555 Eleventh Street, N.W., Suite 1000
Washington, D.C. 20004-1304
Tel: +1.202.637.2200 Fax: +1.202.637.2201
www.lw.com

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November 27, 2019

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

Re: Docket ID FDA-2019-P-3855

On behalf of Genus Lifesciences, Inc. ("Genus"), we submit the attached documents in response to a request by FDA's Office of the Chief Counsel.

On July 14, 2016, representatives for Genus participated in a teleconference with FDA regarding the QT prolongation study ("QT study"), renal toxicity study, and a hepatic toxicity study described in our Citizen Petition.[1] Representatives from FDA included Dr. Rigoberto Roca, Deputy Director, DAAAP; Dr. Leah Crisafi, Clinical Team Leader; and Amelia Luckett, Medical Officer/Clinical Reviewer. During the teleconference, Dr. Roca told Genus's representatives that Genus would be required to submit the results from the QT study and the renal and hepatic toxicity studies as part of its initial NDA submission. This meeting is described in the four attached emails.[2] FDA did not provide Genus with meeting minutes after this teleconference.

As a result of this teleconference, Genus then conducted the renal and hepatic toxicity studies over several months in 2016[3] and included the results of these studies in its NDA

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[1] *See* Citizen Petition from Latham & Watkins LLP on behalf of Genus, Docket No. FDA-2019-P-3855-0001 at 1, 4-6 (Aug. 16, 2019), https://www.regulations.gov/document?D=FDA-2019-P-9855-0001.

[2] See Exhibit A (declaration of Melissa Goodhead), Attachment 1 (July 24, 2016 Email from Melissa Goodhead to Larry Dalesandro and Jeff Moshal); Attachment 2 (July 24, 2016 Email from Melissa Goodhead to Jeff Moshal and Bill Reightler); Attachment 3 (July 25, 2016 Email from Hilary Sheevers to Cynthia Dinella, Jeff Moshal, Robert Guttendorf, Pauline McEwan, Tacey White, and Melissa Goodhead); Attachment 4 (July 27, 2016 Email from Melissa Goodhead to Robert Guttendorf, Jeff Moshal, Cynthia Dinella, Bill Reightler, and Jacqueline Sterner).

[3] *See* Center for Drug Evaluation and Research Summary Review, Application 209963 (Dec. 14, 2017), at 2 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000SumR.pdf (describing the "Study Objective" of "Study 2015013 as "evaluat[ing] the systemic PK

submission.[4] Because Genus was required to submit the renal and hepatic toxicity studies as part of its NDA, the submission was delayed until November 23, 2016. Based on the results of these studies, FDA ultimately concluded that no adjustment to the initial dose administered to patients with renal or hepatic impairment was required.[5] However, as a result of these studies, Genus discovered that there is a "sustained higher exposure of cocaine in the post-absorptive phase and the potential for a cumulative increase in systemic concentrations;" in other words, patients with renal or hepatic impairment are exposed to the active ingredient for a longer period of time after its administration, and, as a result, there is potential for higher concentration of the active ingredient in these patients. As a result of this discovery, and to ensure that the drug is properly and safely administered to patients, FDA required Genus to include the following language in its labeling: "[D]o not administer a second dose of GOPRELTO to these patients [with hepatic impairment] within 24 hours of the first dose."[6]

In sharp contrast, it appears that FDA applied a different and much more lenient standard to the application submitted by Lannett Company, Inc. ("Lannett") for its substantially similar cocaine hydrochloride product. Specifically, in July 2017, Lannett submitted its original 505(b)(2) application for its cocaine hydrochloride product. It appears that FDA accepted Lannett's 505(b)(2) application for filing without completed renal and hepatic toxicity studies. Specifically, the publicly available information regarding Lannett's clinical trials suggests that patients with renal and hepatic impairments were excluded from these trials, and there is no publicly available information suggesting that Lannett conducted separate trials for or including patients with renal and/or hepatic impairments.[7] It also appears that Lannett had not completed any pharmacokinetic

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[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").

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

[5] *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.").

