U.S. FOOD & DRUG ADMINISTRATION

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MEMORANDUM

To: Furoscix (furosemide) subcutaneous injection (NDA 209988) File
Lasix ONYU (furosemide) subcutaneous injection (NDA 217294) File

From: CDER Exclusivity Board

Re: Eligibility of Furoscix (NDA 209988) for 3-year exclusivity and impact on approval of Lasix ONYU (NDA 217294)

Date: October 9, 2024

This memorandum addresses whether scPharmaceuticals, Inc.'s (scPharmaceuticals) Furoscix (furosemide) subcutaneous injection (NDA 209988) (Furoscix) is eligible for 3-year exclusivity under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and if so, whether any such exclusivity delays approval of SQ Innovation, Inc.'s Lasix ONYU (furosemide) subcutaneous injection (NDA 217294) (Lasix ONYU).

Upon review of the administrative record related to the approval of Furoscix, the Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with the Division of Cardiology and Nephrology in the Office of Cardiology, Hematology, Endocrinology, and Nephrology; the Division of Cardiometabolic and Endocrine Pharmacology in the Office of Clinical Pharmacology; and the Division of Drug Delivery and General Hospital Devices, and Human Factors in the Office of Product Evaluation and Quality in the Center for Devices and Radiological Health, recommends that Furoscix is eligible for 3-year exclusivity based on three clinical investigations assessing skin tolerability of the novel subcutaneous route of administration: Studies scP-01-002, CP-00001, and CP-00002. The Board further recommends that Furoscix's 3-year exclusivity should delay the approval of Lasix ONYU until the exclusivity expires on October 7, 2025.

The Board recommends that NDA 209988 for Furoscix qualifies for 3-year exclusivity because it contains new clinical investigations (other than a bioavailability study) – Studies scP-01-002, CP-00001, and CP-00002 – that were essential to approval and conducted or sponsored by the applicant. Studies scP-01-002, CP-00001, and CP-00002 answered, for the first time, a unique clinical question as to whether furosemide administered subcutaneously is safe. The Board therefore concludes that the "innovation" represented by Furoscix's approval – and thus its exclusivity-protected condition of approval for which the new clinical investigations were essential – is subcutaneous administration of furosemide.[1] More specifically, Furoscix is the

(b) (5)

first approved drug containing the active moiety furosemide delivered by subcutaneous administration.

Lasix ONYU is a proposed furosemide product for subcutaneous administration (b) (4) (b) (4) is seeking approval of the exclusivity-protected condition of approval, the Board recommends that Lasix ONYU's approval should be delayed by Furoscix's exclusivity.

The Board's reasoning is described below.

I. Factual and Procedural Background

This section describes the factual and procedural background relevant to the Board's exclusivity recommendation. Section I.A. provides a general overview of furosemide as a treatment of congestion due to fluid overload in patients with chronic heart failure in the United States. Section I.B. provides an overview of skin tolerability studies. Section I.C. provides detailed background regarding the development, supportive studies, and approval of Furoscix.

A. Furosemide for the Treatment of Fluid Overload in Patients with Chronic Heart Failure

Furosemide is a loop diuretic that was approved in 1966 as an oral tablet and later approved in 1968 for intravenous (IV) and intramuscular (IM) administration and as an oral solution.[2] Loop diuretics are medications used in the management and treatment of fluid overload conditions such as heart failure.[3] Heart failure is a common serious medical condition affecting approximately 6 million adults in the United States.[4] In patients with heart failure, the heart cannot pump enough blood and oxygen to support the other organs in the body and the body retains water and salt.[5] Diuretics, drugs that causes the kidneys to make more urine and help the body get rid of extra fluid and salt, are a standard of care for patients with heart failure.[6]

Furosemide drug products administered orally are approved for chronic use.[7] Furosemide drug products administered through IV or IM routes are approved for use in emergency situations and for acute pulmonary edema.[8] In patients with signs and symptoms of heart failure, intravenous furosemide is administered in an outpatient clinic, in special infusion centers known as "diuresis

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[2] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018). See also NDA 209988, Pharmacology/Toxicology Review and Evaluation (Apr. 30, 2018).

[3] Huell C, Raja A, Olivera-Lawrence MD. Loop Diuretics. [Updated 2023 May 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546656/.

[4] "About Heart Failure," Center for Disease Control, available at https://www.cdc.gov/heart-disease/about/heart-failure.html.

[5] "About Heart Failure," Center for Disease Control, available at https://www.cdc.gov/heart-disease/about/heart-failure.html.

[6] "Diuretics," National Cancer Institute, available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/diuretic.

[7] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 9.

[8] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 9.

clinics," in the emergency room, or during an in-patient stay in a hospital.[9] Furoscix is the first furosemide drug product approved for subcutaneous administration. Furoscix produces a similar effect to IV administration of furosemide[10] and can be administered by patients, caregivers, or a healthcare professional at home or in a clinic or hospital setting.[11]

B. Skin Tolerability Studies

The design of certain drug products can raise skin tolerability concerns that pertain to the safety and effectiveness of the drug product. Skin tolerability studies measure the potential for the product to cause skin irritation or sensitization.[12] Such studies can provide information essential to approval of an NDA such as informing labeling recommendations regarding adverse reactions and where and when to apply the drug product (e.g., to rotate the site for each administration). In terms of study design, a skin irritation and sensitization assessment can be conducted as part of other safety and efficacy clinical trials for the drug product, or as a separate, smaller study primarily focused on assessing skin irritation and sensitization generally via an irritation score clinical endpoint.

