K&L GATES

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VIA REGULATIONS.GOV

Division of Dockets Management
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Food and Drug Administration
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CITIZEN PETITION

On behalf of Genus Lifesciences, Inc. ("Genus"), the undersigned submits this Citizen Petition electronically to the Food and Drug Administration ("FDA") under Section 505(q) of the U.S. Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. §§ 10.20, 10.30, 10.31, and 314.150(a)(2)(iv).

Genus requests that the Commissioner of Food and Drugs refuse to accept any submissions by Lannett Company, Inc. ("Lannett") in furtherance of its application submitted under the 21 U.S.C. § 355(b)(2) approval pathway (a "505(b)(2)") for cocaine hydrochloride, 4% and 10%. Any such submissions by Lannett are barred by the new chemical entity exclusivity arising from FDA's approval of Genus's new drug application ("NDA") 209963 under Section 505(c)(3)(E)(ii) of the FDCA.

As explained below:

- Genus obtained approval of NDA 209963 for cocaine hydrochloride nasal solution, 4%, on December 14, 2017;
- NDA 209963 is the first application approved for a cocaine drug product;
- FDA awarded NDA 209963 new chemical entity ("NCE") exclusivity under 21 U.S.C. § 355(c)(3)(E)(ii), which does not expire until December 14, 2022 (five years from approval);
- The FDCA unequivocally states that "no application . . . may be submitted" on the same active ingredient—cocaine—"before the expiration of five years from the date

of the approval of the application," (i.e., the NCE exclusivity period). 21 U.S.C. § 355(c)(3)(E)(ii); and

- No section 505(b)(2) or section 505(j) ("Abbreviated New Drug Application") application may be submitted before December 14, 2022, including any 505(b)(2) submissions by Lannett.

Based on these facts, FDA must refuse to accept any submission by, or on behalf of, Lannett, in furtherance of Lannett's 505(b)(2) application for a cocaine drug product after December 14, 2017. FDA should refuse such submissions by Lannett for at least the following reasons:

First, Congress provides an applicant, like Genus, that obtains FDA approval for the first time on a new chemical entity the benefit of five years of market exclusivity. Congress mandated that "no application . . . may be submitted," and FDA itself defines an "application" to be "the application described under 314.50, including all amendments and supplements to the application." *See* 21 C.F.R. § 314.3. Furthermore, Lannett's failure to obtain approval of its 505(b)(2) application within its 10-month PDUFA date, and its corresponding receipt from FDA of a Complete Response Letter ("CRL"), converts Lannett's pending application into a "resubmission." FDA itself defines a "resubmission" as a *submission* (*see id*.), and Congress mandates that no application "may be submitted" on the same active ingredient before the expiration of the NCE, barring any resubmission. Even if Lannett filed its initial papers in support of a new 505(b)(2) application for a cocaine drug product before FDA awarded NCE exclusivity to Genus's NDA 209963, FDA cannot accept any additional papers, including amendments, supplements, or resubmissions, in support of Lannett's application.

Second, FDA's past statements suggesting that it may permit the submission of a 505(b)(2) application before the approval of another 505(b)(2) application for the same drug that ultimately receives NCE exclusivity are incorrect, contrary to the intent of Congress, and should be rejected. FDA's outdated statements have never been invoked to undermine NCE exclusivity: FDA has never approved a second filed 505(b)(2) application that was "submitted" before the approval of an application receiving NCE exclusivity for the same drug product.

The facts and law demonstrate that FDA may not accept any submissions in furtherance of Lannett's 505(b)(2) application for a cocaine drug product, as discussed in greater detail below.

ACTION REQUESTED

Genus respectfully requests that FDA take the following action:

1. Refuse to accept any further submissions in furtherance of Lannett's 505(b)(2) application for any cocaine product, including any amendments, supplements, or resubmissions.

2. Treat as withdrawn any submissions FDA may have accepted from Lannett in support of Lannett's 505(b)(2) application after December 14, 2017.

3. Consider Lannett's 505(b)(2) application for a cocaine product withdrawn.

The basis for Genus's request is discussed in detail below.

STATEMENT OF GROUNDS

I. Factual Background

A. Goprelto®: Genus's FDA-Approved Cocaine Hydrochloride Intranasal Solution

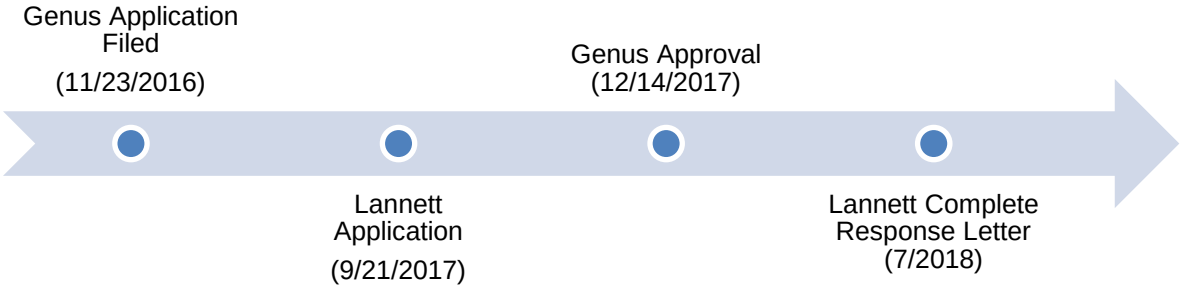
Genus originally filed its application for cocaine hydrochloride intranasal solution 4%, NDA 209963, on November 23, 2016. To support its approval, Genus performed five clinical trials, comprising 742 human subjects, including: one Phase 3 pivotal clinical safety and efficacy trial, one pharmacokinetic study, one study on renally impaired patients, one study on hepatically impaired patients, and one thorough QT study looking for specific heart arrhythmias. Additionally, Genus performed ten non-clinical trials to further characterize the safety of the drug for its intended use.