[6] *See* FDA, Goprelto Labeling at 9 (Dec. 14, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209963lbl.pdf ("Monitor patients with hepatic impairment for adverse reactions such as headache, epistaxis, and clinically-relevant increases in heart rate or blood pressure and do not administer a second dose of GOPRELTO to these patients within 24 hours of the first dose").

[7] *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 (last accessed Nov. 21, 2019); *Topical*

studies in patients with renal or hepatic impairment before FDA accepted Lannett's 505(b)(2) resubmission for filing on or before December 1, 2017, and has not since completed these studies.

The results of the renal and hepatic toxicity studies that FDA instructed Genus to conduct were directly material to the dosage information that FDA required Genus to include in its labeling. Such studies should be material to Lannett's application and proposed labeling for the same reasons. 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.[8] Moreover, FDA's erroneous decision was highly prejudicial 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.[9] 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.[10]

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").[11] FDA approved Genus's Goprelto on December 14, 2017. Any submission or resubmission by Lannett after that date for a duplicate of Genus's product must be in the form of an ANDA.[12] FDA has nonetheless accepted for filing a resubmission from Lannett as a 505(b)(2) application. That decision, too, was contrary to law, or

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Application of Cocaine HCl 4% and 10% on Safety and Efficacy in Local (Topical) Anesthesia, NCT01746940, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT01746940 (last accessed Nov. 21, 2019). The exclusion criteria for these two clinical trial protocols 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.

[8] 5 U.S.C. § 706(2)(A).

[9] 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.

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

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

[12] *See* 21 C.F.R. § 314.101(d)(9). 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.

at a minimum arbitrary, capricious, and an abuse of discretion. FDA must rescind its acceptance of that resubmssion 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, and must only accept a new NDA submission after Lannett has completed the renal and hepatic studies that Genus was required to complete.

We are providing this additional information at FDA's request, and are simultaneously filing this information in the pending Citizen Petition docket FDA-2019-P-3855. This information provides additional detail and thereby supplements and amends that Citizen Petition. This information illustrates clearly that any approval of Lannett's product without requiring the same renal and hepatic studies FDA mandated for Genus, and without the resulting dosage requirements also mandated by FDA for Genus, would be arbitrary and capricious and contrary to law. In addition, to eliminate any possible ambiguity, we are amending the Citizen Petition in accordance with 21 C.F.R. § 10.30(g) to add a third request (which is related to those already presented) that FDA refuse to approve any NDA for a cocaine hydrochloride product without completing similar QT, renal, hepatic, and leachable studies conducted by Genus and described in our Citizen Petition that demonstrate the safety and efficacy of the product.

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about October 22, 2019. If I receive 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 the document.

Respectfully submitted,

John R. Manthei
Philip J. Perry
Andrew D. Prins
Monica C. Groat
of LATHAM & WATKINS LLP

EXHIBIT A

DECLARATION OF MELISSA L. GOODHEAD, M.SC., RAC

1. I am the founder and owner of Pharmaceutical Project Solutions, Inc. I am submitting this declaration in support of Genus Lifesciences, Inc. ("Genus") and Citizen Petition FDA-2019-P-3855.

2. I have personal knowledge of the facts in this declaration or believe them to be true based on my experience in the pharmaceutical industry, and I would testify truthfully about them if asked to do so.

3. I was the regulatory agent for IND 118,527 and NDA 209963, which sought and obtained approval for cocaine hydrochloride nasal solution, 4%. NDA 209963 was submitted to FDA on November 23, 2016 and approved as Goprelto® on December 14, 2017.

4. On July 14, 2016, I and two other consultants retained by Genus, Ms. Cindy Dinella from Advyzom, LLC, and Dr. Tom Hochadel, from Cognitive Research, participated in a conference call with FDA at 12:30 pm EST. The participants on the call included me, Ms. Dinella, Dr. Hochadel and the following employees from FDA: Dr. Rigoberto Roca, M.D., Deputy Director, DAAAP; Dr. Leah Crisafi, M.D., Clinical Team Leader; and Dr. Amelia Luckett, M.D., Medical Officer and Clinical Reviewer.

