (i.e., between October 1, 2019 and September 30, 2020) which are classified as complex products[1] (N=31). Brief summary statistics describing the proportion of NDAs approved for complex products in FY 2020 by submission classification[2], route of administration, and dosage form are provided in Tables 2, 3, and 4, respectively.

APPROVAL DATE	NDA NUMBER	PROPRIETARY NAME	ACTIVE INGREDIENT	ROUTE OF ADMINISTRATION	DOSAGE FORM	SUBMISSION CLASSIFICATION[2]	APPLICATION HOLDER
10/4/2019	211527	AKLIEF	TRIFAROTENE	TOPICAL (SKIN)	CREAM	TYPE 1	GALDERMA LABORATORIES LP
10/4/2019	211939	BONSITY	TERIPARATIDE	SUBCUTANEOUS	SOLUTION	TYPE 5	ALVOGEN INC
10/8/2019	210797	SCENESSE	AFAMELANOTIDE	SUBCUTANEOUS	IMPLANT	TYPE 1	CLINUVEL INC
10/11/2019	212268	SECUADO	ASENAPINE	TRANSDERMAL	SYSTEM	TYPE 3	HISAMITSU PHARMACEUTICAL CORPORATION INC
10/18/2019	212379	AMZEEQ	MINOCYCLINE HYDROCHLORIDE	TOPICAL (SKIN)	AEROSOL, FOAM	TYPE 3	VYNE PHARMACEUTICALS INC
11/5/2019	209359	EPINEPHRINE (COPACKAGED)	EPINEPHRINE	INTRAVENOUS	SOLUTION	TYPE 7	HOSPIRA INC.
11/7/2019	212279	EXEM FOAM KIT	AIR POLYMER-TYPE A	INTRAUTERINE	FOAM	TYPE 1	GISKIT BV
11/20/2019	212194	GIVLAARI	GIVOSIRAN SODIUM	SUBCUTANEOUS	SOLUTION	TYPE 1	ALNYLAM PHARMACEUTICALS INC
12/12/2019	211970	VYONDYS 53	GOLODIRSEN	INTRAVENOUS	SOLUTION	TYPE 1	SAREPTA THERAPEUTICS INC
12/18/2019	211882	ARAZLO	TAZAROTENE	TOPICAL (SKIN)	LOTION	TYPE 5	BAUSCH HEALTH AMERICAS INC
1/10/2020	211635	VALTOCO	DIAZEPAM	NASAL	SPRAY	TYPE 3	NEURELIS INC
1/16/2020	208171	MONOFERRIC	FERRIC DERISOMALTOSE	INTRAVENOUS	SOLUTION	TYPE 5	PHARMACOSMOS AS
1/24/2020	213138	DIFICID	FIDAXOMICIN	ORAL	FOR SUSPENSION	TYPE 5	CUBIST PHARMACEUTICALS LLC
1/28/2020	213224	BYNFEZIA PEN	OCTREOTIDE ACETATE	SUBCUTANEOUS	SOLUTION	TYPE 5	SUN PHARMACEUTICAL INDUSTRIES LIMITED
2/14/2020	204017	TWIRLA	ETHINYL ESTRADIOL; LEVONORGESTREL	TRANSDERMAL	SYSTEM	TYPE 3	AGILE THERAPEUTICS
2/20/2020	210583	ANJESO	MELOXICAM	INTRAVENOUS	SOLUTION	TYPE 3	BAUDAX BIO INC
3/4/2020	211911	DURYSTA	BIMATOPROST	OPHTHALMIC	IMPLANT	TYPE 3	ALLERGAN INC
3/27/2020	212860	TRIFERIC AVNU	FERRIC PYROPHOSPHATE CITRATE	INTRAVENOUS	SOLUTION	TYPE 3	ROCKWELL MEDICAL INC
4/15/2020	211728	JELMYTO	MITOMYCIN	PYELOCALYCEAL	POWDER	TYPE 5	UROGEN PHARMA LTD
4/29/2020	201110	MILPROSA	PROGESTERONE	VAGINAL	SYSTEM	TYPE 3	FERRING PHARMACEUTICALS INC
5/1/2020	213150	FENSOLVI KIT	LEUPROLIDE ACETATE	SUBCUTANEOUS	POWDER	NOT CLASSIFIED	TOLMAR INTERNATIONAL LIMITED
5/19/2020	213691	IMPEKLO	CLOBETASOL PROPIONATE	TOPICAL (SKIN)	LOTION	TYPE 5	MYLAN PHARMACEUTICALS INC
5/22/2020	208352	PHEXXI	CITRIC ACID; LACTIC ACID; POTASSIUM BITARTRATE	VAGINAL	GEL	TYPE 3 & TYPE 4	EVOFEM INC
5/28/2020	213690	ZILXI	MINOCYCLINE HYDROCHLORIDE	TOPICAL (SKIN)	AEROSOL, FOAM	TYPE 5	VYNE PHARMACEUTICALS INC
6/19/2020	209388	GIMOTI	METOCLOPRAMIDE HYDROCHLORIDE	NASAL	SPRAY, METERED	TYPE 3 & TYPE 4	EVOKE PHARMA INC
7/20/2020	213422	WYNZORA	BETAMETHASONE DIPROPIONATE; CALCIPOTRIENE	TOPICAL (SKIN)	CREAM	TYPE 5	MC2 THERAPEUTICS LTD
7/23/2020	212122	BREZTRI AEROSPHERE	BUDESONIDE; FORMOTEROL FUMARATE; GLYCOPYRROLATE	INHALATION	AEROSOL, METERED	NOT CLASSIFIED	ASTRAZENECA AB
7/24/2020	206966	XEGLYZE	ABAMETAPIR	TOPICAL (SCALP)	LOTION	TYPE 1	DR REDDYS LABORATORIES SA
8/12/2020	212154	VILTEPSO	VILTOLARSEN	INTRAVENOUS	SOLUTION	TYPE 1	NIPPON SHINYAKU CO LTD
8/26/2020	213433	WINLEVI	CLASCOTERONE	TOPICAL (SKIN)	CREAM	TYPE 1	CASSIOPEA SPA
8/28/2020	209511	XARACOLL	BUPIVACAINE HYDROCHLORIDE	IMPLANTATION	IMPLANT	TYPE 3 & TYPE 4	INNOCOLL PHARMACEUTICALS