C. NDA 209988 for Furoscix (Furosemide) Subcutaneous Injection

i. Submissions and Approval

FDA approved Furoscix (NDA 209988) on October 7, 2022.[13] Furoscix was originally indicated for the treatment of congestion due to fluid overload in adult patients with NYHA Class II and Class III chronic heart failure.[14] Furoscix is a drug-device combination product, which consists of a single-use, on-body infusor with prefilled cartridge that adheres to the patient's abdomen where it subcutaneously injects 80 mg of a pH neutral formulation of furosemide over a period of 5 hours. Furoscix is the first approved drug product to deliver furosemide using subcutaneous

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[9] See NDA 209988, Pharmacology/Toxicology NDA Review and Evaluation (Apr. 30, 2018), at 3.

[10] NDA 209988, prescribing information (Oct. 7, 2022), section 12.2 "Pharmacodynamics," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209988Orig1s000Correctedlbl.pdf. However, Furoscix is not indicated for emergency situations or in patients with acute pulmonary edema. See id. at "Highlights of Prescribing Information." Also, Furoscix is not for chronic use and should be replaced with oral diuretics as soon as practical. See id.

[11] See NDA 209988, Cross Discipline Team Leader Review (Oct. 3, 2022), at 3.

[12] Sensitization concerns can include the potential for a drug product to cause increased sensitivity to an ingredient in the drug product formulation (e.g., the active ingredient), the medical adhesive used to adhere the drug product to the patient's skin, or sunlight (i.e., photosensitivity).

[13] See NDA 209988, corrected NDA approval letter (Dec. 21, 2022), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/209988Orig1s000Correctedltr.pdf.

[14] See NDA 209988, prescribing information (Oct. 7, 2022), section 1 "Indications and Usage," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209988Orig1s000Correctedlbl.pdf. On August 9, 2024, FDA approved NDA 209988, supplement 1, which expanded the indication for Furoscix to the treatment of congestion due to fluid overload in adult patients with chronic heart failure, which includes patients with NYHA Class II through Class IV chronic heart failure. See NDA 209988, prescribing information (Aug. 9, 2024), section 1 "Indications and Usage," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/209988s001lbl.pdf.

administration. The formulation of furosemide used in this product is adjusted to a neutral pH (7.4) [redacted] (b) (4)

In patients with heart failure, subcutaneous administration by Furoscix produces similar diuresis (i.e., increased production of urine) and natriuresis (i.e., increased excretion of sodium in urine) to IV administration of furosemide at 8 and 24 hours post-dose.[16] The systemic risks of furosemide are well-established and, based on the data submitted to support approval of NDA 209988, the systemic risks of furosemide delivered subcutaneously are expected to be no greater than those of IV furosemide due to the similar systemic exposure from these two routes.[17] Thus, FDA's only safety concern for Furoscix was skin tolerability due to the novel subcutaneous route of administration, which involves injecting a furosemide formulation into a subcutaneous layer of tissue and adhering the product to the skin for a period of five hours, which is much longer than the one to two minute time period for IV administration of furosemide products.[18] In the pre-investigational new drug application (IND) and IND phases, FDA advised the sponsor to include targeted skin tolerability assessments of adverse events of interest such as pain, rash, and itching at the site of the product's connection with the skin.[19]

a. Initial Submission and Complete Response

On August 23, 2017, scPharmaceuticals submitted the original NDA submission (SN0001) pursuant to section 505(b)(2) of the FD&C Act that relies, in part, on FDA's previous findings of safety and effectiveness for Furosemide Injection for intravenous or intramuscular use (NDA 018667), for which Hospira is the application holder.[20] To justify reliance on Furosemide Injection (NDA 018667), the applicant conducted Study scP-01-002 which compared the pharmacokinetics and bioavailability of the pH neutral formulation of furosemide administered subcutaneously in the proposed product to the same furosemide dose (80mg) administered intravenously in Furosemide Injection. A product design clinical validation study (CP-00001) was submitted to demonstrate the performance of the to-be-marketed drug-device combination product using the proprietary device component of the drug product. The application was also supported by a pilot study (CP-00002) that evaluated the suitability of methods and procedures for tolerability assessments.

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[15] Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 5. The pH of Furoscix is 7.4, which differs from that of Furosemide Injection, USP. See NDA 209988, prescribing information (Oct. 7, 2022), section 11 "Description," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209988Orig1s000Correctedlbl.pdf.

[16] NDA 209988, prescribing information (Aug. 9, 2024), section 12.2 "Pharmacodynamics," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/209988s001lbl.pdf.

[17] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 18.

[18] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018) at 55 and at 59. For IV administration times see e.g., NDA 018667, prescribing information (Aug. 31, 2022), Highlights of Prescribing Information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018667Orig1s043Corrected_lbl.pdf.

[19] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 24.

[20] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 9.

On June 11, 2018, FDA issued a complete response letter based on its review of the original submission. The complete response letter explained, among other issues, that Study CP-00001 failed to meet the study's primary endpoint of absence of major product failure.[21] The letter further explained that the four failures to deliver the full dose in Study CP-00001 also failed to trigger an alarm that would alert the user to the incomplete delivery of the dose.[22]

Although deficiencies with the device component prevented approval of the proposed product during this review cycle, the applicant successfully established a scientific bridge from bolus IV infusion of furosemide approved for use in Furosemide Injection (NDA 018667) to subcutaneous infusion of furosemide using the Perfusor Space Infusion Pump by B. Braun in Study scP-01-002.[23] As discussed below, FDA found the skin tolerability data from Studies scP-01-002, CP-00001, and CP-00002 to be adequate and relied upon this data to support approval of the product during the third review cycle.

(i) Study scP-01-002

Study scP-01-002 was a "proof-of-principle" study to determine whether subcutaneous administration of furosemide could produce drug blood levels and pharmacodynamic effects similar to those of IV furosemide.[24] This was an open-label, 2 period, random-sequence, cross-over trial performed in 16 adults with compensated NYHA Class II/III chronic heart failure undergoing chronic treatment with oral furosemide at a dose of at least 40 mg daily.[25] The trial was conducted in a research unit where subjects were observed for at least 24 hours before and after their infusions.[26] The pump used to deliver the subcutaneous furosemide was not the proprietary Furoscix infusor, but the Perfusor Space Infusion Pump by B. Braun, which is cleared by the Center for Devices and Radiological Health (CDRH) for subcutaneous infusion.[27] This study compared the pharmacokinetics and bioavailability of the pH neutral formulation of furosemide administered subcutaneously in the proposed product to the same furosemide dose (80mg) administered intravenously approved for use in Furosemide Injection.

