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VIA REGULATIONS.GOV

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

On behalf of Genus Lifesciences, Inc. ("Genus"), the undersigned submits this Citizen Petition electronically under Sections 505(e) and (q) of the 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's 505(b)(2) New Drug Application ("NDA") 209963 for Goprelto® ("Goprelto"), a cocaine hydrochloride product, was approved on December 14, 2017.[1] Lannett Company, Inc.'s ("Lannett's") application for its cocaine hydrochloride product is currently under review. It has recently become apparent that the U.S. Food and Drug Administration ("FDA" or the "Agency") has applied two different standards of review to these applications. Specifically, FDA required Genus to complete **at least** five studies—(1) a QT prolongation potential study ("QT study"), (2) a renal toxicity study, (3) a hepatic toxicity study, (4) an extractable study, and (5) a leachable study (collectively, "Pre-Filing Studies")—*before* FDA would accept Genus's NDA for filing.[2] The Agency determined (and memorialized in writing) that these Pre-Filing Studies were necessary for the submission of Genus's NDA to be "sufficiently complete to permit a substantive review" by FDA.[3] Accordingly, to fulfill FDA's requirements, Genus completed these studies before it submitted its NDA on November 23, 2016.

In sharp contrast, FDA applied a different and much more lenient standard to Lannett's substantially similar cocaine hydrochloride product. Specifically, in July 2017, Lannett submitted its original 505(b)(2) application for its cocaine hydrochloride product, but did not first complete

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[1] FDA, Approval Letter for NDA 209963 (Dec. 14, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/209963Orig1s000ltr.pdf.

[2] June 15, 2015 Meeting Preliminary Comments from FDA to Genus [Exhibit 1]; July 10, 2015 Response to Preliminary Comments from Genus to FDA [Exhibit 2]; July 15, 2015 Meeting Minutes from FDA to Genus [Exhibit 3].

[3] 21 C.F.R. § 314.101(a).

at least one, and it appears, multiple, of these Pre-Filing Studies. For example, Lannett recently publicly acknowledged that it did not complete a QT study before submitting this application,[4] and other publicly available information suggests that Lannett also did not complete the renal and hepatic toxicity studies.[5] Nor, apparently, did Lannett complete the leachable studies. Nonetheless, FDA accepted Lannett's application for filing on or before December 1, 2017.

FDA's decision to apply a substantially more lenient standard and accept Lannett's application without the same studies it required Genus to supply was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, in violation of the Administrative Procedure Act.[6] Moreover, FDA's erroneous decision was highly material to Genus: After prematurely accepting Lannett's application for filing on or before December 1, 2017, FDA erroneously concluded that Lannett's application predated and was not impacted by Genus's new chemical entity ("NCE") exclusivity, which took effect on December 14, 2017, and applies until December 14, 2022.[7] To correct both these violations of law, FDA must rescind its erroneous decision to accept Lannett's 505(b)(2) application for filing, and must now refuse to accept for filing any subsequent application by Lannett for a cocaine hydrochloride product until the expiration of Genus's NCE exclusivity.[8]

FDA's regulations also prohibit the submission or resubmission of a 505(b)(2) application for a duplicate of an already-approved drug—such an applicant must instead submit an Abbreviated New Drug Application ("ANDA").[9] FDA approved Genus's Goprelto on December 14, 2017. Any submission or resubmission by Lannett after that date for a duplicate of Genus's

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[4] *See* SEEKING ALPHA, LANNETT (LCI) Q1 2019 RESULTS - EARNINGS CALL TRANSCRIPT at 3 (Nov. 7, 2018) [Exhibit 4]; *see also* Press Release, Lannett Co., Lannett Announces FDA Acceptance of 505(b)(2) New Drug Application for Cocaine Hydrochloride Topical Solution, a Proprietary Anesthetic Product (Dec. 1, 2017) [Exhibit 5].

[5] *See Topical Application of Cocaine HCl 4%, or 10%, or Placebo Solution in Local (Topical) Anesthesia, NCT02500836*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02500836 (excluding patients with renal and hepatic impairment as part of exclusion criteria) (last accessed Aug. 11, 2019) [Exhibit 6]; *Topical Application of Cocaine HCl 4% and 10% on Safety and Efficacy in Local (Topical) Anesthesia, NCT01746940*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT01746940 (same) (last accessed Aug. 11, 2019) [Exhibit 7].

[6] 5 U.S.C. § 706(2)(A).

[7] *See* Citizen Petition from K&L Gates on behalf of Genus, Docket No. FDA-2019-P-0538-0001 (Feb. 1, 2019), https://www.regulations.gov/document?D=FDA-2019-P-0538-0001 [Exhibit 8].

[8] *See* 21 U.S.C. § 355(c)(3)(E)(ii).

