



Philip J. Perry
Latham & Watkins LLP
555 Eleventh Street, N.W., Suite 1000
Washington, DC 20004-1304

Re. Docket No. FDA-2019-P-3855

JAN 10 2020

Dear Mr. Perry:

This letter responds to your citizen petition (Petition) submitted on behalf of Genus Lifesciences, Inc. (Genus or Petitioner),¹ that was received by the Food and Drug Administration (FDA, Agency, or we) on August 14, 2019, as well as the amendments to the Petition received on December 2, 2019 (December 2 CP Amendment), and December 4, 2019 (December 4 CP Amendment). Genus is the new drug application (NDA) holder of Goprelto (cocaine hydrochloride (HCl)) nasal solution (NDA 209963), which was received on November 23, 2016, through the pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and approved on December 14, 2017. Because Goprelto did not contain any previously approved active moiety, upon approval, FDA recognized 5-year new chemical entity (NCE) exclusivity for Goprelto under section 505(c)(3)(E)(ii) of the FD&C Act (21 U.S.C. 355(c)(3)(E)(ii)) and FDA's implementing regulations.² Goprelto's NCE exclusivity expires on December 14, 2022.

Before Goprelto's approval, the Lannett Company, Inc. (Lannett), submitted NDA 209575 for Numbrino (cocaine hydrochloride), 4% and 10% nasal solutions, through the pathway described in section 505(b)(2) of the FD&C Act. FDA received Lannett's 505(b)(2) application on September 21, 2017. After conducting its filing review, FDA determined that Lannett's NDA was sufficiently complete to permit a substantive review and considered the application filed 60 days after the date FDA received it.³ Lannett's application subsequently received a Complete Response (CR) letter on July 20, 2018.⁴

¹ Ownership of the investigational new drug application for Goprelto was transferred several times. Pennsylvania Pain Specialists, P.C. (PPS) opened the initial Pre-IND on May 3, 2013, and FDA received the original new IND 118527 for Goprelto on May 6, 2014. On September 8, 2016, FDA received notification that PPS transferred ownership of IND 118527 to Lehigh Valley Technologies, Inc. (LVT) effective as of September 7, 2016. On June 2, 2017, FDA was notified that LVT underwent a legal name change on May 1, 2017, and the sponsor name of IND 118527 was changed accordingly from LVT to Genus Lifesciences, Inc. For simplicity, the IND sponsor/NDA holder for Goprelto will be referred to as "Genus" throughout this response.

² See 21 CFR 314.3(b) (defining active moiety), 314.108(a) (defining new chemical entity), 314.108(b)(2).

³ See November 29, 2017, letter from Sharon H. Hertz, MD, to Lannett Holdings, Inc., "Filing Communication—Filing Review Issues Identified."

⁴ See July 20, 2018, letter from Rigoberto Roca, MD, to Lannett Holdings, Inc., "Complete Response."

Genus asserts that FDA applied a “substantially more lenient standard” for filing and erroneously filed Lannett’s NDA without the same studies that the Agency purportedly required Genus to provide to secure acceptance for filing.⁵ Genus further asserts that FDA’s regulations prohibit Lannett from resubmitting its 505(b)(2) application in response to the July 2018 CR letter. Genus contends that Lannett may resubmit its application only as an abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act, and only after the expiration of Goprelto’s NCE exclusivity.⁶

Accordingly, in its August 14, 2019, Petition, Genus requests that FDA take the following actions with respect to Lannett’s application:

1. Rescind its acceptance for filing of Lannett’s 505(b)(2) application if Lannett did not complete the QT, renal, hepatic, leachable, and/or other studies⁷ deemed necessary for an NDA for a cocaine hydrochloride product to be sufficiently complete to permit substantive review; and refuse to file any reapplication by Lannett of its application until the expiration of the NCE exclusivity attached to NDA 209963.
2. Rescind its acceptance for filing of Lannett’s 505(b)(2) application that was resubmitted in response to FDA’s [July 2018 CR letter] because such a submission is prohibited by FDA’s regulation on duplicate 505(b)(2) filings, and permit Lannett to resubmit its application only as an ANDA after the expiration of the NCE exclusivity attached to NDA 209963.⁸

In its December 2 CP Amendment, Genus also requests that FDA:

3. [R]efuse to approve any NDA for a cocaine hydrochloride product without completing similar QT, renal, hepatic, and leachable studies conducted by Genus and described in [Genus’s] Citizen Petition that demonstrate the safety and efficacy of the product.⁹

In its December 4 CP Amendment, Genus further requests that FDA:

4. [M]ust accept a new NDA submission from Lannett *only* after Lannett has completed the renal and hepatic toxicity studies that Genus was required to complete for its own cocaine hydrochloride application to be accepted for

⁵ Petition at 2.

⁶ Petition at 2-3.

⁷ To differentiate studies conducted by the sponsor from studies conducted as described in literature, in this response, we refer to sponsor-generated studies as “*dedicated*” studies.

⁸ Petition at 3.

⁹ December 2 CP Amendment at 4.

filing.^{10, 11}

We have carefully considered the Petition, the December 2 CP Amendment, the December 4 CP Amendment, and all comments submitted to the docket. For the reasons described below, the Petition, as amended, is denied. Today, FDA approved Lannett's NDA 209575 for Numbrino (cocaine hydrochloride) nasal solution 4%, indicated for the induction of local anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities of adults.¹²

I. FACTUAL AND LEGAL/REGULATORY BACKGROUND

On February 1, 2019, Genus submitted a citizen petition under docket number FDA-2019-P-0538 requesting that the Agency refuse to accept any submissions by Lannett in furtherance of Lannett's 505(b)(2) application for a cocaine hydrochloride product (Genus February 2019 CP).¹³ Specifically, Genus claimed that any submissions by Lannett were barred by the NCE exclusivity attached to Genus's NDA 209963. FDA issued a detailed response on July 1, 2019 (FDA July 2019 CP Response), denying the Genus February 2019 CP. To the extent that Genus's current Petition raises factual and legal/regulatory issues that overlap with those raised in the Genus February 2019 CP, we refer to the FDA July 2019 CP Response for a more detailed factual and legal/regulatory history.¹⁴ We summarize certain relevant factual and legal/regulatory background issues below.

A. Cocaine

Before the approval of Genus's NDA 209963 for Goprelto, cocaine HCl was marketed as an unapproved drug.¹⁵ Since the 1880s, cocaine has been used clinically in nasal and sinus surgery as a topical anesthetic and vasoconstrictive agent.¹⁶ Because of its high potential for abuse, cocaine is a controlled substance in Schedule II of the Controlled Substances Act (21 U.S.C. 801 et seq.).

¹⁰ December 4 CP Amendment at 1.

¹¹ Although Genus claims this is an additional request, FDA is unable to discern how this request differs from the requests in the Petition and the December 2 CP Amendment.

¹² A copy of the Numbrino approval letter and approved labeling are available on the FDA's web page at <https://www.accessdata.fda.gov/scripts/cder/daf/>.

¹³ A copy of the February 1, 2019, citizen petition is available at <https://www.regulations.gov/docket?D=FDA-2019-P-0538>.

¹⁴ A copy of the July 1, 2019, CP Response is available at <https://www.regulations.gov/docket?D=FDA-2019-P-0538>.

¹⁵ Goprelto Summary Review at 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000SumR.pdf.

¹⁶ See, e.g., M. Redman, 2011, *Cocaine: What is the Crack? A Brief History of the Use of Cocaine as an Anesthetic*, Anesth Pain Med, Autumn; 1(2): 95–97, available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4335732/>.