Study scP-01-002 established a bridge to Furosemide Injection (NDA 018667) because the data from the study demonstrated that delivery of furosemide by the subcutaneous route over 5 hours

[21] See NDA 209988, Complete Response (Jun. 11, 2018), at 1-2, 12-13.

[22] See NDA 209988, Complete Response (Jun. 11, 2018), at 1, 12-13. See also NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 1.

[23] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 13.

[24] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 9.

[25] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 9.

[26] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 9.

[27] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 10.

using the Perfusor Space Infusion Pump by B. Braun provided exposure and pharmacodynamic effects comparable to those obtained with bolus IV administration in Furosemide Injection.[28]

Prespecified secondary endpoints of Study scP-01-002 assessed skin irritation and showed that application site erythema and edema were minimal.[29]

(ii) Study CP-00001

Study CP-00001 was an open label, single-arm, single-dose study at five U.S. centers to evaluate the clinical performance of the to-be-marketed drug-device combination product in up to 70 adult male and female subjects previously diagnosed with NYHA Class II-IV heart failure.[30] Study CP-00001 used a Furoscix proprietary infusion pump based on the Perfusor Space Infusion Pump by B. Braun (Furoscix pre-change pump).[31] The objectives of the study were: (1) to demonstrate that the proposed Furoscix combination product performed as intended and delivers 80 mg of furosemide subcutaneously in the abdominal area and (2) to assess safety and local tolerance of the combination product. The study treatment was a 5-hour infusion of the pH neutral formulation of furosemide (total of 80 mg) into the subcutaneous tissue of the abdomen, using the pre-change pump.

This study was intended to establish a bridge between the subcutaneous infusion data using the commercial B. Braun pump from Study scP-01-002 to the propriety Furoscix infusor pre-change pump.[32] However, the study failed to meet its pre-specified performance goal with respect to reliable delivery of furosemide to study subjects. Four of the 67 subjects who completed the treatment did not receive the entire planned 80 mg dose of furosemide. Three of these failures were due to filling errors and one to a dispensing error related to the presence of an air bubble in the intra-device infusion path. None of these failures produced any sort of alarm to alert the user or clinician. FDA determined that the failure of the device to deliver the entire dose to the patient, coupled with the lack of a device feature to alert the patient or caregiver to the under-delivery, could result in an unacceptable rate of under diuresis and fluid overload.[33] Device failure to deliver the entire dose, especially if repeated over several days, could lead to fluid overload and hospitalization for acute decompensated heart failure, which is associated with an increased risk of death: (1) during hospitalization and (2) for over a year after discharge.[34]

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[28] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 12-13, 16.

[29] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63-65.

[30] See NDA 209988, Cross Discipline Team Leader Review (Jun. 7, 2018).

[31] Study CP-00001 used a proprietary Furoscix pump (b) (4) (b) (4), which shall be referred to in this memo as the "Furoscix pre-change pump" because the applicant changed the device component from a pump to an injection device in the second review cycle.

[32] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 13.

[33] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 16.

[34] See NDA 209988, Division of Cardiovascular and Renal Products Cross-Discipline Team Leader Review (Jun. 7, 2018), at 16.

Further, the study was not designed to assess the patient's ability to self-administer the product because the product was administered by trained study staff.[35]

Prespecified secondary endpoints of Study CP-00001 assessed skin irritation and device dislodgment, among other things, and showed that, for the majority of patients, there are no serious concerns regarding skin-related safety.[36] The only safety signal was skin-related adverse events, which were mild to moderate and resolved.[37] For local skin tolerance, the adhesive site on the patient's skin was inspected for erythema, edema, and other local reactions including papular response and vesicular eruption.[38] All subjects had either no evidence of skin irritation or minimal erythema.[39] There were three cases of partial dislodgement of the product from the skin, but this did not interfere with drug delivery and the adhesive seemed adequate for the proposed use.[40] Study CP-00001 identified an additional risk of infection if skin is not prepared properly before application of the product.[41]

(iii) Study CP-00002

Study CP-00002 was the pilot study for Study CP-00001. Study CP-00002 evaluated the suitability of methods and procedures for the tolerability assessments that would be used in Study CP-00001. Study CP-00002 was conducted in 24 heart failure patients (NYHA Class II-IV) using the pre-change pump. Prespecified secondary endpoints of Study CP-00002 assessed skin irritation, among other things, and showed minimal erythema, papules, edema, and bruising.

(iv) Skin Tolerability Data from Studies scP-01-002, CP-00001, and CP-00002

The skin tolerability data from Studies scP-01-002, CP-00001, and CP-00002 were assessed together and used to support the Agency's conclusion regarding the skin tolerability and adverse skin reaction potential of Furoscix from the first review cycle and then carried forward to support approval during the third review cycle.[42,43] The skin assessments from these three studies included photographs and skin irritation scores.[44] The clinical reviewer's assessment of the photographs done at baseline, immediately after placement, one hour post-removal and one week

[35] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 9.

[36] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 13, 22.

[37] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 13.

[38] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 38.

[39] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 58.

[40] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 58.

[41] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 31.

[42] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63.

[43] Study scP-01-001, an exploratory PK/PD study that administered furosemide subcutaneously using the Perfusor Space Infusion Pump manufactured by B. Braun, was also submitted during the first review cycle. See NDA 209988, Safety Update (Aug. 11, 2022) at 2. While this study did not have prespecified clinical endpoints to assess skin tolerability, it did report AEs of bruise at injection site and burning/stinging at injection site consistent with those reported from Studies scP-01-002, CP-00001, and CP-00002.