[9] *See* CENTER FOR DRUG EVALUATION AND RESEARCH, GOOD REVIEW PRACTICE: REFUSE TO FILE, Manual of Policies and Procedures ("MaPP") 6025.4 (2018), at 4 n.8, https://www.fda.gov/media/87035/download [hereinafter "Refuse to File MaPP"].

product must be in the form of an ANDA. *See* 21 C.F.R. § 314.101(d)(9).[10] FDA has nonetheless accepted for filing a reapplication from Lannett as a 505(b)(2) application. That decision, too, was contrary to law, or at a minimum arbitrary, capricious, and an abuse of discretion. FDA must rescind its acceptance of that reapplication for filing. And, because of Genus's NCE exclusivity, FDA cannot consider any new ANDA submissions from Lannett to be received until December 14, 2022.

ACTION REQUESTED

Genus respectfully requests that FDA take the following actions:

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 studies 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 CRL 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.

The bases for Genus's request are discussed in detail below.

STATEMENT OF GROUNDS

BACKGROUND

A. FDA Approved Goprelto, Genus's Cocaine Hydrochloride Product

FDA accepted Genus's Goprelto (NDA 209963) application for filing on November 23, 2016. Prior to acceptance, FDA and Genus discussed the specific studies necessary for acceptance for filing in pre-IND, post-IND, and pre-NDA meetings, as well as other conversations with Agency officials, occurring in 2013, 2015, and 2016. Before FDA would accept the Goprelto NDA for filing, FDA required Genus to complete multiple Pre-Filing Studies, including a QT

[10] Lannett has announced that it has "addressed and responded to all comments in the . . . Complete Response Letter including conducting a QT prolongation study," and that it believes it "will receive approval by early 2020." *See* Press Release, Lannett Co., FDA Clears Path for the Continuing Review of Lannett Company's New Drug Application (Jul. 3, 2019), http://lannett.investorroom.com/2019-07-03-FDA-Clears-Path-For-The-Continuing-Review-Of-Lannett-Companys-New-Drug-Application [Exhibit 9]. The anticipated approval date identified by Lannett suggests that it was required to conduct Pre-Filing Studies over the course of several months following the Complete Response Letter ("CRL").

study, pharmacokinetic studies on renally and hepatically impaired patients, and risk assessments related to leachables and extractables. The Agency 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.

In order to satisfy FDA requirements, Genus performed five clinical trials over a lengthy period of time, comprising 742 human subjects, including one Phase 3 pivotal clinical safety and efficacy trial, one thorough QT prolongation potential study, one pharmacokinetic study on renally impaired patients, and one pharmacokinetic study on hepatically impaired patients. Genus also performed ten non-clinical trials to further characterize the safety of the drug for its intended use, including risk assessments of potential leachables and extractables. Discussions with FDA regarding, and completion of, the required studies for Genus's cocaine hydrochloride product took years, beginning in 2013, and culminated when Genus's application was accepted for filing in January 2017.[11]

1. FDA Required Genus to Complete a QT Study Prior to NDA Submission

In advance of its pre-NDA meeting, FDA stated that Genus must complete a QT study at the time of NDA submission, *i.e.*, before FDA would file the application:

> 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 population including, but not limited to: . . . QT prolongation potential.[12]

Genus responded to FDA's preliminary comments on July 10, 2015, specifically asking whether Genus could forgo a QT study.[13] During the July 14, 2015 pre-NDA meeting, FDA again reiterated

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[11] Center for Drug Evaluation and Research Administrative and Correspondence Documents, Application 209963 (Feb. 6, 2017) at 96, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000Admincorres.pdf ("Please refer to your New Drug Application (NDA) dated and received November 23, 2016 . . . We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application."). By contrast, Lannett does not appear to have begun its process to seek drug approval until very late in 2015 or early in 2016. *See* Citizen Petition from Lannett et al. to FDA, Docket No. FDA-2012-P-0189-0001 (Feb. 24, 2012) at 1, https://www.regulations.gov/document?D=FDA-2012-P-0189-0001 [Exhibit 10]; Response to Citizen Petition from FDA to Lannett et al., Docket No. FDA-2012-P-0189-0006 (Nov. 12, 2015), at 16, https://www.regulations.gov/document?D=FDA-2012-P-0189-0006 [Exhibit 11].

[12] Exhibit 1 at 11.

[13] *See* Exhibit 2 at 11.

that, if Genus submitted an application without a QT study, and if the justification for not including a QT study was not accepted by the Agency, FDA would refuse to file the NDA.[14] Based on these demands by the Agency, Genus conducted the QT study to support the NDA as required by FDA, which was completed on June 29, 2016.[15] This study was conducted over the course of multiple months and included 24 patients.[16] Based on the results of this study, FDA ultimately concluded that "no safety events [were] identified that were deemed to be of clinical importance with respect to conduction abnormalities (syncope, significant ventricular arrhythmias or sudden cardiac death), that the overall electrocardiogram acquisition and interpretation were acceptable, and that there was no effect on the PR or QRS intervals."[17]

2. FDA Required Genus to Complete Pharmacokinetic Studies on Renally and Hepatically Impaired Patients Prior to NDA Submission