[1] Complex products are defined in the Generic Drug User Fee Amendments (GDUFA) II Commitment Letter of 5/12/2016 accessible at https://www.fda.gov/media/101052/download (Last accessed 5/27/2021)

[2] Submission classification codes are defined in the Center for Drug Evaluation and Research Manual of Policies and Procedures (MAPP) 5018.2 accessible at https://www.fda.gov/media/94381/download (Last accessed 5/27/2021)

Table 2: Proportion of NDAs approved for complex products in FY 2020 by submission classification.

SUBMISSION CLASSIFICATION	PROPORTION OF NDAs APPROVED FOR COMPLEX PRODUCTS IN FY 2020
TYPE 5- NEW FORMULATION OR NEW MANUFACTURER	**29%** (9/31)
TYPE 1- NEW MOLECULAR ENTITY	**26%** (8/31)
TYPE 3- NEW DOSAGE FORM	**26%** (8/31)
TYPE 3- NEW DOSAGE FORM and TYPE 4- NEW COMBINATION	**10%** (3/31)
NOT CLASSIFIED	**6%** (2/31)
TYPE 7 - DRUG ALREADY MARKETED WITHOUT APPROVED NDA	**3%** (1/31)

Table 3: Proportion of NDAs approved for complex products in FY 2020 by route of administration.

ROUTE OF ADMINISTRATION	PROPORTION OF NDAs APPROVED FOR COMPLEX PRODUCTS IN FY 2020
TOPICAL (SKIN/SCALP)	**26%** (8/31)
INTRAVENOUS	**19%** (6/31)
SUBCUTANEOUS	**16%** (5/31)
NASAL	**6%** (2/31)
TRANSDERMAL	**6%** (2/31)
VAGINAL	**6%** (2/31)
IMPLANTATION	**3%** (1/31)
INHALATION	**3%** (1/31)
INTRAUTERINE	**3%** (1/31)
OPHTHALMIC	**3%** (1/31)
ORAL	**3%** (1/31)
PYELOCALYCEAL	**3%** (1/31)

Table 4: Proportion of NDAs approved for complex products in FY 2020 by dosage form.

DOSAGE FORM	PROPORTION OF NDAs APPROVED FOR COMPLEX PRODUCTS IN FY 2020
SOLUTION	**29%** (9/31)
CREAM	**10%** (3/31)
IMPLANT	**10%** (3/31)
LOTION	**10%** (3/31)
SYSTEM	**10%** (3/31)
AEROSOL, FOAM	**6%** (2/31)
POWDER	**6%** (2/31)
AEROSOL, METERED	**3%** (1/31)
FOAM	**3%** (1/31)
FOR SUSPENSION	**3%** (1/31)
GEL	**3%** (1/31)
SPRAY	**3%** (1/31)
SPRAY, METERED	**3%** (1/31)

Table 5: List of 11 products approved under an NDA that contained a new chemical entity (NCE) which were approved after October 1, 2017, which are classified as complex products, and for which ≥ 2 years have passed since NDA approval (as of June 23, 2021). The table indicates the status of a product-specific guidance (PSG).