[44] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63.

later was that all skin reactions were minimal to mild and most were absent by follow-up.[45] Skin irritation, erythema, and edema were absent or minimal problems for most patients in the three studies.[46] The most common skin AEs were stinging/burning (12.1-40%), application site erythema (25-50%), application site bruising (0-14.9%), and edema (4-43.8%).[47] The skin reactions were related to the use and removal of the adhesive and the physical effects of infusion.[48] FDA determined that the clinical skin effects may have been secondary to toxicity from subcutaneously administered furosemide, but the toxicity, if it is responsible for some of the pain, erythema, and bruising, was mostly mild and therefore of limited concern.[49] The skin tolerability of Furoscix was found to be adequate.[50]

b. Second Submission and Complete Response

On June 30, 2020, scPharmaceuticals resubmitted NDA 209988 (submission SN0034) for FDA's review. During this review cycle, the applicant initially proposed to use the Furoscix pre-change pump, as was done in the first review cycle, but changed the device component to a proprietary injection device based on the SmartDose® Gen II 10 mL delivery system during this review cycle.[51]

On December 3, 2020, FDA issued a second complete response letter. The letter explained that, among other issues, the applicant had changed the device component during this review cycle, which raised questions about the relevance of all documentation previously provided by the applicant and how such documentation relates to the safety and effectiveness of the to-be-marketed drug product.[52] As a result, FDA could not determine whether the information presented by the applicant supported the safety and effectiveness of the to-be-marketed product.[53] In addition, the letter explained that the product lacked appropriate alarms to notify users in a timely fashion of occlusion events (i.e., a blocking of delivery of the medication into the patient's body) so that a user would not unknowingly experience an underdose event for a significant period of time.[54] The letter also explained that the applicant had not provided evidence for all essential performance requirements for an infusion pump.[55]

c. Third Submission and Approval

[45] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63.

[46] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63.

[47] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 64.

[48] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 64.

[49] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 64.

[50] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 66.

[51] See NDA 209988, Cross-Discipline Team Leader Review (Dec. 2, 2020), at 1-2.

[52] See NDA 209988, Complete Response (Dec. 3, 2020), at 1-2. See also NDA 209988, Cross-Discipline Team Leader Review (Dec. 2, 2020), at 3, 5.

[53] See NDA 209988, Complete Response (Dec. 3, 2020), at 1-2.

[54] See NDA 209988, Complete Response (Dec. 3, 2020), at 7.

[55] See NDA 209988, Complete Response (Dec. 3, 2020), at 11.

On April 8, 2022, scPharmaceuticals resubmitted NDA 209988 (submission SN0058) for FDA's review. The device component of the drug product is a proprietary Furoscix on-body infusor, which is based on the SmartDose® Gen II 10 mL delivery system.[56] Based on the CDRH classification of this infusor device component as an injection device, rather than an infusion pump, as in the first two review cycles, the information provided by the applicant was found to be adequate to address risks associated with use of the product.[57] With the device component deficiencies addressed, FDA approved Furoscix (NDA 209988) on October 7, 2022.

D. NDA 217294 for Lasix ONYU (Furosemide) Subcutaneous Injection

The Lasix ONYU application (NDA 217294) was submitted pursuant to section 505(b)(2) of the FD&C Act and relies upon FDA's previous findings of safety and effectiveness for Furosemide Injection for intravenous or intramuscular use (NDA 018667) held by Hospira, Inc.[58] Lasix ONYU is a drug-device combination product, which consists of an on-body infusor with a prefilled cartridge that adheres to a patient's abdomen (b) (4) (b) (4).[59] The proposed indication for Lasix ONYU is (b) (4).[60]

II. Legal and Regulatory Background

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs).

i. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[61] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as 505(b)(1) NDAs or stand-alone NDAs.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed,

[56] See NDA 209988, Cross Discipline Team Leader Review (Oct. 3, 2022), at 2.

[57] See NDA 209988, Cross Discipline Team Leader Review (Oct. 3, 2022), at 4.

[58] See NDA 217294, Reviewer Guide (Apr. 19, 2004), SQ Innovation, Inc., at section 1.1.

[59] See NDA 217294, Reviewer Guide (Apr. 19, 2004), SQ Innovation, Inc., at section 1.2.

[60] See NDA 217294, Reviewer Guide (Apr. 19, 2004), SQ Innovation, Inc., at section 1.2.

[61] See section 505(b)(1)(A) of the FD&C Act.

recommended, or suggested in the proposed labeling, and that it meets other applicable requirements.[62]

ii. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[63] amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[64] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[65] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[66]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the "full reports" requirement in section 505(b)(1)(A)(i) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[67] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the applicant owns or to which it has a right of reference, the 505(b)(2) applicant may also rely on, for example, the Agency's findings of safety and/or effectiveness for one or more previously approved drugs.[68]

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[62] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

[63] Public Law 98-417 (1984).

[64] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent (BE) to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only a 505(b)(2) NDA, it is not necessary to discuss the ANDA pathway here.

[65] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[66] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[67] Section 505(b)(2) of the FD&C Act provides for approval of an application:

> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

See 21 CFR 314.3(b) (defining right of reference or use).

[68] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 &

A 505(b)(2) application can be submitted for a change to a previously approved drug and, in some instances, may describe a drug product with substantial differences from a listed drug.[69] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can bridge[70] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability (BA)[71] of the two products, or other appropriate scientific information. FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.[72] FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. The 505(b)(2) pathway permits applicants and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the listed drug on which the 505(b)(2) application seeks to rely.[73]

B. 3-Year Exclusivity Under the FD&C Act

This section explains the framework applied by the Agency in determining whether 3-year exclusivity recognized for an approved drug product blocks approval of a subsequent pending 505(b)(2) application. It explains the Agency's reasoning in interpreting "conditions of approval" as the innovation established by the new clinical investigations essential to approval of the

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C5, 2002P-0447/CP1, and 2003P- 0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

[69] In October 1999, the Agency issued a draft guidance for industry titled "Applications Covered by Section 505(b)(2)" (505(b)(2) Draft Guidance) which states that "[a] 505(b)(2) application may be submitted for an NCE [new chemical entity] when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[70] The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the relied-upon FDA-approved drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA. See FDA's Guidance for Industry: "Determining Whether to Submit an ANDA or a 505(b)(2) Application" (May 2019), at 4.