Throughout correspondence and meetings in June and July 2015, FDA repeatedly stated that Genus must complete pharmacokinetic studies on renally and hepatically impaired patients before FDA would accept its NDA for filing. FDA regulations require safety and effectiveness data from subgroups of the population of patients treated, such as "patients with different levels of severity of the disease."[18] Prior to its pre-NDA meeting, Genus was informed by FDA that Genus "must address all pertinent clinical pharmacology information related to the following aspects of the drug and the pharmacokinetics of the drug in special population including, but not limited to: . . . PK [pharmacokinetic] and dosing in special populations (e.g., . . . hepatic and renal impairment)."[19] Genus provided a scientific justification to the Agency for why such studies were not necessary for its cocaine hydrochloride product, which FDA rejected. Specifically, Genus asked FDA to agree that studies conducted in special populations were not relevant because Goprelto is "primarily a topical product designed to have minor systemic exposure, and thus special population studies are not relevant as they would be for a systemic drug product."[20] At the July 14, 2015 pre-NDA meeting, FDA reiterated that, "a complete clinical pharmacology package is required *at the time of NDA submission* . . . address[ing] all pertinent clinical pharmacology information related to the following aspects of the drug and the pharmacokinetics of the drug in

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[14] *See* Exhibit 3 at 17-18. *See id*. at 20 ("All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.").

[15] Center for Drug Evaluation and Research Summary Review, Application 209963 (Dec. 14, 2017), at 3, 8, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000SumR.pdf [hereinafter "Goprelto Summary Review"].

[16] *See id*. at 3 (describing the "Study Objective" of "Study 2015017 as "exclud[ing] an effect of 4% and 8% topical cocaine solution following topical intransal administration of a single dose on placebo-corrected QT by Fridericia's formula (QTcF)").

[17] *Id*. at 12-13.

[18] 21 C.F.R. § 314.50(d)(5).

[19] Exhibit 1 at 11.

[20] Exhibit 2 at 11.

special populations including but not limited to . . . PK and dosing in special populations (e.g., effect of . . . hepatic and renal impairment . . .)," and stated that Genus "must provide evidence of low systemic exposure levels using data from the PK study."[21] As required, Genus then conducted the pharmacokinetic studies over several months in 2016[22] and included the results of these studies in its NDA submission.[23] Based on the results of these studies, FDA ultimately concluded that initial dose adjustments were not required in patients with renal or hepatic impairment.[24] However, due to Genus's discovery of "sustained higher exposure of cocaine in the post-absorptive phase and the potential for a cumulative increase in systemic concentrations," FDA "recommended that a second dose of topical cocaine solution not be administered to subjects with hepatic impairment within 24 hours of the initial dose."[25]

3. FDA Required Genus to Complete Risk Assessments of Both Leachables and Extractables Prior to NDA Submission

Similarly, FDA repeatedly insisted that Genus complete risk assessments regarding potential leachables and extractables following specific parameters before filing its application.[26]

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[21] Exhibit 3 at 17-18 (emphasis added).

[22] *See* Goprelto Summary Review at 2 (describing the "Study Objective" of "Study 2015013 as "evaluat[ing] the systemic PK [pharmacokinetic] and safety of 4% topical cocaine solution following topical intranasal administration of a single dose to subjects with either normal renal function or severe renal impairment"); *id*. at 2-3 (describing the "Study Objective" of "Study 2015014 as "evaluat[ing] the systemic PK and safety of 4% topical cocaine solution following topical intranasal administration of a single dose to subjects with normal hepatic function or hepatic impairment").

[23] *See id*. Genus also conducted a thorough literature search for relevant, well-controlled studies including patients with renal or hepatic impairments, but found none.

[24] *See id*. at 12 ("[T]he minimal effect of renal impairment on exposure of the active parent drug, cocaine, coupled with the possible loss of efficacy at the site of action if dose were to be reduced, led the team to recommend that a dose adjustment is not required in subjects with reduced renal function. . . . The team did not recommend a dose adjustment in patients with reduced hepatic function for the same reasons as was cited for patients with renal impairment.").

[25] *Id*.

[26] Certain drug formulations and container closure systems present a risk that compounds from the container closure may "leach" from the container closure to the formulation as a result of direct contact with the formulation. Furthermore, certain compounds can be "extracted" from a container closure system in the presence of a solvent. Studies can be performed to determine whether a specific combination of drug product formulation and container closure system presents risks of leachables or extractables by testing for relevant compounds. *See* U.S. Pharmacopeia <1663>, <1664>. Although each NDA must include a chemistry, manufacturing, and controls section, FDA regulations do not specifically require pre-submission leachable and extractable risk assessment before filing an NDA, *see generally* 21 C.F.R. § 314.50; U.S. Pharmacopeia <1663>, <1664>

On August 20, 2013, FDA responded to questions submitted by Genus before a pre-IND meeting and stated that Genus's "NDA submission must contain information on potential leachables and extractables from the drug container closure system, unless specifically waived by the Division."[27] The Agency did not waive this requirement, and referred Genus to two guidance documents for conducting its required safety assessment.[28]

On June 15, 2015, FDA reiterated its position that Genus's submission must include "information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division" and stated that "evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc."[29] The Agency also stated that:

> The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a

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(testing guidelines for conducting these tests); 21 C.F.R. Parts 210 and 211 (establishing current Good Manufacturing Practices for drug products), in part because not all drug product formulations and container closure systems present the same risks. In guidance, FDA has described general principles for submitting information on packaging materials used for human drugs and has stated that"[e]ach application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use." CENTER FOR DRUG EVALUATION AND RESEARCH & CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY: CONTAINER CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS (May 1999), at 5, https://www.fda.gov/media/70788/download.