FDA approved Genus's application on December 14, 2017, permitting Genus to market Goprelto® for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults. Otolaryngologists use cocaine hydrochloride while performing medical procedures such as biopsies, endoscopies, nasal cauterization, foreign body removal, and nasal debridement, among others. Otolaryngologists use cocaine hydrochloride over alternative anesthetics because it provides, *inter alia*, localized vasoconstriction, i.e., the ability to constrict blood vessels thereby reducing bleeding during medical procedures.

The decision to approve an application, and the determination of whether and how much exclusivity should be granted, are two separate issues considered by FDA. Accordingly, after Genus's application was approved, FDA had to decide which, if any, exclusivity applied. Sections 505(c) and (j) of the FDCA provide for either three years or five years of marketing exclusivity for drugs approved in NDAs. The length of exclusivity depends on whether clinical trials were needed to support approval and whether the drug has ever been approved before. FDA awarded Goprelto® NCE exclusivity under section 505(c)(3)(E)(ii) on February 16, 2018, pursuant to these statutory exclusivity provisions and corresponding implementing regulations. Goprelto®'s NCE exclusivity is currently set to expire on December 14, 2022, which is five years from approval.

B. Lannett's NDA for Cocaine Hydrochloride Topical Solution

Lannett apparently filed a 505(b)(2) application for a cocaine drug product on September 21, 2017 ("Lannett 505(b)(2) application") prior to the approval of Genus's Goprelto®.[1]



Commentators have referred to this scenario as "dueling applications," where two applications eligible for NCE exclusivity are filed before the approval of either.

In November 2018, Lannett publicly stated that FDA issued a Complete Response Letter to Lannett in July 2018 "which required an additional study and other information," and Lannett "is in the process of addressing the Complete Response Letter[.]" Exhibit 2.[2]

II. Legal Overview

A. Hatch-Waxman Exclusivities

In 1984 Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 ("Hatch-Waxman Amendments"). This Act created an incentive structure that balanced Congress's desire to increase innovation while providing consumers with access to more affordable medicines.[3]

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[1] According to Lannett, its PDUFA date is July 21, 2018, which is presumably within 10 months of the official submission date. *See* Press Release, Lannett Announces FDA Acceptance of 505(b)(2) New Drug Application for Cocaine Hydrochloride Topical Solution, a Proprietary Anesthetic Product (Dec. 1, 2017) Exhibit 1 ("The FDA has assigned a Prescription Drug User Fee Act (PDUFA) goal date of July 21, 2018, ten months from the official NDA submission date."). If the application was filed in September 21, 2017, it may have been submitted in July 2017.

[2] Lannett Co. Inc., Form 10-Q at 34 (Nov. 8, 2018) Exhibit 2; *see also* Special Investor Conference Call, LANNETT.COM (August 20, 2018), http://lannett.investorroom.com/events-and-webcasts?item=85.

[3] *See generally Actavis Elizabeth LLC v. U.S. Food & Drug Admin.*, 625 F.3d 760, 765 (D.C. Cir. 2010) (finding that the exclusivity provisions "struck a balance between expediting generic drug applications and protecting the interests of original drug manufacturers" (citations omitted)).

Congress recognized that the research and development costs associated with bringing a new drug to market were high.[4] To ensure that manufacturers had the incentive to make this investment, Congress created exclusivity periods whereby a new drug or use would enjoy a period of exclusivity against competitors. Congress specifically mandated that approvals on new chemical entities be eligible for five years of exclusivity. 21 U.S.C. § 355(c)(3)(E)(ii); 21 C.F.R. § 314.108(b)(2).

Section 505(c)(3)(E)(ii) defines the 5-year NCE exclusivity. It provides in pertinent part the following:

> If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after September 24, 1984, **no application** which refers to the drug for which the subsection (b) application was submitted . . . **may be submitted** under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b). . . .[5]

21 U.S.C. § 355(c)(3)(E)(ii) (emphasis added).[6]

Section 505(c)(3)(E)(ii) contains both an eligibility clause and a bar clause:

> *Eligibility Clause*: A drug is eligible for five years of NCE exclusivity "[i]f an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) . . . ." This eligibility must also be perfected by actual FDA approval of the application: The statute states that the application must be "approved after September 24, 1984."
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> *Bar Clause*: The bar clause prevents the "submission" of any "application" that "refers to the drug" that receives NCE exclusivity. This bar on submission lasts for "five years from the date of the approval of the application" receiving the NCE exclusivity. [7]

Congress made no exceptions to NCE exclusivity in the statute. Instead, Congress prohibits without qualification any NDA submissions for drugs entitled to NCE exclusivity during

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[4] The amendments describe three different routes for obtaining approval to market a prescription drug: 505(b)(1) NDAs; 505(b)(2) NDAs; and Abbreviated New Drug Applications.