[71] *BA* is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action (21 CFR 314.3(b)). BA data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics (PK) of the drug. See, e.g., FDA's Guidance for Industry: "Bioavailability Studies Submitted in NDAs or INDs — General Considerations" (Apr. 2022) (BA NDA/IND Guidance), at 2.

[72] See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P- 0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[73] 21 CFR 314.54(a) states that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug."

eligible product. As further discussed below, to identify this innovation, the Agency asks: what unique clinical question(s) about the safety and/or efficacy of the active moiety for the relevant use do the new clinical investigations essential to approval answer for the first time?

In sum, as explained below, the conditions of approval to which 3-year exclusivity applies are defined by a drug product's innovation supported by the new clinical investigations, which the Agency identifies by comparing the product to previously approved drugs with the same active moiety. The scope of innovation thus is determined relative to previous drug approvals. Its scope may be further defined by particular characteristics of the product supported by the new clinical investigations essential to approval, if these characteristics are clinically meaningful.

i. General Framework

An application for a drug containing a previously approved active moiety[74] (including a 505(b)(2) application) is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The statute and regulations for 3-year exclusivity describe which approved NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval, meaning that approval will be delayed until the expiration of that exclusivity.

For NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:

> *If an application submitted under subsection (b) [of this section] for a drug, which includes an active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been approved in another application approved under subsection (b) [of this section], is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in subsection (b)(1)(A)(i) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[75]

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for drugs that are not eligible for 5-year new

[74] FDA regulations define "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 CFR 314.3(b).

[75] See section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4). Section 505(j)(5)(F)(iii) of the FD&C Act similarly describes the conditions under which approval of an ANDA will be blocked by 3-year exclusivity.

chemical entity (NCE) exclusivity (because they contain an active moiety "that has been approved in another application")[76] are eligible for 3-year exclusivity if they include new clinical investigations (other than BA studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA's implementing regulations interpret certain aspects of the statutory language regarding 3-year exclusivity. Among other things, they define the terms *clinical investigation*,[77] *new clinical investigation*,[78] *essential to approval*,[79] and *conducted or sponsored by the applicant*.[80]

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (underlined), often referred to as the bar clause, describes the conditions under which certain 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity.

Under the Agency's interpretation of the bar clause, a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. The first step of the scope inquiry focuses on the drug with 3-year exclusivity. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause, i.e., "a drug, which includes an active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been approved in another application." Thus, 3-year exclusivity for a drug only bars drugs that contain the same active moiety (or the same active moieties for fixed-combination drugs). The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred.

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[76] The longest period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is provided for a drug "no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) of which has been approved in any other application under [section 505(b)]." FDA has interpreted this exclusivity to generally prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

[77] "Clinical investigation" is defined as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." 21 CFR 314.108(a). "Bioavailability study" is defined as "a study to determine the bioavailability or the pharmacokinetics of a drug." 21 CFR 314.108(a).

[78] "New clinical investigation" is defined, in relevant part, as "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 CFR 314.108(a).

[79] "Essential to approval" means "with regard to an investigation, that there are no other data available that could support approval of the NDA." 21 CFR 314.108(a).

[80] "Conducted or sponsored by the applicant" is defined, in relevant part, as "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation." 21 CFR 314.108(a). The preamble to FDA's final rule on Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338 (Oct. 3, 1994) (1994 Final Rule) also described examples of studies that would not qualify for exclusivity.

The Agency's interpretation of "conditions of approval," and its approach to assessing whether exclusivity blocks approval of a 505(b)(2) application, are discussed below.

ii. Interpretation of "Conditions of Approval"

Although neither the statute nor the regulations define the phrase *conditions of approval* for purposes of determining whether exclusivity blocks approval of a 505(b)(2) application,[81] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[82] addresses the Agency's interpretation. It makes clear FDA's view that conditions of approval for the purposes of 3-year exclusivity means the innovative change for which new clinical investigations are essential to approval:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[83]

FDA interprets the scope of exclusivity to be related both to the underlying *new clinical investigations* that were essential to the approval and to aspects of the approval that were supported by those new clinical investigations. Exclusivity does not cover aspects of the drug product for which new clinical investigations were not essential.

Thus, in the case of an application submitted for a drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations (other than BA studies) essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity- protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval.

The Agency's interpretation ties the incentive provided by 3-year exclusivity to the innovative change supported by the new clinical investigations conducted by an applicant, reflecting the way in which the statute's *eligibility clause* and *bar clause* operate together. That is, it considers the "conditions of approval" to which exclusivity applies under the bar clause to be determined by the "new clinical investigations (other than bioavailability studies) essential to the approval of the application"[84] that establish the drug product's eligibility for exclusivity. In this way, "[t]he [FD&C Act] sets up a 'logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [NDA], and the scope of any resulting

[81] 21 CFR 314.108(a) and 314.108(b)(4)(iv).

[82] See generally Abbreviated New Drug Application Regulations, 54 FR 28872 (Jul. 10, 1989).

[83] 1989 Proposed Rule at 28896-97.