[27] August 20, 2013 Pre-IND Meeting Request – Written Responses from FDA to Genus at 7 [Exhibit 12].

[28] *See id*. at 7 ("The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the FDA Guidance document '*Container Closure Systems for Packaging Human Drugs and Biologics*' and '*Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*'").

[29] Exhibit 1 at 9. *See also id*. (also requiring Genus to justify "[t]he choice of solvents and conditions for the extraction studies;" use "[t]he results of the extraction studies . . . to assure that you are adequately monitoring the drug product stability samples for potential leachables;" "evaluate at least three batches of your drug product over the course of your stability studies and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration;" base "[t]he approach for toxicological evaluation of the safety of leachables . . . on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing);" and, in its safety assessment, "take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds.").

> toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, **you should still evaluate at least three batches of your drug product over the course of your stabilities studies and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration**. . . . The risk assessment should be based on the levels of leachables detected in the long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.[30]

FDA also stated that the Agency may refuse to file Genus's NDA if "the submission lacks an adequate extractable/leachable risk assessment."[31]

Genus then again proposed that the application not contain leachable and extractable information, and, in response to FDA's preliminary comments, asked whether Genus could use "only water . . . as a solvent for the extraction studies."[32] FDA did not agree (and again did not waive the requirement), and stated that, "the extraction studies should use multiple solvents and that container-closure materials should be exposed to harsh environments so that the compounds that will be assayed for . . . long-term stability can be identified."[33] Regarding the toxicology assessment, FDA stated that the assessment "will be based on what is found in the leachables, ideally over long-term stability" and that Genus "should test for leachables in 3 batches over multiple timepoints throughout the expiry."[34]

By requiring this 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 solvents to harsh environments for long-term stability (at least twelve months) over three batches and collecting data at beginning, middle, and end time points. To comply with FDA's requirement, Genus conducted the lengthy required assessment and included the results in its NDA submission.

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[30] *Id*. (emphasis added).

[31] *Id*. at 10-11. During the pre-NDA meeting, FDA suggested that, if Genus could "obtain an LOA [letter of analysis] from the DMF [Drug Master File] holder" and "[i]f the DMF has appropriate extractable/leachable data to support the proposed product," then Genus might "not need to conduct the study." Exhibit 3 at 13. Such a letter of analysis was not available from the DMF for the cocaine hydrochloride product.

[32] Exhibit 2 at 8 (stating that Genus's application will "address extractables and leachables of the container closure system as per the applicable guidances 'and the USP general chapters' requirements" and asking whether FDA agreed that Genus could use "only water . . . as a solvent for the extraction studies.").

[33] Exhibit 3 at 13.

[34] *Id*. at 14.

4. FDA Accepted the Genus NDA for Filing, and Approved Goprelto

After Genus conducted the Pre-Filing Studies, FDA accepted Genus's NDA for filing and, on December 14, 2017, approved 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.[35] The Agency also awarded Goprelto NCE exclusivity under section 505(c)(3)(E)(ii). Goprelto's NCE exclusivity is currently set to expire on December 14, 2022 (five years from approval).

B. Lannett Submitted a 505(b)(2) NDA for its Cocaine Hydrochloride Product Without the Required Pre-Filing Studies

In 2006, FDA published its first guidance on marketing unapproved drug products, which stated that "illegally marketed drugs must obtain FDA approval."[36] In 2008, Lannett began marketing a version of its cocaine hydrochloride product without FDA approval.[37] In 2011 and while Lannett marketed its unapproved cocaine hydrochloride product, FDA published a second guidance on unapproved drug products, reiterating that illegally marketed drugs must obtain FDA approval and describing FDA's priorities for taking enforcement action against illegally marketed unapproved drugs.[38] Despite this guidance from FDA, Lannett continued selling its unapproved cocaine hydrochloride product.

On February 24, 2012, Lannett petitioned FDA to acknowledge (1) the "grandfather" status of cocaine hydrochloride pursuant to the FDCA's 1938 "grandfather clause," and (2) "that Lannett's . . . Cocaine HCl Product[] may be legally marketed based on [its] 'grandfather' status."[39] FDA denied the Citizen Petition, finding that Lannett did not produce sufficient information to justify the "grandfather" status of its product.[40] FDA stated that "[t]he evidence" Lannett provided is "inadequate to support a conclusion" that both Lannett's product, and "cocaine HCl products in

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[35] Otolaryngologists use cocaine hydrochloride while performing medical procedures such as biopsies, endoscopies, nasal cauterization, foreign body removal, and nasal debridement, among others.

[36] CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR FDA STAFF AND INDUSTRY: MARKETED UNAPPROVED DRUGS - COMPLIANCE POLICY GUIDE (Jun. 2006), https://www.regulations.gov/docket?D=FDA-2003-D-0030-0008.