5. Attachments 1, 2, and 4 are true and correct copies of emails that I sent documenting what was discussed on the July 14, 2016 conference call. Attachment 3 is a true and correct copy of an email that I received documenting what was discussed on the July 14, 2016 conference call. Each of these emails accurately reflect what was discussed on the July 14, 2016 conference call, to the best of my recollection.

I declare under penalty of perjury that the foregoing is true and correct. Executed on November 26, 2019.

Melissa L. Goodhead, M.Sc., RAC

City, State: Lithia, Florida

ATTACHMENT 1

CTS- Change orders

From: mgoodhead[redacted]
To: Larry Dalesandro[redacted], Jeff Moshal[redacted]
Date: Sun, 24 Jul 2016 19:10:08 -0400

Hi Larry:

As discussed with Jeff, during our FDA call last week FDA indicated we would need to submit the QTc, hepatic and renal studies in the original NDA filings. Originally we planned to submit the QTc study as a stand alone study and update the filing with the renal/hepatic studies at the 120-day update.

In that the 3 studies now must be included, this now requires all of the data from these studies to be integrated with the previously pooled data (2013011 and PK studies). Additionally, Jeff authorized two additional costs to the hepatic study to aid in expediting the enrollment. Below are the change order costings that will occur:

Hepatic Study:
$20,000- additional advertising
$6,000- increase in patient stipend from $1400 to $2,000 for the last 10 patients
$ 25,260- ANOVA statistical analysis of the renal/hepatic to integrate.

QTC:
$159,976- SDTM/ADAM Datasets for integration and submission
*NOTE: Original cost proposal was $269,654- I was able to negotiate cost reduction.

ISS:
$ 53,300- Statistical integration, analysis and output of pooled data

As always, do not hesitate to reach out to me with any questions.

Best Regards,
Melissa

Melissa L. Goodhead, MSc, RAC
President
Pharmaceutical Project Solutions, Inc.
11705 Boyette Road
Suite 171
Riverview, Florida 33569
[redacted]***- Office***
- Cell

[redacted]

ATTACHMENT 2

Summary of FDA Call July 14, 2016- Renal/Hepatic

From: mgoodhead[redacted]
To: Jeff Moshal[redacted], Bill Reightler[redacted], Melissa Goodhead[redacted]
Date: Sun, 24 Jul 2016 18:51:12 -0400

7/14/16

Diana Walker @ FDA sent an email request for a call regarding the renal and hepatic studies.
Call took place at 12:30 PM.

Participants:
Melissa Goodhead- PPS Regulatory Agent
Tom Hochadel- Cognitive Research
Cindy Dinella- Adozym
Rigoberto Roca, MD – Deputy Director, DAAAP
Leah Crisafi, MD – Clinical Team Leader
Amelia Luckett, MD – Medical Officer/Clinical Reviewer

RE: IND 118,527- Protocols 2015013 and 2015014

Dr. Roca indicated the Division has reviewed the protocols submitted previously and noted there were no individual stopping rules nor study stopping rules. Dr. Roca indicated the Division would like PPS to amend the protocols to include study stopping rules that Dr. Luckett would describe.

Dr. Luckett indicated they would like to see individual stopping rules to include SAEs but also parameters around vitals signs and symptoms and specifically quantified tolerable thresholds. Individual stopping rules should be in place regardless of causality to drug and timing related to removal of pledgets or discontinuation from the study.

Additionally, study stopping rules should be AEs related to known pharmacology (i.e., increase in blood pressure and CNS).

Dr. Luckett asked that PPS submit these proposed stopping rules as redlined versions of the protocols, via email, prior to submission to IND. Melissa indicated we would submit proposed language no later than Monday, 7/18.

Dr. Roca asked an estimate of when we would be submitting the NDA (estimate not to be held to). Melissa indicated we were targeting end of September/first of October. Dr. Roca asked if PPS has had our pre-NDA meeting. Melissa indicated yes, on August 15, 2015. Dr.Roca indicated we would need to have the PSP agreed upon prior to submission. Melissa asked when we could expect comments, Diana indicated within the next two weeks. Dr. Roca indicated we would need to also have the QTc study as well as the renal and hepatic protocols included in the submission. Cindy asked if there was anything from PPS, prior to submission, that would help the Division in preparing for review. Dr. Roca indicated no, however, we should make sure the submission was complete when submitted.