[84] FD&C Act § 505(c)(3)(E)(iii).

three-year exclusivity.'"[85] The interpretation "respects the relationship between [section 505(c)(3)(E)(iii)]'s complementary clauses, Congress's intent, and is a first step toward filling the statutory ambiguity."[86] The legislative history indicates that Congress intended 3-year exclusivity to protect only innovations that required the support of new clinical investigations essential to approval.[87]

Moreover, we believe that other interpretations of "conditions of approval" would lead to results that are inconsistent with the statute's purpose. For example, under a different interpretation, *conditions of approval* might be understood to mean all of the conditions stated in FDA-approved labeling. That is, the conditions of approval might include all the information in approved labeling, meaning that exclusivity for one product would block a subsequent product's approval only where the labeling is exactly the same. But this interpretation would risk rendering an eligible product's exclusivity meaningless because of the high likelihood that a subsequent product's labeling would differ from the protected product's labeling in at least some ways. If any difference in labeling were sufficient to take a subsequent product outside of the scope of a prior approved product's exclusivity, 505(b)(2) applications (which are not subject to a "same labeling" requirement) would almost never be blocked.[88] Interpreted in this manner, section 505(c)(3)(E)(iii), which governs the application of 3-year exclusivity to 505(b)(2) applications, might be considered superfluous because the only products that might be blocked by such narrow exclusivity likely would be ANDAs, which are subject to the exclusivity provision in section 505(j)(5)(F)(iii) of the FD&C Act. It is also significant that section 505(c)(3)(E)(iii) does not make reference to approved labeling. Thus, it is reasonable to conclude that the scope of exclusivity is not limited to blocking products only with the same labeling. At the same time, if "conditions of approval" means that any approved uses or characteristics of the product with exclusivity might block approval of a subsequent 505(b)(2) application with the same active moiety if it has any of the same characteristics or uses (even those not associated with new clinical investigations essential to approval), then almost any 505(b)(2) application with the same active moiety would be blocked. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.[89] Given that section 505(c)(3)(E)(iii) is silent on reliance, a subsequent 505(b)(2)

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[85] *See Elois Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 120-21 (D.D.C. 2015).

[86] *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, at 24 (D.D.C. 2019).

[87] *See* 59 Fed. Reg. 50338, at 50357 (Oct. 3, 1994).

[88] As the court noted in its decision in *Braeburn Inc. v. FDA*, "[p]rotecting exclusivity rights only if a follow-on product matches every condition listed in the first product's label would curtail exclusivity narrowly to exclude only precisely identical drug products, a result plainly at odds with Congress's goal of incentivizing research with market exclusivity." 389 F. Supp. 3d at 21. In that case, Braeburn Inc. challenged the Agency's conclusion that 3-year exclusivity recognized for a previously approved monthly injectable buprenorphine product, Sublocade, precluded final approval of Braeburn's monthly buprenorphine product, Brixadi. The court vacated the Agency's exclusivity decision and remanded to the Agency to reconsider whether approval of Braeburn's NDA was blocked by Sublocade's exclusivity and to provide additional explanation for its decision. FDA issued its reconsidered exclusivity analysis in a November 7, 2019 letter (referred to here as the "Braeburn Remand Letter") (No. 19-cv-00982-BAH, ECF No. 53 (D.D.C. Nov. 7, 2019)).

[89] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court

application need not rely upon the drug product with unexpired exclusivity to be considered within the scope of and blocked by that product's exclusivity.[90]

iii. Defining the Scope of Exclusivity

The link between the scope of exclusivity and the new clinical investigations essential to approval means that, in assessing the scope of 3-year exclusivity for a drug product containing the same active moiety or same active moieties as a previously approved drug product, the Agency looks at the innovation represented by the drug product eligible for exclusivity relative to previously approved drug products.[91]

a. Identifying the Innovation Relative to Previously Approved Drug Products

In identifying the innovation, the Agency asks a key question: for what aspects relative to previously approved drug products were the new clinical investigations essential to approval? More specifically, we ask *what unique clinical question(s) about the safety and/or efficacy of the active moiety for the relevant use do the new clinical investigations essential to approval answer for the first time?* By framing the inquiry in this way, the Agency seeks to ensure that the incentive provided by exclusivity rewards sponsors for conducting studies that will answer clinical questions relevant to the drug's approval, and not for establishing or confirming what is already known about the drug.

To determine the clinical questions for which the new clinical investigations were essential to approval, the Agency evaluates what has been shown in clinical investigations for the product at issue in comparison to what was known about previously approved drug products with the same active moiety. The analysis is, by definition, context-specific: a change that may have significance as an innovation in one instance—that is, a change for which studies were needed to demonstrate its safety or efficacy—may not require further studies in another instance, for example, in another therapeutic area. The nature of what aspect(s) of a drug will constitute an innovation must be determined on a case-by-case basis.[92]

b. Effect of Previously Approved Drug Products on Scope of 3-Year Exclusivity

Because the Agency evaluates the scope of a drug product's innovation in relation to previously approved drug products, the scope of 3-year exclusivity for a drug product is generally affected by previously approved drug products containing the same active moiety or the same active

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concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although the latter two cases involved the statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

[90] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F.Supp.3d 104, at 116-120.

[91] A product eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) will by definition not be the first approved product containing the active moiety (or active moieties) at issue.

[92] For example, circumstances including the development of new technologies or evolving understanding of a disease area may affect whether an aspect of a drug constitutes an innovation.

moieties.

In practice, where two drug products that have the same active moiety or same active moieties are sequentially approved, the result is often that the scope of exclusivity of the second drug product is limited—often narrower in scope—relative to any exclusivity recognized for the first drug product. This is because exclusivity is recognized only for new clinical investigations that are "essential to approval," which "means, with regard to an investigation, that there are no other data available that could support approval of the NDA."[93] As explained above, exclusivity does not protect aspects of the drug product for which new clinical investigations were not essential – that is, it does not cover aspects of the product which have already been demonstrated to be safe and effective (or which could be supported without the new clinical investigations).