B. Genus's Goprelto

On November 23, 2016, FDA received Genus's NDA 209963 for cocaine hydrochloride nasal solution, which was submitted under the 505(b)(2) pathway. FDA approved that application with the proprietary name of Goprelto on December 14, 2017. Before the approval of Goprelto, the Agency had not approved any application that contained cocaine as an active moiety. Accordingly, FDA recognized 5-year NCE exclusivity for Goprelto that expires on December 14, 2022.¹⁷

C. Lannett's Numbrino

The Agency received Lannett's 505(b)(2) application (NDA 209575) for cocaine hydrochloride topical solution, 4% and 10%, on September 21, 2017, before the December 14, 2017, approval of Goprelto. After conducting its filing review, FDA determined that Lannett's NDA was sufficiently complete to permit a substantive review and considered the application filed 60 days after the date FDA received it.¹⁸ Lannett's application subsequently received a CR letter on July 20, 2018.¹⁹ Lannett responded to that CR letter on June 21, 2019, by providing additional data to support approval of its NDA.

D. Legal/Regulatory Background: Filing Determinations

To legally market a new drug, an applicant must submit, and FDA must approve, an NDA or ANDA for that drug.²⁰ With respect to NDAs, FDA expects an application to be sufficiently complete upon submission to permit a substantive review.²¹ Within 60 days of receipt of the NDA, FDA makes a filing determination, including whether the NDA is complete and contains the information required as described in section 505(b) of the FD&C Act and FDA's regulations in § 314.50 (21 CFR 314.50).²² FDA will file an application only after it makes a threshold determination that the NDA is sufficiently complete to permit a substantive review.²³ Any

¹⁷ See 21 CFR 314.108(b)(2); see also *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), available at <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>.

¹⁸ See November 29, 2017, letter from Sharon H. Hertz, MD, to Lannett Holdings, Inc., "Filing Communication—Filing Review Issues Identified."

¹⁹ See July 20, 2018, letter from Rigoberto Roca, MD, to Lannett Holdings, Inc., "Complete Response."

²⁰ Section 505(a) of the FD&C Act.

²¹ See 21 CFR 314.101(a)(1) ("Within 60 days after FDA receives an NDA, the Agency will determine whether the NDA may be filed. The filing of an NDA means that FDA has made a threshold determination that the NDA is sufficiently complete to permit a substantive review."); PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022 (PDUFA VI Letter) at 9, available at <https://www.fda.gov/media/99140/download>.

²² See § 314.101(a)(1) (21 CFR 314.101(a)(1)).

²³ See § 314.101(a)(1). See also FDA's draft guidance for industry *Refuse to File: NDA and BLA Submissions to CDER* (December 2017), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/refuse-file-nda-and-bla-submissions-cder-guidance-industry> (when final, this guidance will represent

substantive review issues identified during the filing review will be communicated to the applicant in what is informally referred to as the “Day 74 letter,” which is issued no later than 14 calendar days after the 60-day filing date.²⁴

Incomplete NDAs are subject to a Refuse-to-File (RTF) decision, which means that the application is no longer before FDA for substantive review and an approval decision.²⁵ FDA exercises its RTF authority for incomplete applications to optimize using both the applicant’s and FDA’s resources. RTF actions allow FDA to notify applicants of application deficiencies as soon as possible, rather than waiting until the end of a review cycle and notifying the applicant in a CR letter.

FDA may refuse to file an NDA if any of the deficiencies listed in § 314.101(d) (21 CFR 314.101(d)) apply, and will refuse to file an NDA if any of the deficiencies listed in § 314.101(e) apply. For example, § 314.101(e)(2) states that FDA will refuse to file a 505(b)(2) NDA (or refuse to receive an abbreviated new drug application (ANDA)) if another drug with the same active moiety qualifies for 5-year NCE exclusivity.

For NDAs that are filed, FDA will review the contents of the NDA and make a decision to either approve the NDA under 21 CFR 314.105 or send a CR letter under § 314.110 (21 CFR 314.110).²⁶ The Agency will issue a CR letter when the Agency determines that it will not approve the application in its present form.²⁷ Upon receiving a CR letter, an applicant may elect to file a resubmission, withdraw the application, or request an opportunity for a hearing.²⁸

If the applicant decides to file a resubmission, it must address in the resubmission all deficiencies identified in the CR letter.²⁹ Contrary to what the word *resubmission* may mean or imply in other contexts, a “resubmission” in this context does not require an applicant to “resubmit” any data or information that is already in the NDA, nor does it require a new NDA submission. FDA’s regulation defines a “resubmission” as, “in the context of a complete response letter, [a] submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter.”³⁰ A resubmission is thus an amendment after a CR action to a

(FDA’s current thinking on this topic); FDA CDER, Manual of Policies and Procedures (MAPP) 6025.4 (RTF MAPP), *Good Review Practice: Refuse To File*, available at <https://www.fda.gov/media/87035/download>.

²⁴ PDUFA VI Letter at 10.

²⁵ § 314.101(d) and (e).

²⁶ § 314.101(a)(1).

²⁷ § 314.110(a) (21 CFR 314.110(a)).

²⁸ § 314.110(b).

²⁹ § 314.110(b)(1).

³⁰ 21 CFR 314.3. The regulatory definition of *resubmission* also states, “An NDA or ANDA for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.” See also FDA CDER MAPP 6020.4, Rev. 2, *Classifying Resubmissions of Original NDAs, BLAs, and Efficacy Supplements in Response to Complete Response Letters* (Resubmission MAPP), at 4, available at <https://www.fda.gov/media/72727/download>.

pending, unapproved application. Accordingly, no filing determination is made for a resubmission to an application, because applications for which a CR action has been taken have already been filed.³¹

In contrast, the submission of an NDA after an RTF decision is given a new original submission date and filing date because the RTF decision effectively removes the application from FDA's review queue such that there is no longer a pending application before the Agency.

II. FDA APPLIED THE SAME FILING STANDARD TO BOTH NDAS

Genus requests that the Agency rescind its filing of Lannett's NDA for Numbrino if that application did not contain what the Petition describes as "Pre-filing Studies," namely, dedicated studies evaluating (1) QT prolongation potential, (2) the pharmacokinetics (PK) in patients with renal impairment, (3) the PK in patients with hepatic impairment, (4) extractables, and (5) leachables.³² Genus claims that FDA "repeatedly informed Genus both orally and in writing that it would refuse to accept Genus's application for filing if it did not include all of the completed Pre-Filing Studies."³³ Genus further asserts that if FDA did not require Lannett to conduct the same Pre-Filing Studies before filing its NDA, then FDA applied a more lenient filing standard to Lannett's application than to Genus's application in a manner that was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.³⁴

As the record demonstrates, FDA informed Genus that the Agency expected a complete clinical pharmacology package at the time of its NDA submission. At the same time, FDA provided Genus with multiple options to obtain the data for that package. FDA presented the same expectations and options to Lannett, but, as the discussion below demonstrates, Genus and Lannett chose to use different options to provide information in their clinical pharmacology package at the time of each NDA submission. The record is also clear that FDA expected certain nonclinical information at the time of the NDA submission, and both Genus and Lannett provided the requested information at the time of their respective submissions.