[37] *See, e.g.*, *Cocaine Hydrochloride*, DAILYMED, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=24faa247-fe12-4574-881d-445b078b3e87, and downloadable drug label information available at that site (last updated May 9, 2019) ("Unapproved Labeling for Lannett's Cocaine Hydrochloride Product") [Exhibit 13].

[38] CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR FDA STAFF AND INDUSTRY: MARKETED UNAPPROVED DRUGS – COMPLIANCE POLICY GUIDE (Sept. 2011), https://www.fda.gov/media/71004/download.

[39] Exhibit 10 at 1.

[40] Exhibit 11 at 16.

general . . . meet the requirements of the 1938 grandfather clause."[41] FDA also denied Lannett's request to not apply "the new drug requirements, including premarket approval and user fees" to Lannett's products."[42] Despite FDA's clear response to Lannett that its unapproved drug product was illegal, Lannett continued to market its unapproved cocaine hydrochloride product,[43] and even continued to advertise its product as "pre-1938" after the FDA decision.[44]

In or around July 2017, Lannett submitted a 505(b)(2) application for its cocaine hydrochloride product. Lannett did not include at least one and, it appears, multiple of the Pre-Filing Studies that FDA expressly required Genus to submit in its original submission to FDA, which include a QT study, a renal toxicity study, a hepatic toxicity study, a leachable study, and an extractable study.[45] Despite these deficiencies in Lanett's submission, FDA nonetheless accepted Lannett's application for filing on or before December 1, 2017, and set a 10-month Prescription Drug User Fee Act ("PDUFA") date of July 21, 2018.[46]

Genus subsequently learned that Lannett's application lacked at least one of the key studies Genus was required to submit, and Lannett may not have completed **any** of the Pre-Filing Studies before FDA accepted its NDA for filing. For example, during their November 7, 2018 First Quarter Financial Results Conference Call, Lannett stated that their "NDA continues to progress with the FDA and we expect to conclude a gating QT study by January."[47] Thus, publicly available information demonstrates that Lannett had not completed a QT study as of November 7, 2018 and that FDA accepted Lannett's 505(b)(2) application for filing on or before December 1, 2017 without a completed a QT study.

Likewise, even though FDA repeatedly stated that pharmacokinetic studies on renally and hepatically impaired patients are necessary for a sufficiently complete NDA for cocaine hydrochloride product to permit a substantive review, it appears that the Agency accepted Lannett's 505(b)(2) application for filing without completed pharmacokinetic studies on renally

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[41] *Id*.

[42] *Id*. at 17.

[43] We understand that Lannett has agreed to cease distribution of its unapproved cocaine hydrochloride product on August 15, 2019. *See* Lannett Quarterly Report (Form 10- Q), at 37 (May 7, 2019), https://www.sec.gov/Archives/edgar/data/57725/000110465919027244/a19-5884_110q.htm [Exhibit 14].

[44] This false advertising, among other allegations of false advertising, is the subject of a Lanham Act case pending in the Northern District of California. *See Genus Lifesciences Inc. v. Lannett Co.*, No. 3:18-cv-07603-WHO (N.D. Cal. filed Dec. 18, 2018).

[45] Even if Lannett did include some data from leachable and extractable studies in its original application, Lannett may have not conducted the results of the full studies expressly required by FDA of Genus.

[46] Exhibit 5.

[47] Exhibit 4 at 3.

and hepatically impaired patients. The exclusion criteria for the two clinical trial protocols published on clinicaltrials.gov related to Lannett's cocaine hydrochloride product (NCT02500836 and NCT01746940) suggest that patients with hepatic impairment (e.g., high serum ALT, AST, and bilirubin) and renal impairment (e.g., normal serum potassium) were not included in the studies.[48] It appears that Lannett had not completed any pharmacokinetic studies in patients with renal or hepatic impairment before FDA accepted Lannett's 505(b)(2) application for filing on or before December 1, 2017, *and has not since completed these studies*).

Finally, Lannett's proposed packaging in its 505(b)(2) application includes an amber glass vial with a polypropylene cap,[49] materially identical to the amber glass vial with a polypropylene cap for which FDA required Genus to conduct leachable and extractable risk assessment. It appears that Lannett did not complete such a risk assessment for leachables in the manner FDA insisted Genus perform these studies prior to Lannett's submission and FDA's acceptance for filing of Lannett's 505(b)(2) application.

Although FDA accepted Lannett's application for filing notwithstanding these filing deficiencies, in July 2018, FDA issued a CRL to Lannett. Lannett subsequently announced that it "is in the process of addressing the Complete Response Letter,"[50] including completing a QT study,[51] which Lannett has subsequently said was completed in December 2018.[52] Based on Lannett's public statements, Lannett has resubmitted its application in response to the CRL, and FDA has wrongfully accepted that reapplication for filing.