If an earlier-approved drug product was approved for a particular condition of approval, new clinical investigations would not be considered "essential" to support the same condition of approval for a later-approved drug product containing the same active moiety. Rather, the new clinical investigations would be considered essential only to support conditions of approval for the later-approved drug product that are different from the conditions of approval of the earlier-approved drug product. Thus, because 3-year exclusivity generally covers only the innovative differences from a previously approved product, as a practical matter each later-approved product typically will have a narrower scope of exclusivity than the product(s) approved previously.

Under FDA's interpretation, the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety or active moieties. A drug product may, however, qualify for exclusivity for an aspect that differs from the earlier-approved drug product, thus providing a continued exclusivity incentive—albeit one that is typically narrower in effect—for manufacturers to conduct new clinical investigations of previously approved drugs. In this way, the Agency's interpretation encourages both further innovation and expansion of what is known about a drug.[94]

III. Analysis

[93] 21 CFR 314.108(a). See 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) ("The phrase 'essential to the approval' suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement . . . '[T]o qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective.'" (internal citations omitted)); 1989 Proposed Rule at 28900 ("In addition, there must not be an already approved drug product for which the applicant could submit an ANDA or 505(b)(2) application. A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.").

[94] Under certain circumstances, it may be appropriate for the Agency to consider whether certain characteristics of the eligible product, supported by new clinical investigations essential to the product's approval, may further define the scope of its innovation (i.e., the scope of its exclusivity). This assessment requires the Agency to make a fact-specific determination. The Agency does this by determining whether the relevant characteristics of the drug studied are clinically meaningful (for example, as opposed to merely reflecting the conditions under which the study was conducted). See Braeburn Remand Letter at 24-25; Memorandum re: Whether the unexpired 3-year exclusivity for Jatenzo (NDA 206089) delays the approval of Tlando (NDA 208088) at 11-12 (Dec. 8, 2020) (Jatenzo Memorandum).

This section applies the 3-year exclusivity framework to analyze whether Furoscix (NDA 209988) is eligible for 3-year exclusivity and, if yes, whether any such exclusivity should delay approval of Lasix ONYU. The Board concludes that Furoscix satisfies the requirements for 3-year exclusivity under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and 21 CFR 314.108. The Board therefore recommends that the 3-year exclusivity for Furoscix should delay the approval of Lasix ONYU because the Lasix ONYU application is seeking approval of the exclusivity-protected condition of approval for Furoscix.

A. Furoscix is Eligible for 3-Year Exclusivity

Upon review of the administrative record, the Board concludes that Studies scP-01-002, CP-00001, and CP-00002, which included skin tolerability assessments conducted to evaluate the safety of the product's subcutaneous route of administration, were new clinical investigations essential to the approval of Furoscix that were conducted or sponsored by scPharmaceuticals.

First, Studies scP-01-002, CP-00001, and CP-00002 were experiments in which the pH neutral formulation of furosemide used in Furoscix was administered to human subjects. Therefore, these three studies qualify as clinical investigations under 21 CFR 314.108 if they are considered "other than" bioavailability studies. As described above, all three studies included prespecified clinical endpoints for assessing skin tolerability, which was the only product specific safety concern that FDA had for Furoscix. The information from these skin tolerability assessments was necessary to establish the safety of the Furoscix formulation for subcutaneous administration. In terms of study design, a skin irritation and sensitization assessment can be conducted as part of other safety and efficacy clinical trials for a drug product, as was done for these three studies. The skin assessments from these three studies included photographs and skin irritation scores.[95] Photographs were taken at baseline, immediately after placement, one hour post-removal, and one week later to document skin reactions.[96] Although Studies scP-01-002, CP-00001, and CP-00002 also collected information on the bioavailability of the drug product, the clinical skin irritation objectives of the skin tolerability tests conducted in the studies were not bioavailability endpoints and went beyond routine safety monitoring. Accordingly, we consider Studies scP-01-002, CP-00001, and CP-00002 to be "other than" bioavailability studies (which would generally capture only data regarding the bioavailability of pharmacokinetics of a drug along with routine adverse event data),[97] and thus meet the definition of clinical investigations under 21 CFR 314.108.

Studies scP-01-002, CP-00001, and CP-00002 were also new clinical investigations under 21 CFR 314.108 because the study results were submitted to FDA for the first time in NDA 209988 and, therefore, the results of these studies were not previously relied upon to support substantial evidence of effectiveness of a previously approved drug product or for safety in a new patient population.

Additionally, Studies scP-01-002, CP-00001, and CP-00002 were essential to the approval of NDA 209988. For an investigation to be essential to approval, there can be no other data

[95] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63.

[96] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 63.

[97] See 21 CFR 314.108.

available that could support the approval of the application.[98] In other words, there can be no other data available that could support the approval of the aspect(s) of the application for which the investigation is considered essential. As noted above, in the pre-IND and IND phases, FDA advised the applicant to include targeted assessment of adverse events such as pain, rash, and itching at the site of the product's connection with the skin.[99] FDA needed this information because given its subcutaneous route of administration, the only product specific safety concern for Furoscix was skin tolerability.[100] In contrast, the systemic risks of furosemide are well-established and were expected to be the same for subcutaneous furosemide compared to IV administration of furosemide. The skin tolerability data from Studies scP-01-002, CP-00001, and CP-00002 did not raise any significant safety concerns.

These studies provided the only available data to support a safety finding that a subcutaneous administration of furosemide did not raise skin toxicity concerns. Therefore, the studies were essential to the finding of safety of the proposed product and the approval of NDA 209988 for Furoscix.

Finally, Studies scP-01-002, CP-00001, and CP-00002 qualify as being conducted or sponsored by scPharmaceuticals under 21 CFR 314.108 because scPharmaceuticals is named on Form FDA-1571 as the sponsor of the IND under which the three studies were conducted.[101]

Therefore, the Board recommends that Studies scP-01-002, CP-00001, and CP-00002 were new clinical investigations essential to the approval of NDA 209988 for Furoscix, and, thus, Furoscix qualifies for 3-year exclusivity.

