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JUL 01 2019

Re. Docket No. FDA-2019-P-0538

Dear Mr. Freno:

This letter responds to your citizen petition (Petition) submitted on behalf of Genus Lifesciences, Inc. (Genus or Petitioner), that was received on February 1, 2019. Genus is the new drug application (NDA) holder of Goprelto (cocaine hydrochloride) nasal solution, 4% (NDA 209963) (Goprelto), which was approved on December 14, 2017. Genus requests that the Food and Drug Administration (FDA, the Agency, or we) refuse to accept any submissions by Lannett Company, Inc. (Lannett), in furtherance of Lannett's application submitted through the pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)), for cocaine hydrochloride, 4% and 10%.<sup>1</sup> According to the Petition, any submissions by Lannett "are barred by the new chemical entity exclusivity arising from FDA's approval of Genus's [NDA] 209963" for Goprelto under section 505(c)(3)(E)(ii) of the FD&C Act.<sup>2,3</sup>

Specifically, Genus requests that FDA take the following actions:

1. Refuse to accept any further submissions for Lannett's 505(b)(2) application for its cocaine product, including any amendments, supplements, or resubmissions.
2. Treat as withdrawn any submissions FDA may have accepted from Lannett in support of its 505(b)(2) application after December 14, 2017, which is the date of Goprelto's approval and the commencement of Goprelto's 5-year exclusivity period.
3. Consider Lannett's 505(b)(2) application for its cocaine product withdrawn.<sup>4</sup>

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<sup>1</sup> Petition at 1.

<sup>2</sup> Petition at 1.

<sup>3</sup> A comment dated April 24, 2019, was submitted by Foley & Lardner, LLP, on behalf of Lannett (hereafter referred to as Lannett Letter).

<sup>4</sup> Petition at 2-3.

We have carefully considered the Petition. For the reasons described below and consistent with FDA's regulations and policies, the Petition is denied.

## I. FACTUAL BACKGROUND

### A. Cocaine

Before the approval of Genus's NDA 209963 for Goprelto, cocaine was marketed as an unapproved drug.<sup>5</sup> Since the 1880s, cocaine has been used clinically in nasal and sinus surgery as an anesthetic and vasoconstrictive agent.<sup>6</sup> 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.).

### B. Genus's Goprelto

NDA 209963 for Goprelto was received by FDA on November 23, 2016, and was approved on December 14, 2017. The active ingredient in Goprelto is cocaine hydrochloride; cocaine is the active moiety. Goprelto is a topical, intranasal solution, approved as a local anesthetic that is indicated for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults.<sup>7</sup> Genus did not conduct or have a right of reference to all the investigations necessary for Goprelto's approval. Rather, Genus relied, in part, on published literature describing the use of cocaine topical solution, in concentrations ranging from 4% to 10%, as an anesthetic and vasoconstrictor agent during nasal procedures over several decades.<sup>8</sup> The Goprelto NDA relied on published literature to support certain aspects of the application, such as nonclinical and clinical pharmacology, carcinogenicity, toxicology, and clinical safety, in addition to data from Genus's own drug development program.<sup>9, 10</sup> Therefore, the Goprelto NDA is classified as a 505(b)(2) application. Before the approval of Goprelto, the Agency had not approved any application that contained cocaine as the active moiety. Accordingly, FDA recognized 5-year new chemical entity (NCE) exclusivity for Goprelto that expires on December 14, 2022.<sup>11</sup>

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<sup>5</sup> Goprelto Summary Review at 2, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209963Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000SumR.pdf).

<sup>6</sup> See e.g., M. Redman, *Cocaine: What is the Crack? A Brief History of the Use of Cocaine as an Anesthetic*, *Anesth Pain Med.* 2011 Autumn; 1(2): 95–97, available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4335732/>.

<sup>7</sup> Goprelto Prescribing Information, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/209963lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209963lbl.pdf).

<sup>8</sup> Goprelto Clinical Review at 10, 14-15, 40, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209963Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000MedR.pdf).

<sup>9</sup> Goprelto Summary Review at 2.

<sup>10</sup> Goprelto 505(b)(2) Assessment, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209963Orig1s000OtherR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209963Orig1s000OtherR.pdf).

<sup>11</sup> See Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), available at <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>.