The Petition, in asserting that FDA applied a more lenient filing standard to Lannett's application, conflates fileability issues and review issues. Under FDA regulations, "[t]he filing of an NDA means that FDA has made a threshold determination that the NDA is sufficiently complete to permit a substantive review."³⁵ As noted above, the NDA filing review is concerned with identifying filing deficiencies. As stated in FDA's MAPP 6025.4, *Good Review Practice: Refuse To File*, refuse-to-file actions "should be based only on filing issues, not on review

³¹ Resubmission MAPP at 2.

³² Petition at 3.

³³ Petition at 4.

³⁴ Petition at 2.

³⁵ 21 CFR 314.101(a)(1).

issues.”³⁶ As described in the MAPP:

Filing issues are deficiencies that on their face render an application unreviewable, administratively incomplete, or inconsistent with regulatory requirements. Review of the individual application is important in determining the extent and type of deficiencies, if any, considering the significance of the missing information in the context of the drug product, the proposed indication, and the amount of time needed to address any deficiency Review issues are concerns that require in-depth review and complex judgments.³⁷

Whether FDA will refuse to file an application is a case-specific determination that depends on the data submitted in an application at the time of filing.

Below, we address separately Genus’s assertions about the requested clinical pharmacology information Genus alleges FDA required before filing its NDA (i.e., dedicated clinical studies to address QT prolongation potential and PK and dosing in patients with renal and hepatic impairment), and certain nonclinical information (leachables/extractables).³⁸

A. Clinical Pharmacology Information

1. Pre-NDA Meeting Communications for Goprelto

Because the Petition relies heavily on Genus’s pre-NDA meeting communications with FDA around expected clinical pharmacology information, we provide a chronology of those communications here.

On June 15, 2015, FDA provided preliminary meeting comments to Genus in advance of the pre-NDA meeting for Genus’s investigational new drug application (IND) 118527 (Goprelto).³⁹ Those preliminary comments included, among other things, standard advice provided to all sponsors who develop a drug that has not been previously approved regarding the expectation for a complete clinical pharmacology package at the time of filing an application. The advice, in addition to outlining the expectations for addressing clinical pharmacology information, provided several options to the sponsor on how it could obtain this information. Specifically, the

³⁶ See RTF MAPP at 10.

³⁷ Id.; see also 21 CFR 314.101(d)(3) (permitting FDA to refuse to file an NDA if the NDA “is incomplete because it does not *on its face* contain information required under section 505(b) [...] of the Federal Food, Drug, and Cosmetic Act and § 314.50 [...].”) (emphasis added).

³⁸ As defined in the United States Pharmacopeia, “extractables” are organic and inorganic chemical entities that can be released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction and into an extraction solvent under laboratory conditions. “Leachables” are foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under normal conditions of storage and use or during accelerated product stability studies. See United States Pharmacopeia, General Chapter, <1664>, Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems.

³⁹ See June 15, 2015, Preliminary Meeting Comments for IND 118527 (Goprelto).

Agency wrote:

We remind you that a complete clinical pharmacology package is expected at the time of NDA submission. You must address all pertinent clinical pharmacology information related to the following aspects of the drug and the pharmacokinetics of the drug in special populations including but not limited to: (1) absorption, (2) distribution (e.g., in vivo study with radiolabeled product), (3) metabolism (e.g., in vitro study using human microsomes/hepatocytes and/or analyze plasma samples from in vivo studies for assessment of potential metabolites), (4) elimination (e.g., collect urine and feces samples in Phase 1 studies to determine elimination pathways), (5) PK and dosing in special populations (e.g., effect of age, gender, hepatic and renal impairment), (6) drug interaction potential (e.g., in vitro enzyme and transporter induction and inhibition properties of your drug and in vivo studies if warranted), and (7) QT prolongation potential. **This information can be obtained from dedicated studies or sub-population analyses in Phase 3 studies or from the public domain (if information of adequate quality is available in the published literature). If literature articles are used for obtaining this information, full articles must be included in the NDA [bold added for emphasis].**⁴⁰

These preliminary comments are virtually identical to the ones provided to Lannett (pp. 14-15, *infra*).

On July 10, 2015, Genus responded to the Agency's preliminary meeting comments.⁴¹ In its response, Genus stated its belief that published literature would provide sufficient data to address all pertinent clinical pharmacology and PK information:

[Genus] believes that sufficient data will be available in the literature to address all pertinent clinical pharmacology and pharmacokinetic information. We are also aware of the literature addressing the potential for cardiovascular problems (QTc prolongation; hypertension etc.) with cocaine, when administered by systemic routes (i.v.; intranasal; pulmonary inhalation). We have not observed cardiovascular safety problems in our clinical trial; however, we will provide a thorough discussion of this dose-related topic in the NDA submission.⁴²

This response demonstrates that Genus understood it could use literature to address clinical pharmacology and pharmacokinetic information, and FDA understood at that time that Genus was expecting to do so. At the same time, Genus also maintained that dedicated studies conducted in special populations were not relevant given that Genus believed its product to be primarily topical and designed to have minor systemic impact. Genus also indicated that it was considering a dedicated PK study to provide bridging information for its product with the literature:

Additionally, we also believe that this is primarily a topical product designed to have minor systemic exposure, and thus special population studies are not relevant as they

⁴⁰ See June 15, 2015, Preliminary Meeting Comments for IND 118527 (Goprelto) at 11.

⁴¹ See July 10, 2015, letter from Melissa L. Goodhead, MSc, RAC, to Sharon Hertz, MD, FDA.

⁴² Id. at 11.

would be for a systemic drug product. Finally, we are considering a dedicated pharmacokinetic study, if necessary, to bridge the pharmacokinetics of our 4% topical Cocaine HCl formulation with the literature values and to support the pharmacokinetic safety during routine procedures and/or surgeries conducted in the nasal cavity. Does the Division agree that studies conducted in special populations are not relevant with this drug product and do not need to be conducted?⁴³

During the July 14, 2015, pre-NDA meeting, Genus and the Agency discussed Genus's response and FDA summarized these discussions in meeting minutes provided to Genus on August 14, 2015.⁴⁴ Regarding Genus's assertion that studies conducted in special populations are not relevant, the Agency neither agreed nor disagreed. Rather, FDA informed Genus that it would need to include in its application a justification (i.e., a scientific rationale supported by evidence, which can be based on sponsor data, public literature, or other appropriate sources) that supported that assertion. Because Genus claimed that its product was designed to have minor systemic exposure, the Agency noted that Genus must include evidence in its application demonstrating such low systemic exposure. Given that Genus had proposed to conduct a dedicated PK study to bridge the pharmacokinetics of its product with the literature values (PK bridging study), FDA pointed out that Genus could try to obtain such evidence of low systemic exposure from that PK bridging study. FDA also provided advice on factors Genus should consider when designing its PK bridging study. Notably, however, this advice did not preclude Genus from including in its application other assertions (backed by supporting evidence) for why studies in special populations were not relevant, and it did not preclude alternative means of meeting the expected clinical pharmacology information described in the Goprelto Pre-NDA Meeting Minutes.

Finally, because Genus expressed a belief that sufficient data would be available in the literature to address all pertinent clinical pharmacological and pharmacokinetic information, FDA recommended that Genus attempt to obtain analytical reports cited in those literature sources and submit them along with those literature sources as additional evidence to strengthen the evidence from those literature sources.

FDA memorialized these discussions in the July 14, 2015, Goprelto Pre-NDA Meeting Minutes as follows:

The Agency stated that the Sponsor must provide justification as to why special population studies are not relevant to their product. The Sponsor must provide evidence of low systemic exposure levels using data from the PK study. The PK study must be of adequate sample size, and include validated analytical assays for cocaine and its metabolites. The Agency also recommended that the Sponsor attempt to obtain analytical reports cited in literature sources and submit these as additional evidence.⁴⁵

Contrary to Genus's assertions, these minutes do not demonstrate that FDA informed Genus that it had to conduct dedicated studies in patients with renal and hepatic

⁴³ Id.