It was agreed if any questions should arise during preparation of the NDA, we could reach out to the Division for discussion.

Post-Call Note:
7/15/16- Redlined versions of the protocols were submitted, via email, for review and agreement.
7/18/16- Email from Diana Walker, Division agreed to proposed stopping rules.
7/18/16- Protocol amendments submitted to IND 118,527.

Melissa L. Goodhead, MSc, RAC

[redacted]

President
Pharmaceutical Project Solutions, Inc.
11705 Boyette Road
Suite 171
Riverview, Florida 33569
[redacted] ***- Office***
- Cell

ATTACHMENT 3

Re: August 3 meeting?

From:

Hilary Sheevers [redacted]

To:

Cynthia Dinella [redacted]

Cc:

Jeff Moshal [redacted], Robert Guttendorf [redacted], Pauline McEwan [redacted], Tacey White [redacted], Melissa Goodhead [redacted]

Date:

Mon, 25 Jul 2016 10:17:39 -0400

Thank Cindy!

Sent from my iPad

On Jul 25, 2016, at 6:48 AM, Cynthia Dinella [redacted] wrote:

> Helllo All, yes we are still on for a F2F on Aug 3 and in Jersey. The time we start is always dependent on what time would be best for all to travel. Melissa is flying in. Since we need to go thru the summaries and ISS I would say we need Bob, Pauline from Aclairo. We also need to discuss strategy based on FDA recent inquiries regarding how to handle renal, liver, TQT studies, pooling and perhaps a new submission date. If we get to label strategy, we can do the rest independent of pregnancy labeling so do not think Tacey needs to come, would love to see her but may want to be efficient. Cindy
>
> ---
>
> **From:** "Hilary Sheevers, Ph.D." [redacted]
> **Date:** Friday, July 22, 2016 at 7:12 PM
> **To:** Cynthia Dinella [redacted], Jeff Moshal [redacted]
> **Cc:** Robert Guttendorf [redacted], Pauline McEwan [redacted], Tacey White [redacted], Melissa Goodhead [redacted]
> **Subject:** August 3 meeting?
>
> Hello,
>
> I'd like to confirm that we are still having the Aug 3 face to face?
>
> Will it be at Advyzom or Aclairo?
>
> What time do we start?
>
> From Aclairo: Bob, Pauline? If we are to discuss label, Tacey?
>
> Do I need to come or should I just call in, if meeting is being held at Advyzom?
>
> Thank you!
>
> Sincerely,
>
> Hilary

[redacted]

ATTACHMENT 4

RE: CTD section 2.7.2 (Clin Pharm) for review

From:

mgoodhead[redacted]

To:

Robert Guttendorf[redacted], mgoodhead[redacted], Jeff Moshal [redacted], Cynthia Dinella[redacted], Bill Reightler [redacted], Jacqueline Sterner[redacted]

Date:

Wed, 27 Jul 2016 17:44:36 -0400

We are estimating mid to end of Oct fillng.

Sent from Yahoo Mail on Android

On Wed, Jul 27, 2016 at 5:40 PM, Robert Guttendorf [redacted] wrote:

> Melissa,
>
> Thanks for the update. Is that going to hold things up any further? I'll begin making the relevant changes to 2.7.2.
>
> Vacation was wonderful, thank you.
>
> Best,
>
> Bob
>
> *Robert J. Guttendorf, RPh, PhD*
>
> *Aclairo Pharmaceutical Development Group, Inc.*
>
> [redacted] *(Office)*
>
> [redacted] *(Cell)*
>
> *www.aclairo.com*
>
> **From:** mgoodhead@[redacted] [mailto:mgoodhead[redacted]]
> **Sent:** Wednesday, July 27, 2016 5:39 PM
> **To:** Robert Guttendorf[redacted]; mgoodhead@[redacted]; Jeff Moshal[redacted]; Cynthia Dinella[redacted]; Bill Reightler [redacted]; Jacqueline Sterner[redacted]
> **Subject:** RE: CTD section 2.7.2 (Clin Pharm) for review

[redacted]

Hi Bob,

How things change with one FDA call. FDA has asked us to include QTC, hepatic and renal in the application.