APPROVAL DATE	NDA NUMBER	PROPRIETARY NAME	ACTIVE INGREDIENT	ROUTE OF ADMINISTRATION	DOSAGE FORM	APPLICATION HOLDER	PSG STATUS
12/5/2017	209637	OZEMPIC	SEMAGLUTIDE	SUBCUTANEOUS	SOLUTION	NOVO NORDISK INC	ISSUED 03/2020
12/11/2017	208945	XEPI	OZENOXACIN	TOPICAL	CREAM	FERRER INTERNACIONAL SA	ISSUED 02/2019
1/26/2018	208700	LUTATHERA	LUTETIUM DOTATATE LU-177	INTRAVENOUS	SOLUTION	ADVANCED ACCELERATOR APPLICATIONS USA INC	ISSUED 11/2019
5/18/2018	207078	LOKELMA	SODIUM ZIRCONIUM CYCLOSILICATE	ORAL	FOR SUSPENSION	ASTRAZENECA PHARMACEUTICALS LP	ISSUED 06/2020
7/27/2018	210589	OMEGAVEN	FISH OIL TRIGLYCERIDES	INTRAVENOUS	EMULSION	FRESENIUS KABI USA LLC	ISSUED 06/2020
8/10/2018	209627	ANNOVERA	ETHINYL ESTRADIOL; SEGESTERONE ACETATE	VAGINAL	RING	THERAPEUTICSMD INC	UPCOMING
8/10/2018	210922	ONPATTRO	PATISIRAN SODIUM	INTRAVENOUS	SOLUTION	ALNYLAM PHARMACEUTICALS INC	PENDING RESEARCH
10/5/2018	211172	TEGSEDI	INOTERSEN SODIUM	SUBCUTANEOUS	SOLUTION	AKCEA THERAPEUTICS INC	ACTIVE RESEARCH
11/16/2018	210910	AEMCOLO	RIFAMYCIN SODIUM	ORAL	TABLET, DELAYED RELEASE	REDHILL BIOPHARMA INC	ISSUED 03/2020
3/5/2019	211243	SPRAVATO	ESKETAMINE HYDROCHLORIDE	NASAL	SPRAY	JANSSEN PHARMACEUTICALS INC	ISSUED 08/2020
6/21/2019	210557	VYLEESI (AUTOINJECTOR)	BREMELANOTIDE ACETATE	SUBCUTANEOUS	SOLUTION	PALATIN TECHNOLOGIES INC	ISSUED 03/2021

Eight draft PSGs have been issued for 8 of the 11 complex NCE products in Table 5. Of these, 6 of the draft PSGs were issued within 2 years following initial NDA approval. Information about the 3 products for which PSGs have not yet been issued is below:

1. The issuance of a draft PSG for prospective generic products referencing ethinyl estradiol and segesterone acetate vaginal ring (NDA 209627) has been forecasted in FDA's list of Upcoming Product-Specific Guidances for Complex Generic Drug Product Development.
2. The issuance of a draft PSG for prospective generic products referencing patisiran sodium intravenous solution (NDA 210922) is anticipated to be supported by the conduct of research, which has not yet initiated, on bioequivalence approaches for small interfering ribonucleic acid (siRNA) products. FDA is seeking public input about what research on bioequivalence approaches is needed to support the development of draft PSGs for siRNA products
3. The issuance of a draft PSG for prospective generic products referencing inotersen sodium subcutaneous solution (NDA 211172) is being actively supported by research within FDA (aligned with the GDUFA Science and Research Priority Initiatives for Fiscal Year 2021 related to complex active ingredients, e.g., priority A1[3]) on bioequivalence approaches for antisense oligonucleotide (ASO) products. However, analytical methods to assay impurities for ASO products have been challenging to develop and further research is needed to characterize the immunogenicity of ASO drugs and associated impurities. Insights gained from research on ASO products are expected to inform the design and conduct of research involving siRNA products. FDA is seeking public input about what research on bioequivalence approaches is needed to support the development of draft PSGs for ASO products.

FDA is seeking public input about what research on bioequivalence approaches is needed to support the development of draft PSGs for siRNA and ASO products, and about any research that would assist generic industry stakeholders to develop prospective generics for complex siRNA and ASO products in Table 5.

[3] GDUFA Science and Research Priority Initiatives for Fiscal Year 2021, accessible at https://www.fda.gov/media/144140/download (Last accessed 5/27/2021)