⁴⁴ See July 14, 2015, Pre-NDA Meeting Minutes for IND 118527 (Goprelto) (Goprelto Pre-NDA Meeting Minutes).

⁴⁵ Id. at 18.

impairment. Indeed, such an instruction would have been nonsensical given that the purpose for such dedicated studies would have been to provide data to support Genus's justification for why such studies were not relevant and therefore not needed.

Rather, the PK study FDA referenced was the PK bridging study Genus proposed, not dedicated studies in patients with renal and hepatic impairment. FDA recognizes that, with the benefit of hindsight, it would have been clearer to explicitly state that the "must" related to the need for Genus to provide evidence of low systemic exposure levels, but not to where that evidence needed to come from. Genus could also have provided evidence of low systemic exposure from other sources, such as literature, if available.

2. *July 14, 2016, Teleconference for Goprelto*

In the December 2 CP Amendment, Genus claims that during a July 14, 2016, teleconference, FDA representatives informed Genus that Genus would be required to submit results from the QT study and the dedicated renal and hepatic impairment PK studies as part of Genus's original NDA and, as a result, Genus conducted those studies over several months in 2016, delaying submission of its NDA until November 23, 2016.⁴⁶ Genus's characterization is misleading to the extent it suggests that FDA instructed Genus to conduct studies that Genus would otherwise not have undertaken. The record demonstrates that Genus had decided to conduct the dedicated renal and hepatic impairment PK studies before the July 14, 2016, teleconference.⁴⁷

FDA first became aware that Genus had opted to conduct the dedicated renal and hepatic impairment PK studies on March 23, 2016, when Genus submitted its protocol for each study to FDA. According to the protocols, both the dedicated renal and hepatic impairment PK studies started (date of first subject consent) on March 21, 2016, nearly 4 months before the teleconference in question. FDA had questions about the study protocols and contacted Genus to arrange for a teleconference on July 14, 2016. Of the four FDA representatives on this call, two are no longer employed with FDA and the remaining representatives have no independent recollection of the teleconference. Consistent with the Division's practice for informal teleconferences, FDA did not issue minutes for the call.

Based on FDA's Clinical IND Review and email correspondence, the purpose of the call appears to have been to discuss what the Agency deemed to be inadequate stopping rules in the design of the dedicated PK studies Genus was conducting.⁴⁸ Based on the discussions with FDA during the July 14, 2016 call, Genus revised its protocols for the dedicated renal and hepatic impairment PK

⁴⁶ December 2 CP Amendment at 1-2.

⁴⁷ As reflected in the July 24, 2016, 7:10 p.m. email from Melissa Goodhead to Larry Dalesandro and Jeff Moshal (Exhibit A, Attachment 1 to First Amended CP), Genus was planning to include the results of the dedicated QT study it was already conducting before the July 14, 2016, teleconference in its original NDA submission. Genus is not claiming that any statement by FDA about including such study in its NDA filing resulted in delay of that submission. Therefore, we do not address that QT study further in this section.

⁴⁸ See August 2, 2016, IND 118527 (Goprelto) Clinical IND Review for protocol 2015014 at 1, and Exhibit A, Attachment 2 to December 2 CP Amendment (July 24, 2016, 6:51 p.m. email from Melissa Goodhead to Bill Reightler and Jeff Moshal).

studies and submitted protocol amendments to the Agency on July 15, 2016.⁴⁹ FDA indicated on July 18, 2016, that the changes adequately addressed FDA's concerns.⁵⁰

A series of internal Genus emails, submitted to FDA as part of the December 2 CP Amendment, outline what appears to have been Genus's planned approach for addressing dosing in patients with renal and hepatic impairment in its original NDA filing. According to these internal Genus email exchanges, Genus appeared to be planning to submit its NDA before it completed the dedicated renal and hepatic impairment PK studies it had started to conduct in March 2015. Instead, Genus appeared to be planning to submit in its NDA a justification for why Genus did not expect its drug to negatively impact patients with renal or hepatic impairment (one of the subjects of the July 14, 2015, conference)⁵¹ and was discussing whether to include language to the effect that it had not studied the drug in patients with renal or hepatic impairment.⁵² These internal email exchanges also indicate that Genus appeared to be planning to update its NDA with data from the dedicated renal and hepatic impairment PK studies Genus was in the midst of conducting after filing its NDA.⁵³

There is no evidence in the record that Genus informed FDA during the July 14, 2016, teleconference about its plan to include a justification for why Genus did not expect its drug to negatively impact patients with renal and hepatic impairment. Rather, the record reflects that the only information FDA had at that time was that Genus was in the process of conducting dedicated renal and hepatic studies to address PK and dosing in patients with renal and hepatic impairment. In a July 24, 2016, Genus internal email from Melissa Goodhead summarizing the July 14, 2016, teleconference, Ms. Goodhead wrote "during our FDA call last week FDA indicated we would need to submit the QTc, hepatic and renal studies in the original NDA filings."⁵⁴ Ms. Goodhead continued, "[o]riginally we planned to submit the QTc study as a stand alone study and update the filing with the renal/hepatic studies at the 120-update."⁵⁵ Because

⁴⁹ See July 15, 2016, 6:31 p.m. email from Melissa Goodhead to Diana Walker (FDA).

⁵⁰ See July 18, 2016, 1:37 p.m. email from Diana Walker to Melissa Goodhead.

⁵¹ This contradicts the Petition's claim that FDA required Genus to include dedicated studies for patients with renal and hepatic impairment at the time of filing. The fact that Genus was apparently only planning to include in its NDA submission a justification for why it did not expect its drug to negatively impact patients with renal or hepatic impairment indicates that Genus did not interpret FDA's pre-NDA meeting communications from the previous year to mean that FDA would refuse to file its application unless it included dedicated studies to address the impact of its drug on those patients.

⁵² See Exhibit A, Attachment 4, to December 2 CP Amendment (July 19, 2016, 7:20 p.m. email from Melissa Goodhead to Robert Guttendorf, Jeff Moshal, Cynthia Dinella, Bill Reightler, Jacqueline Sterner, and others; July 27, 2017, 4:23 p.m. email from Robert Guttendorf to Melissa Goodhead). In the latter email, Mr. Guttendorf noted that if the dedicated renal and hepatic impairment PK studies were finished in time to include in the filing, Genus would incorporate the data in its NDA and remove the language justifying why it did not expect to see an effect in either renally or hepatically impaired patients.

⁵³ Id. See also Exhibit A, Attachment 1, to December 2 CP Amendment (July 24, 2016, 7:10 p.m. email from Melissa Goodhead to Larry Dalesandro, Jeff Moshal, and others).

⁵⁴ Exhibit A, Attachment 1, to December 2 Amended CP (July 24, 2016, 7:10 p.m. email from Melissa Goodhead to Larry Dalesandro, Jeff Moshal, and others).

⁵⁵ Id.

FDA understood that dedicated studies were the means by which Genus planned to address PK and dosing in patients with renal and hepatic impairment as part of its clinical pharmacology package, an FDA statement that Genus must include these studies at the time of filing would be fully consistent with what FDA had stated in its pre-NDA meeting preliminary meeting comments—that FDA expects every sponsor to submit a complete clinical pharmacology package at the time of filing the application.⁵⁶ Therefore, we disagree that the available information regarding the July 14, 2016, teleconference supports a conclusion that FDA applied a different standard to Genus’s NDA submission than it did to Lannett’s and, in so doing, caused Genus to delay its NDA submission.