ARGUMENT

I. FDA MUST RESCIND ITS ACCEPTANCE FOR FILING OF LANNETT'S 505(B)(2) APPLICATION BECAUSE LANNETT DID NOT COMPLETE MANDATORY PRE-FILING STUDIES

As discussed in detail above, in order to accept Genus's NDA for its cocaine hydrochloride product for filing, FDA required that Genus first complete the Pre-Filing Studies. Lannett's

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[48] *See* Exhibit 6; Exhibit 7.

[49] This statement is based on Lannett's unapproved cocaine hydrochloride product appearing to contain an amber glass bottle with a polypropylene cap.

[50] Lannett Quarterly Report (Form 10-Q), at 34 (Nov. 8, 2018), https://www.sec.gov/Archives/edgar/data/57725/000110465918066991/a18-31123_110q.htm [Exhibit 15].

[51] Exhibit 4 at 3. *See also* Special Investor Conference Call, Verbatim Report of Webcast by Lannett, at 28-29 (Aug. 20, 2018) ("we did receive a complete response letter, and suffice to say, the FDA had asked for additional information along the lines of our expectations, which we are working on.") [Exhibit 16].

[52] SEEKING ALPHA, LANNETT (LCI) Q2 2019 RESULTS – EARNINGS CALL TRANSCRIPT, at 4 (Feb. 6, 2019) [Exhibit 17].

505(b)(2) application for its substantially similar cocaine hydrochloride product lacked at least one and, it appears, multiple other of these required Pre-Filing Studies. Nonetheless, FDA departed from its own requirements and accepted the Lannett 505(b)(2) application for filing. Such action is contrary to law, and arbitrary, capricious, and an abuse of discretion. FDA must correct its error by rescinding its acceptance for filing of Lannett's application. And FDA also cannot accept any reapplication for Lannett's cocaine hydrochloride product until the expiration of Goprelto's NCE exclusivity, and must rescind its acceptance if the Agency has already done so.

FDA must refuse to file an NDA when, among other things, it is materially incomplete.[53] FDA's regulations provide that an NDA is incomplete when it "does not on its face contain information required under" the FDCA and its implementing regulations.[54] FDA has interpreted that regulation such that FDA will also refuse to file an application that is not "complete as agreed upon by the FDA and the applicant at the presubmission meeting."[55]

Prior to accepting Lannett's 505(b)(2) application, FDA determined that the Pre-Filing Studies were necessary for the submission of an NDA for a cocaine hydrochloride product to be "sufficiently complete to permit a substantive review."[56] This determination established the standard for NDA submissions for cocaine hydrochloride. Genus's and Lannett's products are similarly situated in all material respects, and FDA cannot rationalize any appropriate basis for arbitrarily treating them in such an obviously different fashion.[57] Black letter principles of administrative law prohibit the agency from treating similarly-situated applicants in an unlike manner.[58] Specifically, while FDA "has discretion" to determine whether to treat products "identical in all material respects" in a particular way, the Agency cannot "treat them dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason."[59] In this case, Genus's Goprelto and Lannett's cocaine

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[53] *See* Refuse to File MaPP at 5. *See also* CENTER FOR DRUG EVALUATION AND RESEARCH, DRAFT GUIDANCE FOR INDUSTRY: REFUSE TO FILE: NDA AND BLA SUBMISSIONS TO CDER (Dec. 2017), at 1, https://www.fda.gov/media/109758/download.

[54] 21 C.F.R. § 314.101(d)(3).

[55] *See* Refuse to File MaPP at 4.

[56] 21 C.F.R. § 314.101(a).

[57] *See Indep. Petroleum Ass'n of Am. v. Babbitt*, 92 F.3d 1248, 1260 (D.C. Cir. 1996) ("The treatment of cases A and B, where the two cases are functionally indistinguishable, must be consistent. That is the very meaning of the arbitrary and capricious standard.").

[58] *See* 5 U.S.C. § 706(2)(A); *Indep. Petroleum Ass'n of Am.*, 92 F.3d at 1248; *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997) ("The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious." (citation omitted)).

[59] *Bracco Diagnostics*, 963 F. Supp. at 28. *See also PREVOR v. FDA*, 895 F. Supp. 2d 90, 100 (D.D.C. 2012) (holding that FDA failed to distinguish a combination product assigned to Center for Drug Evaluation and Research for review from a combination product assigned to the Center

hydrochloride product are identical in all material respects because they contain the same active ingredient.[60] Furthermore, FDA "cannot silently depart from previous policies or ignore precedent,"[61] such as the precedent it established regarding the necessity of including the results of the Pre-Filing Studies in the Goprelto NDA in order to ensure acceptance for filing of the application.

Yet the Agency has violated those foundational principles by accepting Lannett's 505(b)(2) application when that application did not contain at least one and, it appears, multiple of the required Pre-Filing Studies.[62] Because FDA's decision to accept that application was legally erroneous,[63] FDA should correct that mistake now, without the necessity for judicial intervention, by rescinding its acceptance.[64] FDA must also refuse to accept for filing any subsequent

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for Devices and Radiological Health where the device portions of both of the combination products played "almost identical roles").