B. Scope of 3-Year Exclusivity

Having recommended that Furoscix is eligible for 3-year exclusivity, we must analyze whether the 3-year exclusivity for Furoscix should delay the approval of Lasix ONYU. This entails an evaluation of the scope of 3-year exclusivity for Furoscix under the two-step approach described in section II.B.

The first step focuses on the drug with 3-year exclusivity, because 3-year exclusivity for a drug only bars approval of drugs that contain the same active moiety (or the same active moieties for fixed-combination drug products). Furoscix and Lasix ONYU are single-entity drugs that contain furosemide as the active ingredient and as the active moiety. Because Furoscix and Lasix ONYU have the same active moiety, the 3-year exclusivity for Furoscix may bar the approval of Lasix ONYU.

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred. Although the term "conditions of approval" is not defined by the FD&C Act or implementing regulations, FDA interprets the scope of 3-year exclusivity to cover the innovation

[98] 21 CFR 314.108.

[99] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 24.

[100] See NDA 209988, Joint Clinical and Statistical Review (May 16, 2018), at 55 and 59.

[101] See IND 118919, Form FDA-1571 (Mar. 21, 2017).

in the application for which the underlying new clinical investigations were essential to approval as compared to previously approved drug products containing the same active moiety. Therefore, to determine the scope of exclusivity for Furoscix, FDA must determine the innovation for which a new clinical investigation was essential to approval, and for which 3-year exclusivity attaches. This innovation is assessed relative to previously approved drug products containing the same active moiety. FDA determines what unique clinical question(s) about the safety and/or effectiveness of the active moiety for the relevant use a new clinical investigation essential to approval answers for the first time. If a later 505(b)(2) NDA is seeking the exclusivity-protected conditions of approval of an earlier approved NDA with the same active moiety, it will be blocked from approval even if the two products differ in other ways.

i. Innovation for Which the New Clinical Investigation Was Essential

Furosemide has a long history of use in the United States and there are many previously approved NDAs. Furosemide was approved first in 1966 as an oral tablet and later approved in 1968 as an injection formulation for intravenous and intramuscular administration and as an oral solution. For example, the listed drug, Furosemide Injection for intravenous or intramuscular use (NDA 018667) held by Hospira, Inc., was approved in May 1982. NDA 018667 is indicated for the "treatment of edema associated with heart failure, cirrhosis of the liver, and renal disease" in adults and pediatric patients and "[a]cute pulmonary edema as adjunctive therapy." [102] Similarly, Furosemide Tablets (NDA 018487) for oral use held by Mylan Pharmaceuticals, Inc. was approved in August of 1981. NDA 018487 is indicated "in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome" and "in adults for the treatment of hypertension alone or in combination with other antihypertensive agents."[103] Furoscix was originally indicated for the treatment of congestion due to fluid overload in adult patients with NYHA Class II and Class III chronic heart failure.[104] "Congestion due to fluid overload" is a type of edema and NYHA Class II/III heart failure is a subset of congestive heart failure; thus, the indication for NDAs 018667 and 018487 fully encompass the original indication and patient population for Furoscix. Accordingly, a new clinical investigation was not needed to demonstrate for the first time the safety and effectiveness of furosemide for Furoscix's originally approved indication or patient population because these questions had been answered by the approvals of previous products.

In contrast, new clinical investigations were needed to demonstrate the safety of Furoscix's novel subcutaneous route of administration, and the scope of 3-year exclusivity is thus limited to route of administration. Furoscix's subcutaneous route of administration was novel because furosemide injection products were previously approved for IV or IM administration, as with NDA 018667. The data from the skin tolerability assessments conducted as part of Studies

[102] See, NDA 018667, Prescribing Information, "Highlights of Prescribing Information" (Aug. 31, 2022), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018667Orig1s043Corrected_lbl.pdf.

[103] See NDA 018487, Prescribing Information, "Indications and Usage" (Mar. 8, 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018487s043lbl.pdf.

[104] Furoscix (NDA 209988), prescribing information, section 1 "Indications and Usage" (Aug. 31, 2022), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209988Orig1s000Correctedlbl.pdf.

scP-01-002, CP-00001, and CP-00002 did not raise any significant safety concerns, and thus demonstrated, for the first time, the safety of Furoscix's subcutaneous route of administration.

In summary, the Board recommends that the innovation represented by Furoscix that is supported by Studies scP-01-002, CP-00001, and CP-00002 is the subcutaneous route of administration for which these studies were essential to approval.

C. Approval of Lasix ONYU (NDA 217294) is Delayed by Furoscix's 3-Year Exclusivity

We now consider whether the approval of NDA 217294 for Lasix ONYU should be delayed by the 3-year exclusivity for Furoscix. Lasix ONYU is a proposed drug-device combination product, which consists of an on-body infusor with a prefilled cartridge that adheres to a patient's abdomen (b) (4) (b) (4).[105] The proposed indication for Lasix ONYU is (b) (4) (b) (4).[106] Lasix ONYU is seeking approval of Furoscix's exclusivity-protected condition of approval because Lasix ONYU's proposed route of administration is subcutaneous. Therefore, the approval of Lasix ONYU should be delayed by the 3-year exclusivity of Furoscix.

IV. Conclusion

For the reasons described above, the Board recommends that Furoscix (NDA 209988) is eligible for 3-year exclusivity because it meets the statutory criteria described in sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act. Because Lasix ONYU (NDA 217294) is seeking approval of Furoscix's exclusivity-protected condition of approval, the Board recommends that the approval of Lasix ONYU should be delayed by the unexpired 3-year exclusivity of Furoscix.

[105] See NDA 217294, Reviewer Guide (Apr. 19, 2004), SQ Innovation, Inc., at section 1.2.

[106] See NDA 217294, Reviewer Guide (Apr. 19, 2004), SQ Innovation, Inc., at section 1.2.