3. FDA Provided Genus and Lannett With Multiple Options To Obtain Clinical Pharmacology Information

Genus’s assertion that FDA required Genus to submit a different clinical pharmacology package than Lannett rests on the premise that FDA required Genus to conduct dedicated studies to evaluate QT prolongation and the PK in patients with renal and hepatic impairment as a condition to filing Genus’s NDA. Specifically, Genus claims that FDA stated it would not file Genus’s NDA if Genus submitted an application without a dedicated QT study.⁵⁷ Genus also claims that FDA required dedicated studies in patients with renal and hepatic impairment, after rejecting Genus’s justification for why studies in special populations were not necessary for its cocaine HCl product.⁵⁸ As demonstrated above, these assertions are incorrect.

Genus’s assertions are contradicted by the written pre-NDA meeting communications between FDA and Genus.⁵⁹ As described above, FDA indicated that Genus, like all 505(b)(2) applicants, should address in its application all pertinent clinical pharmacology information, including dosing in special populations (e.g., hepatic and renal impairment) and QT prolongation potential.⁶⁰ FDA did not require dedicated studies to obtain these data, and nowhere in the Goprelto Pre-NDA Meeting Minutes does FDA indicate that it would refuse to file Genus’s

⁵⁶ The 120-day safety update report is not an appropriate means for submitting original portions of a sponsor’s clinical pharmacology package. Under 21 CFR 314.50 (d)(5)(vi)(b), the purpose of the safety update report is to update a pending NDA with new safety information “that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling...”.

⁵⁷ Although the Petition asserts that Genus asked FDA whether Genus could forgo a QT study specifically, no such question appears in the cited documents or elsewhere. Rather, in its July 10, 2015, response to FDA’s June 15, 2015, Preliminary Meeting Comments (at 11), Genus stated that it was aware of literature addressing the potential for QTc prolongation with cocaine when administered intranasally and, though it did not observe cardiovascular safety problems in its clinical trial, it would provide a thorough discussion on the dose-related topic in its NDA submission. Genus also questioned (at 11) whether studies conducted in special populations are relevant to its drug product and whether the Agency agreed that Genus need not include them. As memorialized in the Goprelto Pre-NDA Meeting Minutes, discussions (at 18) at the July 14, 2015 pre-NDA meeting were about studies in special populations broadly, not QT prolongation specifically.

⁵⁸ Petition at 5.

⁵⁹ Genus’s assertions are also contradicted by their own internal email communications. See footnote 52, *supra*.

⁶⁰ Goprelto Pre-NDA Meeting Minutes at 17-18.

application without such dedicated studies. Rather, FDA offered Genus (as it does to all similarly situated sponsors) several options for meeting the expectation to have a complete clinical pharmacology package in its NDA submission, only one of which was to conduct dedicated studies.⁶¹ Alternatively, the expected clinical pharmacology information could have been addressed by relying on literature or other sponsor data.⁶²

Genus misconstrues FDA's summary of the discussions at the July 14, 2015, pre-NDA meeting regarding the clinical pharmacology information expected. Genus claims that FDA required the company to conduct dedicated studies in patients with renal and hepatic impairment and therefore implies that FDA rejected any proposal to use literature to address PK and dosing in these special populations.⁶³ This is not consistent with the discussion notes and FDA's preliminary meeting comments explaining that literature was a possible source for such data. Indeed, because Genus in its July 10, 2015, response had asserted its belief that sufficient data would be available in the literature to address all pertinent clinical pharmacology and pharmacokinetic information, FDA recommended that it attempt to obtain analytical reports cited in the literature sources and submit them as additional evidence (i.e., in addition to what was included in the literature sources).⁶⁴

The Petition also claims that Genus provided a justification to the Agency as to why studies in patients with renal and hepatic impairment were not necessary for Goprelto, but FDA rejected it.⁶⁵ However, the record is clear that FDA never rejected any justification Genus provided during the pre-NDA meeting communications. As reflected in the Goprelto Pre-NDA Meeting Minutes, FDA noted that Genus would need to justify in its application why special population studies are not relevant to its product.⁶⁶ One such justification (as Genus proposed in its response) could have been evidence of low systemic exposure, but Genus would need to include pharmacokinetic data in its application to provide evidence of such low systemic exposure that FDA could consider during the review of the application. As explained in section II.A.1 above, the reference to "the PK study" in the Pre-NDA Meeting Minutes was to the PK bridging study that Genus proposed in its July 10, 2015, response (i.e., the PK study to bridge the pharmacokinetics of Genus's 4% topical Cocaine HCl formulation with the literature values), not to PK studies in special populations. As noted above, it would have made no sense for FDA to require Genus to conduct dedicated hepatic and renal impairment studies in order to show why dedicated hepatic and renal impairment studies were not relevant for its product.

Finally, as noted above, the series of internal emails relating to a July 14, 2016, teleconference that Genus included as exhibits to the December 2 CP Amendment do not support Genus's claim

⁶¹ See June 15, 2015, Preliminary Meeting Comments for IND 118527 (Goprelto) at 11; Goprelto Pre-NDA Meeting Minutes at 17-18.

⁶² Id. (noting that pertinent clinical pharmacology information "can" be obtained from dedicated studies, subpopulation analyses, or literature).

⁶³ Petition at 6.

⁶⁴ See Goprelto Pre-NDA Meeting Minutes at 18.

⁶⁵ Petition at 5.

⁶⁶ See Goprelto Pre-NDA Meeting Minutes at 18.

that FDA instructed Genus to conduct dedicated studies in patients with renal and hepatic impairment. Genus had made the decision to conduct those studies months before the July 14, 2016, teleconference and was conducting those studies at the time. Moreover, given that FDA was aware that Genus was conducting dedicated studies in these special populations, any advice to Genus to include results from these studies in the original NDA filing would be appropriate because an application should be facially complete at filing (i.e., the information Genus intended to rely on to address aspects of the drug's clinical pharmacology in special populations should be included in the original application). Such advice is fully consistent with the advice that FDA provided during the pre-NDA meeting communications.

4. *FDA Applied the Same Filing Standards to Both Genus's and Lannett's NDAs*

The goal of the filing review for an NDA is to determine whether the marketing application is sufficiently complete to permit a substantive review.⁶⁷ FDA *may* refuse to file an application for a number of reasons, including where an application is incomplete because it does not *on its face* contain required information.⁶⁸ To facilitate its NDA filing reviews, the Center for Drug Evaluation and Research (CDER) developed discipline-specific filing review templates. These templates are designed to assist the FDA reviewer in making recommendations on whether the application is fileable and to document the basis for that decision. The filing review team also participates in a filing review meeting to, among other things; decide whether the application is fileable. FDA used the same discipline-specific filing templates to review Genus's NDA for Goprelto and Lannett's NDA for Numbrino and applied the same filing standards to both applications.