### C. Lannett's 505(b)(2) Application for a Cocaine Product

The Agency received Lannett's 505(b)(2) application for a cocaine hydrochloride topical solution, 4% and 10%, on September 21, 2017, before the December 14, 2017, approval of Goprelto.<sup>12</sup> Lannett announced on December 1, 2017, that FDA had deemed the application sufficiently complete for filing and substantive review.<sup>13</sup> Lannett's application subsequently received a Complete Response (CR) letter on July 20, 2018.<sup>14</sup> According to the Petition, "Lannett publicly stated that FDA issued a [CR letter] 'which required an additional study and other information,'" and the company was addressing the deficiencies stated in CR letter.<sup>15</sup> The Petitioner asserts that Lannett is conducting a "gating QT study" that is expected to conclude by January 2019.<sup>16</sup> The Petitioner claims that Lannett is planning to resubmit its NDA to address the deficiencies in the CR letter.<sup>17</sup>

## II. STATUTORY AND REGULATORY BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) reflects Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.<sup>18</sup> The Hatch-Waxman Amendments added section 505(b)(2) and (j) to the FD&C Act, which describes the abbreviated pathways for a 505(b)(2) application and an abbreviated new drug application (ANDA), respectively.<sup>19</sup> The 505(b)(2) pathway permits applicants to rely on studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., the Agency's finding of safety and/or effectiveness for a listed drug, published literature). The potential for speedier submission of an application under the 505(b)(2)

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<sup>12</sup> Lannett Letter at 1; see also Petition at 4.

<sup>13</sup> "Lannett Announces FDA Acceptance Of 505(b)(2) New Drug Application For Cocaine Hydrochloride Topical Solution, A Proprietary Anesthetic Product" (Dec. 1, 2017), available at <http://lannett.investorroom.com/2017-12-01-Lannett-Announces-FDA-Acceptance-Of-505-b-2-New-Drug-Application-For-Cocaine-Hydrochloride-Topical-Solution-A-Proprietary-Anesthetic-Product>.

<sup>14</sup> Lannett Letter at 1.

<sup>15</sup> Petition at 4; see also Petition at 11.

<sup>16</sup> Petition at 11.

<sup>17</sup> Petition at 11-13.

<sup>18</sup> See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

<sup>19</sup> Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to a reference listed drug (RLD) and is the same as the RLD with respect to active ingredient(s); dosage form; route of administration; strength; previously approved conditions of use; and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to describe further the ANDA pathway in this response.

pathway than would be possible compared to a full, stand-alone 505(b)(1) application (described below) may lead to earlier market entry and increased competition.<sup>20</sup>

In addition to the abbreviated pathways, the Hatch-Waxman Amendments created incentives for pharmaceutical innovation in the form of 5-year exclusivity for an NCE and 3-year exclusivity for new clinical investigations; these exclusivities are meant to protect qualified drugs submitted under section 505(b) of the FD&C Act from competition from certain 505(b)(2) applications and NDAs for varying periods of time depending on the factual circumstances. The 505(b)(2) application abbreviated pathway and the two exclusivities are described below.

#### A. Section 505(b) New Drug Applications

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, “full reports of investigations” to show that the drug for which the applicant is seeking approval is safe and effective.<sup>21</sup> NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act, is approved under section 505(c) of the FD&C Act, and must meet both the “full reports” requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a 505(b)(1) NDA. Unlike a stand-alone NDA, however, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations (1) “not conducted by or for the applicant” and (2) “for which the applicant has not obtained a right of reference or use.”<sup>22</sup> Therefore, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA includes studies essential to approval that the applicant owns or to which it has a right of reference, an applicant submitting a 505(b)(2) NDA may rely on sources such as its own studies; published reports of studies to which the applicant has no right of reference; the Agency’s

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<sup>20</sup> See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-1134 (Fed. Cir. 1995).

<sup>21</sup> See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include, among other things: a full list of the articles used as components of such drug described in the NDA; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. See section 505(b)(1) of the FD&C Act.

<sup>22</sup> Section 505(b)(2) of the FD&C Act provides for approval of an application:

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

As defined in 21 CFR 314.3, “right of reference or use” “is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an NDA, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.”

findings of safety and/or effectiveness for one or more previously approved drugs, i.e., a listed drug; or a combination of these sources to support approval.<sup>23</sup> A 505(b)(2) application can be submitted for either a change to a previously approved drug or for an NCE.

## B. Five-Year and Three-Year Exclusivity Statutory Provisions

The longest and most protective period of exclusivity currently available under the Hatch-Waxman Amendments is 5 years of exclusivity for an NCE.<sup>24</sup> The 5-year NCE exclusivity statutory provisions state:

If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted *may be submitted* under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b) . . .<sup>25</sup>

This exclusivity, which Congress meant for drugs that were novel, and believed likely to contain the most innovative changes,<sup>26</sup> generally prevents an applicant from *submitting* a 505(b)(2)

<sup>23</sup> See Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (CDER), FDA, to Katherine M. Sanzo, Esq.; Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq.; Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to the "regulations.gov" website).

<sup>24</sup> Section 505(c)(3)(E)(ii) of the FD&C Act; see also section 505(j)(5)(F)(ii) of the FD&C Act, which is the parallel provision affecting the approvability of 505(j) applications.