[60] *Compare* FDA, Goprelto Labeling at 1 (Dec. 14, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209963lbl.pdf [hereinafter, "Goprelto Labeling"] (listing "cocaine hydrochloride" as the active ingredient) *with* Exhibit 13 at 6 ("Unapproved Labeling for Lannett's Cocaine Hydrochloride Product") (listing "cocaine hydrochloride" as the "Active Ingredient/Active Moiety"). *See also* Response to Citizen Petition from FDA to K&L Gates on behalf of Genus, Docket No. FDA-2019-P-0538-0026 (July 1, 2019), at 2, https://www.regulations.gov/document?D=FDA-2019-P-0538-0026 ("The active ingredient in Goprelto is cocaine hydrochloride; cocaine is the active moiety.") [Exhibit 18].

[61] *AT&T Corp. v. FCC*, 236 F.3d 729, 736-37 (D.C. Cir. 2001) (citations omitted).

[62] *See Bracco Diagnostics*, 963 F. Supp. at 28; *PREVOR*, 895 F. Supp. 2d at 100; *AT&T Corp.*, 236 F.3d at 736-37.

[63] *See* 21 C.F.R. § 314.60(c)(2). FDA cannot fix its error by relying on Genus's Pre-Filing Studies. FDA's own regulations forbid a second applicant (i.e., Lannett) from implicitly relying on the studies of a first applicant (i.e., Genus) who obtains NCE exclusivity during the pendency of the first applicant's exclusivity. *See* 21 C.F.R. § 314.108(b)(2). FDA cannot rely on Genus's Pre-Filing Studies, and must require Lannett to conduct the same studies required of Genus.

[64] It is a longstanding principle of administrative law that agencies have the inherent authority to correct their own errors. *See, e.g., United Gas Improvement Co. v. Callery Props., Inc.*, 382 U.S. 223, 229 (1965) ("An agency, like a court can undo what is wrongfully done by virtue of its order."); *Ivy Sports Med., LLC v. Burwell*, 767 F.3d 81, 86 (D.C. Cir. 2014) ("[A]dministrative agencies are assumed to possess at least some inherent authority to revisit their prior decisions, at least if done in a timely fashion."). Indeed, FDA has made unambiguous statements in federal to court regarding its inherent authority to even rescind *approvals* with or without court order. *See, e.g., Lannett Co. v. FDA*, 300 F. Supp. 3d 34, 38-39 (D.D.C. 2017) (describing FDA's "inherent authority to correct errors"). *See also, e.g., Lannett*, 300 F. Supp. 3d at 38 (FDA has "'inherent authority' [to withdraw approval] if done within a reasonable period of time and if Congress has not otherwise spoken."); *Ranbaxy Labs., Ltd. v. Burwell*, 82 F. Supp. 3d 159, 194 (D.D.C. 2015) ("the FDA has the inherent authority to revisit its own decisions, since 'the power to reconsider is inherent in the power to decide'") (citing *Ivy Sports Med.*, 767 F.3d at 86).

submission by Lannett for a cocaine hydrochloride product until the expiration of Goprelto's NCE exclusivity. Until the expiration of this period of exclusivity, FDA cannot lawfully accept for filing any submission or resubmission by Lannett for its cocaine hydrochloride product.

II. FDA MUST RESCIND ITS ACCEPTANCE OF LANNETT'S RESUBMITTED 505(B)(2) APPLICATION FOR FILING AND PERMIT LANNETT TO SUBMIT ITS APPLICATION ONLY AS AN ANDA

Alternatively, Lannett's recent reapplication for cocaine hydrochloride is barred by 21 C.F.R. § 314.101(d)(9) because it is a duplicate of an already-approved drug (namely, Genus's Goprelto). Lannett's cocaine hydrochloride product is now eligible for approval only under section 505(j) of the FDCA, as an ANDA.[65]

FDA's regulations authorize the Agency to "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 FDCA.[66] By policy, FDA will refuse to file any such 505(b)(2) applications for duplicate products "which may be approved via section 505(j) at the time of the application's submission."[67] The Agency has interpreted "duplicate" to refer to "a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug."[68] Lannett's cocaine hydrochloride product shares the same active ingredient(s), dosage form, strength, route of administration, and may share the same, or overlapping, conditions of use as Goprelto, and is therefore its "duplicate." Goprelto was approved on December 14, 2017 as the first approved cocaine hydrochloride product. In accordance with the relevant regulations and long-standing precedent, Genus's Goprelto is the Reference Listed Drug ("RLD") for cocaine hydrochloride. After the date of Goprelto's approval, Lannett's cocaine

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[65] Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,901 (proposed July 10, 1989). *See, e.g.*, Response to Citizen Petition from FDA to Mutual, Docket No. FDA-2010-P-0614-0072 (May 25, 2011), at 26, https://www.regulations.gov/document?D=FDA-2010-P-0614-0072 (requiring applicant to submit an ANDA for colchicine tablet instead of a 505(b)(2) application) [Exhibit 19].

[66] 21 C.F.R. § 314.101(d)(9).