FDA also provided pre-NDA preliminary meeting comments to Lannett for Numbrino using the same substantive standard language as provided to Genus for Goprelto about the need to include all pertinent clinical pharmacology information in its NDA and provided Lannett the same options for obtaining this information. Specifically, FDA informed Lannett as follows:

You must address all pertinent clinical pharmacology information related to the following aspects of the drug and the pharmacokinetics of the drug in special populations including but not limited to: (1) absorption, (2) distribution (e.g., *in vivo* study with radiolabeled product), (3) metabolism (e.g., *in vitro* study using human microsomes/hepatocytes and/or analyze plasma samples from *in vivo* studies from assessment of potential metabolites), (4) elimination (e.g., collect urine and feces samples in phase 1 studies to determine elimination pathways), (5) PK and dosing in special populations (e.g., effect of age, gender, hepatic and renal impairment), (6) drug interaction potential (e.g., *in vitro* enzyme and transporter induction and inhibition properties of your drug and *in vivo* studies if warranted), and (7) QT prolongation potential. This information can be obtained from dedicated studies or sub-population analyses in Phase 3 studies) [*sic*] or from the public domain (if information of adequate quality is available in the published literature).

⁶⁷ See 21 CFR 314.101(a).

⁶⁸ See 21 CFR 314.101(d). FDA may refuse to file an NDA if any of the deficiencies listed in § 314.101(d) (21 CFR 314.101(d)) apply, and will refuse to file an NDA if any of the deficiencies listed in § 314.101(e) apply.

Thus, the record establishes that Genus and Lannett were given the same options for obtaining the expected clinical pharmacology information and the information each company elected to submit in its application was different. Genus submitted dedicated studies to provide information on QT prolongation potential and to inform dosing in renally and hepatically impaired patients, while Lannett provided information on QT prolongation from a sub-population analysis of its phase 3 clinical studies and literature information to inform dosing in renally and hepatically impaired patients. During the filing review for Lannett's NDA, using the same filing standard applied to Genus's NDA, FDA determined that Lannett provided adequate clinical pharmacology information to permit a substantive review of its application.⁶⁹ Whether that information was sufficient to support approval was a review issue, not a filing issue.

B. Leachables and Extractables Studies and Toxicology Risk Assessment

The Agency finds no basis for the assertion that FDA may not have applied the same filing standards to both Genus's and Lannett's respective NDAs for Goprelto and Numbrino regarding the expectations for data on leachables/extractables.⁷⁰ Using similar standard advice that FDA provides to all sponsors of drug products with parenteral/liquid container closure systems, FDA's pre-NDA preliminary meeting comments to both Genus and Lannett informed each company that its NDA must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation and an adequate leachable/extractable toxicological risk assessment.⁷¹ FDA also provided similar guidance to each sponsor on conducting the leachables and extractables studies and risk assessments.⁷² Additionally, as noted above, the Agency used the same CDER discipline-specific filing templates to evaluate the respective Goprelto and Numbrino NDAs, including the disciplines on pharmacology toxicology and chemistry, manufacturing, and controls.⁷³ The Petition erroneously interprets FDA's comments to Genus about conducting leachables and extractables studies as creating a mandatory pre-filing standard for all 505(b)(2) applications for cocaine HCl products that, if not met, must result in an RTF action.

Specifically, Genus claims that:

⁶⁹ See November 13, 2017, Clinical Pharmacology Filing Form for NDA 209575 and November 20, 2017, Clinical Filing Checklist for NDA 209575.

⁷⁰ Petition at 11.

⁷¹ See April 13, 2017, Preliminary Meeting Comments for IND 106499 (Numbrino) at 10-12 and June 15, 2015, Preliminary Meeting Comments for IND 118527 (Goprelto) at 9-11.

⁷² Id. The purpose of submitting an NDA to FDA is to secure Agency approval to market a sponsor's drug. Simply meeting the filing threshold does not mean that the data provided will be deemed sufficient to secure FDA approval during the substantive review process. As such, FDA provides detailed advice on conducting extractables and leachables studies to assist sponsors in providing more complete information to increase the likelihood that FDA can approve their applications.

⁷³ See January 23, 2017, Office of Pharmaceutical Quality, NDA Filing Review for NDA 209963, and November 13, 2017, Office of Pharmaceutical Quality, NDA Filing Review for NDA 209575; January 20, 2017, Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement for NDA 209963 and November 28, 2017, Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement for NDA 209575.

By requiring [the] risk assessment study, FDA mandated as follows: Before FDA can accept for filing a 505(b)(2) application for a cocaine hydrochloride product, the applicant must include toxicological evaluation and risk assessment for leachables and extractables, including a solvent extraction study exposing the container closure materials to three different . . . batches and collecting data at beginning, middle, and end time points.⁷⁴

In its NDA for Numbrino, Lannett included extractables/leachables studies and a toxicology risk assessment. While these studies and risk assessment were not identical to those performed by Genus for Goprelto, they were sufficient to permit a substantive review and the application could be filed.⁷⁵ Whether the data provided were adequate to support approval was a review issue, not a filing issue.

In any event, FDA mandated no specific pre-filing standard.⁷⁶ Under 21 CFR 314.101(d)(3), FDA *may* refuse to file an NDA if “the NDA [. . .] is incomplete because it does not on its face contain information required under section 505(b) [. . .] of the Federal Food, Drug, and Cosmetic Act and § 314.50 [. . .].” Adopting Genus’s specific study standard would be inconsistent with the flexibility provided in the regulation.⁷⁷ Genus’s proposed standard is also inconsistent with FDA’s public health mission, as it would unduly bind all subsequent applicants to one scientific approach for assessing leachables/extractables and toxicological risk assessment regardless of innovations in the field.

III. FDA WILL NOT REQUIRE ALL APPLICANTS SEEKING APPROVAL FOR A COCAINE HYDROCHLORIDE PRODUCT TO FOLLOW GENUS’S DEVELOPMENT PROGRAM FOR GOPRELTO

In the December 2 CP Amendment, Genus requests that FDA refuse to *approve* any NDA for a cocaine hydrochloride product unless the sponsor completes QT prolongation, renal, hepatic, and leachable studies similar to those Genus conducted. This request is ambiguous as to whether Genus is requesting that subsequent applicants should be required to have the same designs as the studies that Genus conducted or simply dedicated studies in each category. Either way, FDA declines to use Genus’s development program as a limit on the types of data and study designs applicants for a cocaine HCl product can utilize to support their applications.

⁷⁴ Petition at 8.

⁷⁵ See January 23, 2017, Office of Pharmaceutical Quality, NDA Filing Review for NDA 209963, and November 13, 2017, Office of Pharmaceutical Quality, NDA Filing Review for NDA 209575; January 20, 2017, Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement for NDA 209963 and November 28, 2017, Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement for NDA 209575.

⁷⁶ The Agency’s pre-NDA meeting communications with Genus explicitly contradict Genus’s assertion that FDA issued such a mandate. As recognized in the Petition (at 8, footnote 31), during the July 14, 2015, pre-NDA meeting, FDA informed Genus that if Genus buys the glass for its container closure system, Genus could obtain a Letter of Authorization from the Drug Master File (DMF) holder and, if the DMF holder has appropriate extractable/leachable data to support the proposed product, then Genus did not need to conduct a separate study on glass. See Goprelto Pre-NDA Meeting Minutes at 13.

⁷⁷ See 21 CFR 314.101(d)(3).

Below, we address separately Genus's request regarding clinical pharmacology studies (i.e., studies assessing QT prolongation potential and patients with renal and hepatic impairment) and leachables studies.

A. Clinical Pharmacology

As noted above, sponsors have different options for addressing pertinent clinical pharmacology information in their NDAs submitted via the 505(b)(2) pathway.⁷⁸ While dedicated studies are one option, other options are also available, such as subpopulation analyses of phase 3 trials, information from literature, or, in the absence of available data, proposing to address any safety concerns for an identifiable patient population in labeling for the applicable product. Yet, Genus seeks to limit the options available to other applicants for a cocaine HCl product by asking FDA to require dedicated studies in all cases. FDA declines to do so. Genus presents no scientific basis for requiring dedicated studies from all applicants when other options may be available and sufficient to address pertinent clinical pharmacology information.