<sup>25</sup> Section 505(c)(3)(E)(ii) of the FD&C Act (emphasis added); see also section 505(j)(5)(F)(ii) of the FD&C Act. The statute contains a single exception, which is limited to 505(b)(2) and 505(j) applications that contain a "Paragraph IV certification," and states that such applications "may be submitted" after 4 years of the 5-year NCE exclusivity period. A Paragraph IV certification is a certification submitted by a 505(b)(2) or 505(j) applicant claiming that an unexpired patent listed in the Orange Book for the relied-upon listed drug is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the 505(b)(2) or 505(j) application. See section 505(b)(2)(A)(iv), 505(j)(2)(A)(vii)(IV) of the FD&C Act.

<sup>26</sup> Studies presented in Senate and House congressional hearings examined the costs, development, and requirements that branded companies must go through to gain regulatory approval for an NCE. See, e.g., Martin Elsman and William Wardell, *The Decline in Effective Patent Life of New Drugs, in Innovation and Patent Law Reform: Hearing before the Subcomm. on Courts, Civil Liberties, and the Administration of Justice*, 98th Cong. 1209 (1984); Maureen May, et al, *New Drug Development During and After a Period of Regulatory Change: Clinical Research Activity of Major United States Pharmaceutical Firms, 1958 to 1979 in Innovation and Patent Law Reform: Hearing before the Subcomm. on Courts, Civil Liberties, and the Administration of Justice*, 98th Cong. 1285 (1984). Further, the House Committee Report stated that Title I affords additional exclusivity for "drugs approved for the first time." H.R. 98-857, pt.1, at 15, 38 (1984). The report indicated that these extensions should be based on first

application or ANDA that includes an active moiety protected by NCE exclusivity for a 5-year period from the date of approval of the protected drug.<sup>27</sup> This exclusivity does not affect 505(b)(1) applications.

In describing the 5-year NCE exclusivity provisions, Representative Waxman stated:

[T]he amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of the legislation. This provision will give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains . . .<sup>28</sup>

For a drug that is not eligible for 5-year NCE exclusivity, the Hatch-Waxman Amendments provide for a 3-year period of exclusivity under certain circumstances. Representative Waxman stated that 3-year exclusivity would be available for drugs that did not qualify for the longer period of exclusivity recognized for an NCE: “a 3-year period of exclusive market life is afforded to non-new chemical entities approved after enactment of the bill which have undergone new clinical studies essential to FDA approval.”<sup>29</sup> Three-year exclusivity is available as follows:

If an application . . . for a drug which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) . . . is approved . . . and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) . . . for such drug.<sup>30</sup>

An application is eligible for 3-year exclusivity if it is for “a drug which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application.”<sup>31</sup> Moreover, for a drug to be eligible for 3-year exclusivity, its application must contain “reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.”<sup>32</sup> If a drug meets these conditions and is determined to qualify for 3-year exclusivity, FDA cannot approve a

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approval of a product “because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs.” Id.

<sup>27</sup> Section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act.

<sup>28</sup> 130 Cong. Rec. 24425 (1984) (Statement of Rep. Waxman).

<sup>29</sup> Id.

<sup>30</sup> Section 505(j)(5)(F)(iii); see also section 505(c)(3)(E)(iii).

<sup>31</sup> Id.

<sup>32</sup> Id.

505(b)(2) application or ANDA that is seeking approval for the exclusivity-protected conditions of that drug “effective before the expiration of three years from the date of approval” of that drug.<sup>33</sup> In contrast to the 5-year NCE exclusivity provision, which prevents *submission* of a 505(b)(2) application or ANDA during the exclusivity period, 3-year exclusivity is a bar on 505(b)(2) application or ANDA *approval* during the relevant period. Similar to the 5-year NCE exclusivity statutory provisions, 3-year exclusivity does not affect 505(b)(1) applications.

### C. FDA’s Regulations Governing Five-Year and Three-Year Exclusivity

In 1989, FDA published a proposed rule interpreting and implementing the 5-year and 3-year exclusivity statutory provisions, along with other provisions of the Hatch-Waxman Amendments (Proposed Rule).<sup>34</sup> FDA finalized its regulation in § 314.108 (21 CFR 314.108) in 1994 without substantive changes to the exclusivity-related provisions proposed in the Proposed Rule.<sup>35</sup> The regulation, as finalized, describes 5-year NCE exclusivity as follows:

If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person *may submit* a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application . . .<sup>36</sup>

This provision uses several terms that are defined either in § 314.108 or in other sections of the regulations.

- Application, new drug application, or NDA is the application described under §314.50, including all amendments and supplements to the application. An NDA refers to ‘stand-alone’ applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.<sup>37</sup>
- New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.<sup>38</sup>
- Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.<sup>39</sup>

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<sup>33</sup> Id.