Hope you had a great vacation!

Best,

Melissa

Sent from Yahoo Mail on Android

On Wed, Jul 27, 2016 at 4:23 PM, Robert Guttendorf [redacted] wrote:

> Melissa,
>
> Thanks for your review. It looks like the major comments you've made had to do with the hepatic/renal impairment studies. To that end I just wanted to clarify… the last I recall, we weren't expecting to have the hepatic and renal studies finished in time to include in the filing. If it looks like we will have data and final reports in time to include, we will incorporate them. If they are incorporated, the current wording justifying why we don't expect to see an effect in either situation will be removed, as it will be trumped by the actual data. Might opt to retain some of it in a discussion of the results. I've left a placeholder for the QTc study and the remainder of the document will be modified according to whatever LVT studies are ultimately incorporated, so thanks for the reminder that tables, etc. will have to be updated in that case.
>
> I'm not sure we need to include a statement to the effect that we don't expect to treat any/many patients with impaired renal/hepatic function because all that will be dictated by the label. We will ultimately either restrict the relevant population(s) or allow them to receive the drug, either as is or with some dose adjustment. We could say that we haven't studied the drug in patients with renal or hepatic impairment, if we have data from the Phase 3 study that support this statement.
>
> Kind regards,
>
> Bob

Robert J. Guttendorf, RPh, PhD

Aclairo Pharmaceutical Development Group, Inc.

[redacted] *(Office)*

[redacted] *(Cell)*

www.aclairo.com

From: mgoodhead[redacted] [mailto:mgoodhead[redacted]
Sent: Tuesday, July 19, 2016 7:20 PM
To: Robert Guttendorf[redacted]; Jeff Moshal[redacted]; Cynthia Dinella[redacted]; Bill Reightler[redacted]; Jacqueline Sterner[redacted]
Subject: Re: CTD section 2.7.2 (Clin Pharm) for review

Bob:

One further question as it relates to this write-up.... where do we make the argument that it is unlikely that renal- or hepatic-impaired will be compromised, however, we conducted....

We should still have this argument in the pharmacology in case we need any further support to number of subjects dosed.

Thoughts?

Melissa L. Goodhead, MSc, RAC
President
Pharmaceutical Project Solutions, Inc.
11705 Boyette Road
Suite 171
Riverview, Florida 33569
[redacted]***- Office***
[redacted]***- Cell***

From: "mgoodhead[redacted]" <mgoodhead[redacted]>
To: Robert Guttendorf[redacted]; Jeff Moshal[redacted]; Cynthia Dinella[redacted]; Bill Reightler[redacted]; Jacqueline Sterner

[redacted]
Sent: Tuesday, July 19, 2016 3:42 PM
Subject: Re: CTD section 2.7.2 (Clin Pharm) for review

Hi Bob:

Attached with comments.

Thanks!

Melissa L. Goodhead, MSc, RAC
President
Pharmaceutical Project Solutions, Inc.
11705 Boyette Road
Suite 171
Riverview, Florida 33569
[redacted]***- Office***
[redacted]***- Cell***

From: Robert Guttendorf [redacted]
To: Jeff Moshal [redacted]; Cynthia Dinella [redacted]; "mgoodhead [redacted]; Bill Reightler [redacted]; Jacqueline Sterner [redacted]
Sent: Friday, July 8, 2016 4:56 PM
Subject: CTD section 2.7.2 (Clin Pharm) for review

Dear all,

As promised, here is the updated 2.7.2 for your review. Jackie and I look forward to your comments.

Thanks and kind regards,

Bob

Robert J. Guttendorf, RPh, PhD

Chief Scientific Officer and Sr. Consultant, DMPK

[redacted]

Aclairo Pharmaceutical Development Group, Inc.

1950 Old Gallows Rd., Suite 300

Vienna, VA 22182

rguttendorf@aclairo.com

[redacted] *(Office)*

[redacted] *(Fax)*

[redacted] *(Cell)*

www.aclairo.com