Regarding Lannett's application specifically, for the reasons discussed below, FDA determined that dedicated studies in patients with renal and hepatic impairment were not necessary to support approval for Numbrino, while a dedicated study assessing QT prolongation potential was.⁷⁹

1. Studies in Patients With Renal Impairment

The Agency does not agree that a dedicated study in patients with renal impairment was necessary to approve Lannett's NDA for Numbrino. In its NDA, Lannett provided a justification for its recommended dosing in patients with renal impairment based on what was known in the literature about the product's elimination from the body. Specifically, based on the literature, Lannett asserted that renal elimination is not the main elimination pathway for the parent drug or its metabolites; therefore, patients with significant renal impairment would not be expected to be clinically impacted by the product's elimination from the body.⁸⁰ The Agency agrees that Lannett's assertion is supported by the literature. However, because Numbrino was not studied in patients with renal impairment specifically, the approved labeling for Numbrino includes cautionary language stating, "dose initiation in patients with renal impairment should follow a

⁷⁸ See section 505(b)(2) of the FD&C Act (permitting sponsors to rely, for approval of a 505(b)(2) NDA, on data and information not developed by the applicant.)

⁷⁹ See 21 CFR 314.105(c) ("FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling [. . .]. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. *Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards [. . .].*" (emphasis added).

⁸⁰ See Lannett September 21, 2017, Original NDA Submission at Section 2.7.2, and January 19, 2018, letter from Katy Rudnick to Office of New Drugs at 5-6.

conservative approach.”⁸¹ The same literature was available to Genus and Genus could have used literature to address PK and dosing in patients with renal impairment, but chose to conduct a dedicated study instead (also an acceptable option). Regarding dedicated studies where PK is unlikely to be altered by renal impairment, FDA’s guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* (March 2010) (Renal Impairment Guidance) states that “[f]or some drugs, renal impairment is not likely to alter PK enough to justify dosage adjustment. In such cases, a study to confirm that prediction may be helpful, but is not necessary.”⁸² Genus’s dedicated study was indeed helpful for the Goprelto program in confirming that no dose adjustment was necessary for patients with renal impairment who use Goprelto, and therefore the labeling for Goprelto contains no cautionary statement when dosing Goprelto in those patients. However, based on what is known about the elimination of cocaine from the body, a study in renally impaired patients was not necessary for the approval of Goprelto or Numbrino.

2. *Studies in Patients With Hepatic Impairment*

The Agency does not agree that a dedicated study in patients with hepatic impairment was necessary to approve Lannett’s NDA for Numbrino. In its original NDA submission, regarding dosing recommendations in patients with hepatic impairment, Lannett relied on information in the literature on the metabolism of cocaine HCl. Essentially, Lannett noted that the literature demonstrated cocaine was mainly metabolized by esterases, which are hydrolase enzymes present throughout the body. Therefore, Lannett reasoned that hepatic impairment is not expected to significantly alter pharmacologic plasma concentrations of Numbrino because esterases can also be found outside the liver.⁸³ Though Lannett’s scientific rationale was reasonable, the review division takes a conservative approach when considering patient safety. The literature on which Lannett relied demonstrated that metabolism is the main mechanism of elimination for cocaine products and suggested up to 50 percent involvement of hepatic esterases in the metabolism of cocaine. Therefore, decreased liver function has a potential to result in up to a two-fold increased exposure of cocaine in hepatically impaired patients.⁸⁴ Based on this data, FDA determined that more than a cautionary statement in the approved Numbrino labeling was necessary. Specifically, the Agency concluded that, absent data on exposure in hepatically impaired patients using Numbrino, the Numbrino labeling should include restrictive language stating that Numbrino should be avoided in patients with hepatic impairment.

Restrictive language in the labeling for Numbrino is sufficient to address any potential safety

⁸¹ See FDA-approved labeling for Numbrino available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.

⁸² See Renal Impairment Guidance at 3. See, e.g., FDA-approved labeling for Zolinza (“Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat. Patients with preexisting renal impairment should be treated with caution. [See Clinical Pharmacology (12.3).]”), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021991s002lbl.pdf.

⁸³ Specifically, Lannett stated “Plasma cocaine concentrations are not expected to be affected in patients with hepatic impairment due to the primarily, non-renal and non-oxidative, non-CYP450 esterases metabolic pathway of cocaine HCl.” See Lannett September 21, 2017, Original NDA Submission at section 2.7.2.4.1.

⁸⁴ See June 20, 2019, Clinical Pharmacology Review for NDA 209575 at 6.

concern for patients with hepatic impairment. Consistent with FDA's guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003) (Hepatic Impairment Guidance), where no studies of a population with altered hepatic function exist, the drug should be considered extensively metabolized and restrictive language should be used in the labeling to address any safety concerns for these patients.⁸⁵ Hepatically impaired patients are an identifiable population at potential risk where restrictions in labeling can be used to address potential safety concerns for the population. Accordingly, the Numbrino labeling recommends that Numbrino should be avoided in patients with hepatic impairment. Therefore, from a public health perspective, any potential safety concern for these patients is addressed adequately by the Numbrino labeling.⁸⁶ Lannett can choose to conduct a dedicated study in hepatically impaired patients to support a change in the labeling language regarding use of Numbrino in hepatically impaired patients to provide particularized dosing recommendations for patients with hepatic impairment, but from a safety perspective, a dedicated study is not required before approving Numbrino where labeling recommending that Numbrino should be avoided in those patients is sufficient.⁸⁷

3. Studies Assessing QT Prolongation Potential

⁸⁵ See Hepatic Impairment Guidance at 10-11. Other FDA-approved product labeling also contain restrictive language for hepatically impaired patients in the absence of study data in these patients. See, e.g., FDA-approved labeling for Diacomit ("there has been no formal study of the pharmacokinetics of DIACOMIT in patients with liver impairment. However, since the drug is mainly metabolized by the liver, administration to patients with moderate or severe liver impairment is not recommended."), available at <https://www.accessdata.fda.gov/spl/data/9af76bca-c7cc-4980-9bbc-9e056dfa1b2/9af76bca-c7cc-4980-9bbc-9e056dfa1b2.xml>; FDA-approved labeling for Letairis ("The influence of preexisting hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment might be expected to have significant effects on the pharmacokinetics of ambrisentan [see Clinical Pharmacology (12.3)]. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild preexisting impaired liver function; however, exposure to ambrisentan may be increased in these patients."), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022081s033lbl.pdf; and FDA-approved labeling for Bazel ("Use of BANZEL in patients with severe hepatic impairment (Child-Pugh score 10 to 15) is not recommended. Caution should be exercised in treating patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic impairment."), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021911s012lbl.pdf.

⁸⁶ Whether restrictive labeling is appropriate to address safety concerns in an identifiable subpopulation is a case-by-case determination during a product review taking into consideration factors such as clinical context and the subpopulation of interest.

⁸⁷ In the December 2 CP Amendment (at 3), Genus claims that the dedicated renal and hepatic impairment PK studies it conducted were directly material to the dosage information in the Goprelto labeling and such studies should be material to Lannett's application and proposed labeling as well. To the extent that Genus implies that Lannett's application should not be approved if it does not contain dedicated studies in patients with renal or hepatic impairment, FDA does not agree. FDA-approved labeling is generally tailored to each individual NDA based on the data provided in that NDA. The Goprelto labeling reflects the data Genus submitted regarding dosing in patients with renal and hepatic impairment. In general, any study could be characterized as "material," if it is the underlying basis for a recommendation in the labeling. But that does not mean that every application must contain information from such studies, especially given the flexibility that FDA affords sponsors on how to address dosing in special populations. .