[5] *See also* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, §§ 101, 103, 98 Stat. 1585, 1590, 1595–96 (1984).

[6] *See also* 21 U.S.C. § 355(j)(5)(F)(ii).

[7] A 505(b)(2) application or an abbreviated new drug application ("ANDA") may be submitted after the expiration of four years from the date of approval if the 505(b)(2) application or ANDA contains a certification of patent invalidity or noninfringement to a patent listed for the listed drug referenced. 21 U.S.C. § 355(b)(2)(A)(iv), (j)(2)(A)(vii)(IV); *see* 21 C.F.R. § 314.108(b)(2), (3); *see also* 21 U.S.C. § 355(c)(3)(E)(ii), (j)(5)(F)(ii).

the pendency of the exclusivity period. For example, nowhere does the statute state that an application may be submitted before NCE exclusivity expires *if done so before approval of the application under subsection (b)*. Nor does the statute say that an application submitted first in time may supervene on an approved drug's NCE exclusivity. Congress could have chosen any number of such exceptions. But Congress did not do so—it said "**no application** … **may be submitted**". Congress knows how to make an exception, when it wishes, and it made no such exception to NCE exclusivity here.

The statute's plain language makes clear that approval date, not the application date, is critical to perfecting NCE exclusivity. The statute prioritizes the earliest complete submission of an application for a new chemical entity. If a later submitted application obtained approval before the first submitted application, the later submitted application perfects the conditions for NCE exclusivity first—thereby creating a bar against an earlier submitted application. This is consistent with the statute's purpose. The statute intentionally incentivizes the quickest route to market entry of a 505(b)(2) drug, which benefits the public. If the NCE exclusivity was tied only to the application date, this would contravene the statute's policy objective: A first filed application could block all later applicants—including an applicant with a more complete application ready for approval.

B. Legislative History of Section 505(c)(3)(E)(ii)

Prior to the passage of the Hatch-Waxman Amendments, the FDCA required "any new drug" to be approved through a full new drug application ("NDA") process. *See generally*, 21 U.S.C. § 355 (1982).[8] This created a major hurdle for generic drug approval, which required generic applicants to conduct redundant clinical studies. An early attempt to overhaul the FDCA to allow easier access to generics occurred on March 16, 1978, during the Carter Administration, through the 95th Congress's H.R. 16611, the Drug Regulation Reform Act of 1978.[9] This earlier attempt to amend the FDCA never passed.

The legislative history of the Hatch-Waxman Amendments unequivocally voices Congress's concern that the development costs of new chemical entities must be protected. 130 CONG. REC. 24,425 (1984) Exhibit 4 (explaining that the amendment will "give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains")*;* 130 CONG. REC. 23,765 (1984) Exhibit 5 ("There is to be a prospective 5-year waiting period for filing of ANDA's following approval by

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[8] Although FDA established a policy that permitted approval of a generic drug equivalent of a pre-1962 drug under an ANDA, there was no abbreviated avenue for post-1962 generic drugs. *See* 129 CONG. REC. 19,844–19,845 (1983) Exhibit 3 (remarks from Representative Waxman).

[9] The text of the bill is not available online. *See* H.R. 11611 - Drug Regulation Reform Act, 95th Congress (1977–1978), CONGRESS.GOV, https://www.congress.gov/bill/95th-congress/house-bill/11611/text?q=%7B%22search%22%3A%5B%22Drug+REgulation+REform+Act%22%5D%7D&r=2 (last visited Dec. 7, 2018). An identical bill, S. 2755, was also introduced in the Senate on the same day.

FDA of a new chemical entity new drug application. . . . This protects products whose development has taken much time and money in FDA testing and review, but which have little for [sic.] no patent life left when they are finally allowed on the market."); 130 CONG. REC. 24,429 (1984) Exhibit 4 ("We give them 5 years in which to recover their investment.").

Congress was fully aware of the implications for its use of the phrase "no application . . . may be submitted." Other FDA exclusivities block the Secretary from "approving" an application as opposed to prohibiting the "submission" of an application. For example, the three-year exclusivity awarded for new clinical investigations prohibits *approval* of an application, not *submission*. 21 U.S.C. § 355(c)(3)(E)(iii) (stating "the Secretary may not make the approval of an application"). In fact, an earlier proposed, but ultimately failed, version of the NCE exclusivity provision prohibited the *approval* of a second drug application for the same chemical entity for "4 years after the approval of any pioneer new chemical entity drug which, upon FDA approval, is not protected by any existing patent." 130 CONG. REC. 15,847 (1984) Exhibit 6; *see also* H.R. 3605, 98th Cong. (1984) Exhibit 7.[10]

In August 1984, the NCE exclusivity provision was revised to prohibit submission of an application:

> If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection. **No application may be submitted** under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b).