[67] Response to Response to Citizen Petition from FDA to Genpharm, Docket No. FDA-2003-P-0338-0002 (June 24, 2004), https://www.regulations.gov/document?D=FDA-2003-P-0338-0002 (responding to a petition regarding an applicant who had submitted a 505(b)(2) before the approval of a third party's 505(b)(2) application on a duplicate drug product and determining that, in this situation, 21 C.F.R. § 314.101(d)(9) did not require the applicant to convert its 505(b)(2) to an ANDA) [Exhibit 20]. *See also generally* CDER 21ST CENTURY REVIEW PROCESS DESK REFERENCE GUIDE AT 20, Appendix B, https://www.fda.gov/media/78941/download (explaining that "[i]f the application is incomplete on its face and the deficiencies cannot be rectified readily, an RTF should be considered. Missing information is judged against the regulations detailing the requirements of an application and the grounds on which an application can be refused for filing.").

[68] Refuse to File MaPP at 4 n.8.

hydrochloride product was eligible for approval via section 505(j) and, therefore, any submission after that date seeking approval of that duplicate product must be filed as an ANDA to this RLD.[69]

Further, no exception to FDA's refuse to file policy permitting the Agency to file Lannett's 505(b)(2) application applies here. FDA's Manual of Policies and Procedures governing refuse to file procedures authorize FDA to accept a potentially duplicative 505(b)(2) application in limited circumstances, specifically for "certain complex drug products, [where] it may be unclear whether the drug product proposed in a 505(b)(2) application can be shown to contain the *same* active ingredient as a listed drug. . . ."[70] This exception is not applicable to Lannett's 505(b)(2) application: cocaine hydrochloride is not complex, and Lannett's application is for the same active ingredient as Genus's approved NDA for Goprelto.[71] Thus, any attempt by Lannett to submit an application for a duplicate cocaine hydrochloride product after the December 14, 2017 approval of Genus's Goprelto must be submitted as an ANDA.

Nor does Lannett's submission prior to Goprelto's approval permit the Agency to accept the Lannett application as filed. Lannett's receipt of a CRL from FDA converts Lannett's pending application into a "resubmission" that is subject to the regulatory landscape in existence at the time it is submitted, as detailed in Genus's earlier Citizen Petition.[72] A resubmission following the receipt of a CRL constitutes a new application submitted after the approval of Genus's NDA. FDA defines a "resubmission" as, "in the context of a complete response letter, . . . **submission** by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter."[73] The Agency is bound to comply with its own regulations and policy in

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[69] *See* 21 C.F.R. § 314.101(d)(9).

[70] Refuse to File MaPP at 4 n.8 (emphasis in original).

[71] *Compare* Goprelto Labeling (listing "cocaine hydrochloride" as the active ingredient) *with* Exhibit 13 at 1, 6 ("Unapproved Labeling for Lannett's Cocaine Hydrochloride Product") (listing "cocaine hydrochloride" as the "Active Ingredient/Active Moiety"). Indeed, FDA has specifically acknowledged that if a cocaine hydrochloride product were approved before submission of an application for a subsequent cocaine hydrochloride product, such that the subsequent product was a duplicate, that the subsequent product must be submitted as an ANDA. *See* Exhibit 12 at 13 ("Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a 'duplicate' of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.").

[72] *See* Exhibit 8.

[73] 21 C.F.R. § 314.3(b) (emphasis added).

reviewing this submission.[74] Because Lannett's new submission was made *after Goprelto's approval* as a 505(b)(2) application, FDA must rescind its acceptance of Lannett's new submission for filing pursuant to 21 C.F.R. § 314.101(d)(9). FDA may only permit Lannett to submit an ANDA for its cocaine hydrochloride product, and only upon expiration of Goprelto's NCE exclusivity.

Conclusion

Agencies of the United States must treat similar cases in a similar manner, and FDA should follow its own statutes, regulations, guidance documents, and policies. For the reasons set forth above, Genus respectfully requests that FDA take the following action:

1. Rescind its acceptance for filing of Lannett's 505(b)(2) application if Lannett did not complete the QT, renal, hepatic, leachable, or other studies deemed necessary for an NDA for a cocaine hydrochloride product to be sufficiently complete to permit substantive review; and refuse to file any resubmission of Lannett's 505(b)(2) 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 CRL 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.

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

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[74] *Pettiford v. Secretary of Navy*, 858 F. Supp. 2d 86, 91 (D.D.C. 2012) ("An agency is bound by its own regulations."); *Conn. Light & Power Co. v. NRC*, 673 F.2d 525, 536 (D.C. Cir. 1982) ("An agency is bound by its own regulations and commits procedural error if it fails to abide by them.").

submitted on or about the following date: June 30, 2019 (information about specific communications between the applicant's regulatory agent and FDA); January 6, 2019 (information about Lannett's 505(b)(2) application); November 11, 2018 (information about Lannett's 505(b)(2) application related to a QT study); August 20, 2018 (information about Lannett's failure to obtain approval and its receipt of a CRL). Upon information and belief, the party knew about the requirements for submitting and filing an NDA at the time the requirements were told to the party, which occurred in during 2015-2016 timeframe. 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.

Respectfully submitted,

Philip J. Perry
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