FDA declines to require all applicants for a cocaine HCl product nasal solution to conduct dedicated studies to assess QT prolongation potential for their drug. As described above, sponsors have various options for obtaining data on QT prolongation potential, including a dedicated study, subpopulation analyses from clinical trials, and literature. By requiring dedicated studies, Genus seeks to restrict subsequent applicants from receiving the same options that Genus was provided.

As noted above, Lannett opted to submit data on QT prolongation potential for Numbrino from subpopulation analyses of its clinical trials—a common and acceptable approach. While the Agency determined that the data were sufficient for filing purposes, during the review phase, FDA determined that Lannett’s analyses were inadequate to characterize the effects of Numbrino on QT prolongation. To resolve this deficiency, FDA’s July 20, 2018, CR Letter instructed Lannett to conduct a dedicated QT study.

In response to the July 20, 2018, CR Letter, Lannett conducted a dedicated QT study and submitted the results to the Agency on June 21, 2019. FDA was satisfied that Lannett’s QT study was scientifically appropriate to assess the QT prolongation potential for Numbrino.

B. Leachables Studies

Scientifically appropriate data (usually studies) evaluating extractables and leachables of the container closure system for cocaine hydrochloride nasal solutions and an appropriate toxicological risk assessment for leachables that exceed an identified threshold are required of applicants for such products.^{88, 89} However, FDA does not agree that the required extractables and leachables data and toxicological risk assessment need to be identical to the designs of the studies and toxicological risk assessment Genus conducted. FDA provides sponsors the flexibility to perform studies with the most rigorous, scientifically justified techniques, methods, and/or instruments identified as appropriate for the drug product under review.⁹⁰ Genus provides no scientific basis for why FDA should require all applicants for cocaine HCl nasal products to provide FDA with the required extractables and leachables data and toxicological risk assessment using the same design and analysis as Genus.

For the purposes of approving Lannett’s NDA for Numbrino, FDA determined that Lannett provided adequate scientific information to support the safety of its closed container system. As noted above, Lannett submitted in its original NDA extractables and leachables studies and a toxicological risk assessment that FDA deemed sufficient for filing purposes. During the review cycle, FDA determined that the data provided for leachables was inadequate to justify the safety of the proposed container closure system.⁹¹ To resolve this deficiency, FDA instructed Lannett to

⁸⁸ As Genus’s approved Goprelto product is a cocaine hydrochloride nasal solution our response is limited to this dosage form. An alternate dosage form (e.g., tablet) may not require the same extractables and leachables studies.

⁸⁹ See FD&C Act section 501(a)(3) stating that a drug is deemed to be adulterated “if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health.”

⁹⁰ See 21 CFR 314.105(c).

⁹¹ See July 20, 2018, letter from Rigoberto Roca, MD, to Lannett Holdings, Inc., “Complete Response.”

conduct a new leachables study under standard storage conditions that evaluated at least three batches of the to-be-marketed cocaine HCl nasal product over the course of its stability studies⁹² to identify trends in leachables over time.⁹³

Lannett conducted and submitted new leachables studies in response to the July 20, 2018, CR letter. Lannett submitted new leachables data from nine different lots of its cocaine hydrochloride nasal solution evaluated at three time points (beginning of stability, mid, and end of stability) for the 4% solution. FDA determined that the studies were scientifically adequate to characterize the safety of the to-be-marketed container closure system for Numbrino. FDA does not believe that a comparison to Genus's leachables study for Goprelto is appropriate or necessary to consider the safety of Lannett's container closure system.

IV. THE 505(b)(2) PATHWAY WAS APPROPRIATE FOR LANNETT'S APPLICATION FOR NUMBRINO

The Petition asserts that Lannett's "reapplication" of its cocaine HCl product is barred by 21 CFR 314.101(d)(9) because it is a duplicate of an already-approved drug (Genus's Goprelto) and only eligible for approval under section 505(j) of the FD&C Act as an ANDA.⁹⁴ The Agency disagrees. FDA's regulation in § 314.101(d)(9) permits FDA to refuse to file 505(b)(2) applications for products eligible for approval under section 505(j) of the FD&C Act only if the product described in a 505(b)(2) application are eligible for approval under section 505(j) at the time of the application's submission. Lannett submitted its NDA for Numbrino on September 21, 2019, before FDA approved Genus's NDA for Goprelto on December 14, 2019. Therefore, the product described in Lannett's application was not eligible for approval under section 505(j) when the application was submitted. Lannett's NDA was properly submitted as a 505(b)(2) application, consistent with § 314.101(d)(9).⁹⁵

⁹² The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

⁹³ Id. at 2.

⁹⁴ Petition at 14. This assertion reflects the Agency's regulation in § 314.101(d)(9), which provides that FDA may refuse to file an NDA if "[t]he NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act."

⁹⁵ When addressing similar circumstances, the Agency has consistently applied this regulatory framework, explaining that the 505(b)(2), not 505(j), pathway is appropriate when a pharmaceutically equivalent product has not yet been approved at the time the application is submitted. See May 17, 2012, response to Terri Nataline, re: Docket No. FDA-2011-P-0606 (finding that the drug Veltin (clindamycin phosphate and tretinoin topical gel) was properly submitted under the 505(b)(2) pathway, not 505(j), because another 505(b)(2) application for a pharmaceutically equivalent drug was pending, but not yet approved, at the time Veltin was submitted); and July 10, 2014, response to Susan Thornton re: Docket No. FDA-2014-P-0318 (denying the Petitioner's request to require a company to withdraw its 505(b)(2) application and submit a new one referencing the Petitioner's drug Otrexup where the 505(b)(2) application was submitted before Otrexup was approved).

Contrary to Genus's request, FDA does not require 505(b)(2) applicants with pending submissions to withdraw and resubmit their applications under section 505(j) if another pharmaceutically equivalent drug product is subsequently approved. Specifically, Genus asserts that Lannett's submission in response to FDA's July 20, 2018, CR letter constitutes a "reapplication" submitted after FDA approved Goprelto. Therefore, Genus claims that Lannett's "reapplication" is subject to FDA's filing regulations under § 314.101, and FDA should withdraw it and refuse to file any future submissions under § 314.101(d)(9).⁹⁶ As detailed above and in the FDA July 2019 CP Response, a submission in response to a CR letter is considered an amendment after a CR action to a pending, unapproved application, not a new application. No filing determination is made for a resubmission in response to a CR letter because applications for which a CR action has been taken are considered filed, and a CR response does not trigger a new filing review. Therefore, FDA's filing regulations in § 314.101 do not apply to Lannett's submission in response to the Agency's CR letter.

Without presenting any additional information, Genus also repeats the arguments raised in the Genus February 2019 CP that Lannett's receipt of a CR letter from FDA converts Lannett's pending application into a "resubmission" that constitutes a new application submitted after the approval of Genus's NDA for Goprelto and therefore is subject to its NCE exclusivity. The FDA July 2019 CP Response denying the Genus February 2019 CP thoroughly explains why FDA can, consistent with FDA law and policy, accept Lannett's response to the CR letter before Genus's NCE exclusivity expires.

V. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

⁹⁶ Petition at 14-16.