130 CONG. REC. 23,769 (1984) Exhibit 5 (emphasis added).

The difference between blocking "approval" versus blocking "submission" is significant. If the statute blocks *approval*, this allows FDA to accept applications before the expiration of the exclusivity, actively review the application during the exclusivity period, and even grant tentative approval ("TA"). FDA simply cannot grant final approval until the exclusivity expires. If the statute blocks *submission*, on the other hand, FDA cannot even *accept an application* before the expiration of the exclusivity, which effectively postpones FDA review of the application during the exclusivity. Because FDA's review of an application can take months or years, the language that blocks the submission of an application in the draft NCE exclusivity provision was more

[10] This early proposal was criticized by the House Judiciary Committee. The House Judiciary Committee proposed amendments to remove the "authority of the Commissioner of the Food and Drug Administration to grant exclusive marketing authority for unpatentable substances." H.R. Rep. No. 98-857(II) (1984) Exhibit 8. In response, the amended Senate Bill S. 2926 removed the 4-year exclusivity provision for unpatentable products and introduced a 5-year exclusivity provisions for NDAs and ANDAs. *See* 130 CONG. REC. 23,767–23,773 (1984) Exhibit 5.

stringent and effectively elongated the protection for more than five years. For example, if the FDA cannot accept an application until the December 14, 2022 expiration of NCE exclusivity, and it takes another 10 months from submission for the FDA to review a new application on the same drug, the NCE exclusivity effectively provides 10 months of additional benefit to the holder of the exclusivity beyond its expiration.

At least one Senator noticed the change from "approval" to "submission" in the August 1984 proposal. Senator Metzenbaum from Ohio noted that by changing the language, the bill effectively extended the exclusivity beyond five years and prevented any patent challenge by an ANDA applicant during the exclusivity period (because a patent could only be challenged after a second application is filed and the amended language precludes submission). Senator Metzenbaum, however, withdrew his objection to the bill based on Representative Waxman's promise to fix the issue in the House version of the bill:

> Then there is another provision in this bill that breaks even further more new ground, and that is it is a totally new concept. *It provides that the FDA, upon approval of a drug, may grant exclusivity, exclusive rights to use that drug for 5 years*. Then if you read it closely enough, you will learn it really is not 5 years, *it is closer to 6 years because of the date and the manner in which it is written*.
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> Well, that was enough and that was sufficient reason to be concerned about the passage of this legislation. But then we learned just in the last few minutes that the language of the 5-year exclusive marketing provision which the FDA can give may also [sic.], in some way, detour or detract from the right of generic drug manufacturers and perhaps others as well to challenge the patent during that period.
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> I have received an ironclad assurance from the man primarily responsible for the passage of this legislation, the distinguished and well-respected Congressperson from California HENRY WAXMAN, who said if this is a problem, he will see to it that it is taken care of in the House. I want at this point to say very publicly that one of the reasons that I have withdrawn any objection to this bill is because of the distinguished record that the Congressperson from California, Congressman WAXMAN, has had and the confidence that I have in his legislative approach.

130 CONG. REC. 23,767 (1984) Exhibit 5 (emphasis added). The Senate voted to pass S. 2926 on August 10, 1984.

On September 6, 1984, House Bill H.R. 3605 was introduced in the House again,[11] along with individual amendments to it. Keeping his promise to Senator Metzenbaum,

[11] The original bill was introduced, followed by the Judiciary Committee Amendments led by Mr. Kastenmeier. 130 CONG. REC. 24,420 (1984) Exhibit 4. Mr. Kastenmeier explained why the previous proposal for four year exclusivity for non-patentable drugs was removed, and deferred to Mr. Waxman on the replacement with the three and five year exclusivities proposed. *Id*.

Representative Waxman introduced an amendment to the five-year exclusivity provision allowing a patent challenge one year before expiration (the so-called "NCE-1" provision): The amendment included language identical to current law. Representative Waxman explained the amendments:

> Mr. Chairman, this amendment makes several changes to title I of the bill to incorporate compromises reached in negotiations between the brand name drug industry and the generic drug industry. . . .
>
> First, the amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of the legislation. *This provision will give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains*.
>
> Generic drugmakers that wished to challenge the validity of any patent life remaining on such drugs would not be barred from doing so. Such patent litigation could commence at the expiration of the fourth year of the period and the generic drugmaker could begin marketing after a favorable court decision or 7 ½ years after approval of the brand name drug, whichever occurs first.

130 CONG. REC. 24,425 (1984) Exhibit 4 (emphasis added). The House ultimately passed the bill and pursuant to House Resolution, H.R. Res. 569, 98th Cong. (1984), the House called up Senate Bill, S. 1538, and inserted H.R. 3605 as passed. *Id.* at 24,458–65. On September 12, 1984, the Senate considered S. 1538, which was a successor to previously passed S. 2926, and agreed to the House amendments. 30 CONG. REC. 24,970–24,979 (1984) Exhibit 9. On September 24, 1984, Ronald Reagan signed the Hatch-Waxman Amendments of 1984 into law.

A likely explanation for the change from blocking "approval" to blocking "submission" is the fact that, if the NCE exclusivity provision blocked "approval," this would conflict with the 180-day exclusivity afforded to the first generic applicant to file a Paragraph IV certification. For example, if the NCE exclusivity provision had been drafted to allow applicants to file ANDAs during the NCE exclusivity, then a subsequent lawsuit filed by the brand pursuant to a generic's Paragraph IV certification could conceivably be finally adjudicated by a court before the expiration of the five year exclusivity. Under the original Hatch-Waxman Amendments, the 180-day exclusivity began immediately upon a court decision finding a patent invalid or not infringed.[12] Such 180-day exclusivity would be worthless for the generic ANDA applicant because the NCE exclusivity could continue blocking the approval for months or years after the start of the 180-day exclusivity.[13] In short, Congress could not merely block "approval" without eviscerating the 180-day exclusivity incentive for generics.

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[12] The Medicare Modernization Act of 2003 ("MMA") changed the triggering event for 180-day exclusivity to the "first commercial marketing" of the generic drug.

[13] Also, the brand would not benefit from the 30-month stay by suing the generic applicant in the first place.

Regardless of Congress's specific motive, Congress clearly intended drug manufacturers obtaining approval for NCEs to enjoy a five year exclusivity period against all competition. Without this protection, a drug company could not reasonably recoup its investment related to the development of the new drug; and without this, a drug company would have no incentive to develop drug products for new chemical entities.

C. FDA's Implementing Regulations for NCE Exclusivity

In 1994, FDA finalized its rules implementing the exclusivity-related provisions of the Hatch-Waxman Act.[14] The final rule describes NCE exclusivity as follows:

> If a drug product that contains a new chemical entity was approved . . . in an NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, **no person may submit a 505(b)(2) application** or ANDA under section 505(j) of the Federal Food, Drug and Cosmetic Act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved NDA. . . .

21 C.F.R. § 314.108(b)(2) (emphasis added). Under Rule 108(b)(2), if a drug product contains a new chemical entity, then "no person may submit a 505(b)(2) application" for a "drug product that contains the same active moiety as in the new chemical entity" until the five year NCE exclusivity period has expired.

FDA has no separate legislative rule creating an exception for "dueling applications."[15]

III. Because No Applicant May Submit an Application for the Same Drug Product as Another With NCE Exclusivity, FDA Should Not Accept Lannett's Submission of Any Papers in Support of Its 505(b)(2) Application After the December 14, 2017 Approval of Genus's Goprelto®, Including Any Resubmission by Lannett

FDA granted Genus's Goprelto® NCE exclusivity against any cocaine drug product. Section 505(c)(3)(E)(ii) precludes FDA from accepting for submission any *application* for a cocaine drug product before December 14, 2022, which is the expiration of five years from the date of Goprelto®'s December 14, 2017 approval.

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[14] Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338 (Oct. 3, 1994) (to be codified at 21 C.F.R. pt. 314) Exhibit 10.

[15] FDA's regulations state: "[t]he Agency will refuse to file an NDA . . . if any of the following applies: . . . (2) Submission of a 505(b)(2) application . . . is not permitted under section 505(c)(3)(E)(ii) . . . of the Federal Food, Drug, and Cosmetic Act." 21 C.F.R. § 314.101(e). Under this rule, FDA arguably determines after submission of a 505(b)(2) application whether to refuse to file it based on whether another application for the same drug has NCE. In the case of dueling applications, FDA may have already accepted the application before the approval of the application with NCE.

As of the date of this Citizen Petition, FDA may have already improperly accepted amendments, supplements, and additions to Lannett's 505(b)(2) application after Goprelto® was approved on December 14, 2017. Because that information is not public, only FDA and Lannett know. We know, however, that Lannett plans to resubmit its application and submit new information for its application in violation of Section 505(c)(3)(E)(ii). In November 2018, Lannett publicly stated the following:

- "The FDA continues to review the Company's [505(b)(2)] application. . . ." Lannett Co. Inc., Form 10-Q at 34 (Nov. 8, 2018) Exhibit 2.

- FDA issued a Complete Response Letter to Lannett in July 2018 "which required an additional study and other information," and Lannett "is in the process of addressing the Complete Response Letter[.]" *Id*.

- Lannett's 505(b)(2) application "continues to progress with the FDA and we expect to conclude a gating QT study by January." SEEKING ALPHA, LANNETT (LCI) Q1 2019 RESULTS - EARNING CALL TRANSCRIPT at 3 (Nov. 7, 2018) Exhibit 11.

As explained in detail below, Lannett cannot "submit" a "gating QT study," safety update reports, samples, copies of procedures, patent information, amendments, supplements, or anything else because each such submission constitutes part of its "application" for a cocaine product during the period of Goprelto®'s NCE exclusivity. Lannett also cannot "resubmit" its application in response to a CRL because a resubmission constitutes a prohibited submission of an application.

A. The Statute Forbids Lannett From Submitting Anything in Support of Its 505(b)(2) Application after December 14, 2017

FDA defines "application" as a series of submissions during the review period, which includes all amendments and supplements supporting the approval of an NDA:

> **Application**, new drug application, or NDA **is the application described under 314.50, including all amendments and supplements to the application**. An NDA refers to "stand-alone" applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

21 C.F.R. § 314.3 (emphasis added). An application is not a single, discrete package of documents sent to FDA when the applicant begins the application process.[16]

[16] With the initial application, the applicant submits a Form 356h entitled "Application to Market a New or Abbreviated New Drug or Biologic for Human Use." Form 356h Instructions, available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf; 21 C.F.R. § 314.50(a).

If the original submission is accepted as "filed," the applicant must still submit additional information for approval.[17] For example, after the initial submission, "safety update reports" must be "submitted." 21 C.F.R. § 314.50(d)(5)(vi)(b). "Upon request by FDA, the applicant must submit . . . samples," including the drug product, the drug substance used in the product, reference standards, and samples of finished market package. *Id.* § 314.50(e)(1). The applicant "must submit" three copies of the analytical procedures and copies of the label. . . . *Id*. § 314.50(e)(2). "The applicant must submit to FDA additional case report forms and tabulations needed to conduct a proper review of the NDA. . . ." *Id*. § 314.50(f)(3). An applicant may also need to "submit" patent information. *Id*. § 314.50(h).

FDA cannot accept from Lannett a "gating QT study," safety update reports, samples, copies of procedures, patent information, amendments, supplements, or anything else because each submission to FDA in furtherance of the approval of an application constitutes part of the "application" for a cocaine product during the period of Goprelto®'s NCE exclusivity. Accepting any submissions in furtherance of Lannett's 505(b)(2) for any cocaine product after December 14, 2017 and before December 14, 2022 violates the clear mandate of Congress.[18] FDA should treat as withdrawn any submissions in furtherance of Lannett's 505(b)(2) application after December 14, 2017 because such submissions are prohibited by Section 505(c)(3)(E)(ii).

B. FDA Cannot Accept Any Resubmission by, or on Behalf of, Lannett for its 505(b)(2) Application for a Cocaine Drug Product Because the Hatch-Waxman Amendments Preclude Any Submission

FDA cannot permit Lannett to "resubmit" its application in response to a CRL until after the December 14, 2022 expiration of Goprelto® NCE exclusivity.[19]

Congress passed the Prescription Drug User Fee Act ("PDUFA") in 1992 to accelerate FDA's review of drug applications while also allowing FDA to collect fees from drug

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Notably, FDA demands the applicant to "submit a new Form FDA356h with each submission". Form 356h Instructions, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf.

[17] FDA may refuse to file an application based on application deficiencies or regulatory deficiencies. 21 C.F.R. § 314.101(d), (e). Under FDA's own regulations, when FDA receives a purported application for a drug, it "files" the NDA within 60 days of receipt or informs the applicant of the "refusal to file." 21 C.F.R. § 314.101(a); *see also* CENTER FOR DRUG EVALUATION AND RESEARCH, REFUSE TO FILE: NDA AND BLA SUBMISSIONS TO CDER GUIDANCE FOR INDUSTRY at 2 (2017) Exhibit 12.

[18] The Administrative Procedure Act ("APA") provides for the judicial review of the final agency actions by the Food & Drug Administration. 5 U.S.C. § 551 *et seq*. Under the APA, FDA action is unlawful if the agency's action, findings, or conclusions are found to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

[19] Since 1992, Congress amended the original PDUFA several times to increase the fees for filing applications, strengthen FDA performance goals for quicker review, and increase transparency in the drug review process.

manufacturers to fund FDA's review process.[20] Under this accelerated review, if FDA determines that it cannot approve the application in its present form within a specified time, FDA sends the applicant a CRL, indicating that up to that point, all submissions collectively were deficient for approval. 21 C.F.R. § 314.110(a). After an applicant receives a CRL, the applicant has limited options, including withdrawing the application, requesting an opportunity for hearing, or "[r]esubmit[ing] the application . . ., addressing all deficiencies identified in the complete response letter." 21 C.F.R. § 314.110(b).

By Lannett's own public statements, Lannett is not withdrawing its application or requesting an opportunity for hearing. Instead, Lannett plans to resubmit its application. FDA defines a "resubmission" as a submission:

> *Resubmission*, in the context of a complete response letter, is **submission** by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter.

21 C.F.R. § 314.3(b).

Section 505(c)(3)(E)(ii), however, unambiguously precludes Lannett's *submission* related to cocaine until the expiration of Goprelto®'s NCE exclusivity. Because Congress has directly spoken to the precise question at issue—i.e., "may not be submitted"—and the intent of Congress is clear, FDA must give effect to its "unambiguously expressed intent." *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842–43 (1984).

As a policy, this conclusion appropriately dissuades potential applicants from making half-baked "submissions" to FDA in order to beat an NCE exclusivity bar date. In other words, if Lannett suspected that a competitor was near approval of a cocaine product that would receive NCE exclusivity, Lannett may have the incentive to submit a half-baked application before the other application's approval in the hope of exploiting an FDA loophole to Section 505(c)(3)(E)(ii). By closing that door and applying Congress's strict mandate, neither Lannett nor other companies have an incentive to prematurely submit an incomplete application.

In summary, because a "resubmission" after a CRL is itself the "submission," FDA cannot accept a resubmission from Lannett during the period of Goprelto®'s NCE exclusivity. Furthermore, because Lannett is precluded from making any submission until December 17, 2022, FDA should withdraw Lannett's 505(b)(2) application. Under FDA's own rules, FDA "may consider an applicant's failure to take any of such actions within 1 year after issuance of a

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[20] In the fifth authorization of PDUFA, FDA set targets for reviewing an application in a "goals letter," which includes a performance goal to "[r]eview and act on 90 percent of standard NME NDA and original BLA submissions within 10 months of the 60 day filing date." PDUFA V Reauthorization Performance Goals and Procedures; Fiscal Years 2013 through 2017 at 4, Exhibit 13.

complete response letter to be a request by the applicant to withdraw the application." 21 C.F.R. § 314.110(c). In this case, the statute precludes Lannett from taking action, and therefore, FDA should consider Lannett's application withdrawn.[21]

IV. FDA's Prior Statement of Policy Permitting a Later Filed 505(b)(2) Application to be Submitted Despite Another Application Receiving NCE Exclusivity for the Same Drug Is a Non-Binding Advisory Opinion

Since enactment of the Hatch-Waxman Amendments, FDA has never approved a second filed 505(b)(2) application that was "submitted" before the approval of an application receiving NCE exclusivity for the same drug product.[22] This Citizen Petition raises an issue of first impression.

FDA has, however, previously stated in the preamble of its draft regulations implementing the Hatch-Waxman Amendments that it interprets the word "submitted" in Section 505(c)(3)(E)(ii) as permitting FDA to accept 505(b)(2) applications for a drug that ultimately obtains NCE if it is "submitted" before approval of the drug with NCE: "The agency intends to interpret this phrase to mean that any 505(b)(2) application submitted to FDA before the approval of another new drug application that qualifies for exclusivity under Section 505(c)(3)(D)(ii) is not affected by this exclusivity provision." *See* Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, at 28,901 (July 10, 1989) (to be codified at 21

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[21] If Lannett submits a new application after the expiration of Genus's NCE exclusivity period, Lannett would need to file an ANDA, and not a 505(b)(2). *See* 21 C.F.R. § 314.101(d)(9).

[22] In a special situation in 1997, FDA attempted to clean up the poor quality levothyroxine products being marketed as unapproved drugs. Prescription Drug Products; Levothyroxine Sodium, 62 Fed. Reg. 43,535 (Aug. 14, 1997) Exhibit 14. FDA announced that starting on August 14, 2000, it would begin removing unapproved products from the market, thereby encouraging multiple applications. *Id*. at 43,538. FDA also announced that "levothyroxine sodium drug products are new drugs," and "[a]s of June 2001, two orally administered levothyroxine sodium products have been approved by FDA." Guidance for Industry on Levothyroxine Sodium Products, 66 Fed. Reg. 36,794 (July 13, 2001) Exhibit 15. It is unclear whether FDA formally granted NCE to either of these products. Also, in the hyaluronidase case involving ISTA Pharmaceuticals, Inc. ("ISTA"), ISTA filed a Citizen's Petition with FDA demanding that FDA change its NCE exclusivity to a new clinical investigation exclusivity in order to block approval of a competitor. But that case is different. In that case, ISTA received approval of Vitrase (hyaluronidase) in May 2004, based on a reference to FDA's earlier approval of a bovine formulation of hyaluronidase. Citizen Petition from ISTA Pharmaceuticals, Inc. to U.S. Food and Drug Administration at 1 (Apr. 6, 2005) Exhibit 16. In September 2004, FDA granted Vitrase 3-years of marketing exclusivity. *Id.* (citing 21 U.S.C. § 505(j)(5)(D)(iii), (c)(3)(D)(iii)). But in October 2004, FDA told ISTA it was changing its exclusivity to a 5-year NCE, indicating that hyaluronidase was a new chemical entity, never previously approved. *Id*. FDA said that because hyaluronidase is a protein, it had insufficient information to determine whether the active moiety is the same as previously approved. *Id*. at 2. In its Citizen's Petition against FDA, ISTA complained that the 5-year exclusivity determination by FDA was useless because "any new hyaluronidase product submitted for approval is likely to be granted 'new chemical entity' status and five-year exclusivity." *Id*. at 9. FDA denied the petition, but only because each hyaluronidase was deemed a new product. Response to Citizen Petition from U.S. Food and Drug Administration to ISTA Pharmaceuticals, Inc. at 2, 13 (Oct. 25, 2005) Exhibit 17 For example, Amphastar was also granted NCE for a hyaluronidase product. *See id.* at 3 n.4.

C.F.R. pts. 10, 310, 314, 320) Exhibit 18.[23] When FDA published its final rules on October 3, 1994—which became effective on November 2, 1994—FDA did not promulgate a final rule dealing with dueling applications.[24] FDA's 1989 interpretation has never undergone the due process requirements of agency rule-making.

FDA's outdated interpretation contradicts the clear mandate of Congress. Congress stated that "no application . . . may be submitted," and Congress made no exception for dueling 505(b)(2) applications. The indisputable intent was to "give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains." 130 CONG. REC. 24,425 (1984) Exhibit 4. Congress further knew that its prohibition against "submission" as opposed to "approval" effectively extended the prohibition against competition because after the expiration, it would take time for FDA to review the new application. Congress further recognized that the NCE exclusivity granted was more favorable than the other FDA exclusivities, including the three year new clinical investigation exclusivity. One consequence of FDA's 1989 interpretation of Section 505(c)(3)(E)(ii) is that a five year NCE exclusivity becomes less valuable to an applicant compared to the three year new clinical investigation exclusivity. For example, if Genus had a three-year new clinical investigation exclusivity, Lannett's application (although submitted and reviewed) would not be approvable before December 17, 2020.

Specifically, FDA misinterprets both the words "application" and "submitted" in Section 505(c)(3)(E)(ii). Neither is defined in the Hatch-Waxman Amendments.

First, as described in Section III.A above, an "application" is an ongoing negotiation with the FDA for approval; it is not the initial and somewhat arbitrary set of papers sent to the FDA. Under FDA's own definitions, an "application" includes "amendments and supplements." Thus, the unambiguous language of the statute precludes a second applicant like Lannett from continuing to submit its "application," including amendments and supplements, after Genus obtains NCE exclusivity. Second, although FDA focuses on the word "submitted" to support its policy, FDA's interpretation is incorrect. To "submit" means to place oneself in a position of submission or compliance, and therefore, another applicant like Lannett may not place itself in a position of submission or compliance with FDA with regard to a cocaine product if another company, like Genus, has NCE exclusivity. To the extent Lannett's application had already been submitted to FDA before FDA determined Genus's NCE exclusivity, this is irrelevant. Once that determination for NCE exclusivity was made, Lannett's application may not be submitted to FDA after the approval of the application receiving NCE exclusivity. Lannett may

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[23] During notice and comments for its rules, FDA reiterated this interpretation in a subsequent response to comments in 1992. *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,950 (Apr. 28, 1992) (to be codified at 21 C.F.R. pts. 2, 5, 10, 310, 314, 320, 433) Exhibit 19.

[24] Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338 (Oct. 3, 1994) (to be codified at 21 C.F.R. pt. 314) Exhibit 10.

not submit a "gating QT study," safety update reports, samples, copies of procedures, patent information, amendments, supplements, a resubmission, or anything else.

Any interpretation of "submit" that allows FDA to continue to accept amendments, supplements, resubmissions, or any papers from Lannett in furtherance of Lannett's 505(b)(2) application is directly at odds with the language of Section 505(c)(3)(E)(ii) and the intent of Congress: It is contrary to law under the APA, and at odds with FDA's own definitions of "application" and "resubmission" as explained in Section III. Furthermore, FDA's old policy statement is not a legislative rule, and FDA is not bound by it. Policy statements and interpretive rules are not binding and leave an agency free "in any particular case to diverge from whatever outcome the policy statement or interpretive rule might suggest." *Vietnam Veterans of Am. v. Sec'y of the Navy*, 843 F.2d 528, 537 (D.C. Cir. 1988); *see also Sierra Club v. Envtl. Prot. Agency*, 873 F.3d 946, 951 (D.C. Cir. 2017) ("Policy statements 'are binding on neither the public nor the agency,' and the agency 'retains the discretion and the authority to change its position . . . in any specific case.'" (citations omitted)).[25] To the extent FDA deems the preamble statement an advisory opinion subject to 21 C.F.R. § 10.85(d)(1), "it may be amended or revoked at any time after it has been issued." *Id*. § 10.85(g). FDA's preamble statements carry no force of law. *United States v. Regenerative Scis., LLC*, 878 F. Supp. 2d 248, 261–62 (D.D.C. 2012) ("FDA's own regulations provide that statements in a preamble do not carry the force of law."). Therefore, FDA can easily correct its past misinterpretation.

V. Conclusion

Congress created the five year NCE exclusivity to protect the pharmaceutical industry's investment in the development of new chemical entities. Congress could have carved out an exception for dueling 505(b)(2) applications submitted before either application obtained NCE exclusivity: But Congress did not.

FDA should have deemed withdrawn any co-pending 505(b)(2) application for cocaine once Genus obtained NCE exclusivity. At the very least, FDA should refuse to accept any submissions in furtherance of Lannett's 505(b)(2) application for cocaine after December 14, 2017 (the approval date for the first cocaine product) until December 17, 2022 (expiration of exclusivity). Moreover, FDA must withdraw Lannett's 505(b)(2) application now that Lannett has

[25] FDA's past statement regarding dueling 505(b)(2) applications is not a legislative rule because FDA itself stated in the preamble to its draft regulations that "[t]he agency intends to *interpret* this phrase [i.e., "no application . . . may be submitted"] to mean that any 505(b)(2) application submitted to FDA before the approval of another new drug application that qualifies for" NCE exclusivity "is not affected by this exclusivity provision." 54 Fed. Reg. at 28,901 (emphasis added) Exhibit 18. FDA itself views its policy as interpretative at most. FDA also never promulgated a final rule expressly creating the exception for dueling applications, and therefore, the policy statement fails to meet the rulemaking requirements of the APA, 5 U.S.C. § 553. *See, e.g., Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 934 (D.C. Cir. 1997); *Cmty. Nutrition Inst. v. Young*, 818 F.2d 943, 946–49 (D.C. Cir. 1987).

received a CRL because Lannett should not be permitted to "resubmit" its application in response to a CRL.

We therefore respectfully request that the Agency:

1. Refuse to accept any further submissions in furtherance of Lannett's 505(b)(2) application for any cocaine product, including refusing to accept amendments, supplements, or resubmissions.

2. Treat as withdrawn any submissions FDA may have accepted from Lannett in support of Lannett's 505(b)(2) application after December 14, 2017.

3. Consider Lannett's 505(b)(2) application for a cocaine product withdrawn.

ENVIRONMENTAL IMPACT

A categorical exclusion is claimed in accordance with 21 C.F.R. § 25.31(a). Therefore, an environmental impact analysis is not required.

ECONOMIC IMPACT

An economic impact statement will be provided upon request.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and /or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: February 16, 2018.[26] If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Genus Lifesciences Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

[26] Certain facts became known to the party after this date. See above.

Respectfully Submitted,

Michael J. Freno

cc: Jeff Moshal, CEO, Genus Lifesciences, Inc.
Michael H. Hinckle, Partner, K&L Gates LLP

Enclosures