<sup>34</sup> FDA, “Abbreviated New Drug Application Regulations,” Proposed Rule, 54 FR 28872 (July 10, 1989).

<sup>35</sup> FDA, “Abbreviated New Drug Applications; Patent and Exclusivity Provisions,” Final Rule, 59 FR 50338 (Oct. 3, 1994).

<sup>36</sup> 21 CFR 314.108(b)(2) (emphasis added).

<sup>37</sup> 21 CFR 314.3.

<sup>38</sup> 21 CFR 314.108(a).

<sup>39</sup> 21 CFR 314.3.

As described in the preamble to the Proposed Rule, the Agency recognized the 5-year NCE exclusivity statutory text is ambiguous, in part, concerning the treatment of concurrently pending 505(b) applications seeking approval of a drug with the same previously unapproved active moiety. As stated in the preamble to the Proposed Rule:

Section 505(c)(3)(D)(ii), states that “\* no application which refers to the drug for which the subsection (b) application [entitled to exclusivity] was submitted may be *submitted*[’] (Emphasis added). The agency intends to interpret this phrase to mean that any application submitted to FDA before the approval of another new drug application that qualifies for exclusivity under section 505(c)(3)(D)(ii) is not affected by this exclusivity provision.<sup>40</sup>

The Agency then proposed to create an exception: a competing applicant cannot rely, without obtaining a right of reference, on the first applicant’s data and avoid the first applicant’s 5-year NCE exclusivity.<sup>41</sup> If the competing applicant had submitted an amendment that included investigations conducted or sponsored by the first applicant with 5-year NCE exclusivity, the competing application would be deemed to have been withdrawn and resubmitted. Because an application for an active moiety protected by 5-year NCE exclusivity cannot be submitted until the exclusivity expires (or 4 years from the date of approval of the first application if the competing applicant challenged a patent on the first applicant’s drug), the Agency explained that a competing applicant’s resubmission would not be accepted by FDA until the exclusivity expires.<sup>42</sup>

In 1992, this policy was codified in § 314.60 (21 CFR 314.60).<sup>43</sup> From the Proposed Rule to the current version of the regulation, aside from technical amendments, the text remains substantively the same.

Limitation on certain amendments.(1) An unapproved NDA may not be amended if all of the following conditions apply:

- (i) The unapproved NDA is for a drug for which a previous NDA has been approved and granted a period of exclusivity in accordance with section 505(c)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act that has not expired;
- (ii) The applicant seeks to amend the unapproved NDA to include a published report of an investigation that was conducted or sponsored by the applicant entitled to exclusivity for the drug;
- (iii) The applicant has not obtained a right of reference or use to the investigation described in paragraph (c)(1)(ii) of this section; and

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<sup>40</sup> Proposed Rule at 28901.

<sup>41</sup> Id.

<sup>42</sup> Id.

<sup>43</sup> See FDA, “Abbreviated New Drug Application Regulations,” Final Rule, 57 FR 17950 (Apr. 28, 1992) (referred to as the 1992 Final Rule).

(iv) The report of the investigation described in paragraph (c)(1)(ii) of this section would be essential to the approval of the unapproved NDA.

(2) The submission of an amendment described in paragraph (c)(1) of this section will cause the unapproved NDA to be deemed to be withdrawn by the applicant under §314.65 on the date of receipt by FDA of the amendment. The amendment will be considered a resubmission of the NDA, which may not be accepted except as provided in accordance with section 505(c)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act.<sup>44</sup>

In the preamble to the 1992 Final Rule, FDA stated that the rule describes when an applicant can submit an amendment to a pending application and also describes when an unapproved application cannot be amended.<sup>45</sup> In that preamble, FDA also reiterated that for concurrently pending applications, any 505(b)(2) application submitted to FDA before the approval of another NDA that qualifies for 5-year NCE exclusivity is “not affected by” the 5-year NCE exclusivity provision of the first approved application because that provision prohibits only the submission of 505(b)(2) applications, but not the approval of such applications if the 505(b)(2) application had been submitted to the Agency.<sup>46</sup>

#### D. NDA Review Process

To legally market a new drug, an applicant must submit, and FDA must approve an NDA for that drug.<sup>47</sup> The expectation is that an application is complete upon submission.<sup>48</sup> 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.<sup>49</sup> FDA will file an application only after it makes a threshold determination that the NDA is sufficiently complete to permit a substantive review.<sup>50</sup> Any 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.<sup>51</sup> Incomplete applications 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

<sup>44</sup> See 21 CFR 314.60(c).

<sup>45</sup> 1992 Final Rule at 17955.

<sup>46</sup> Id.

<sup>47</sup> Section 505(a) of the FD&C Act.

<sup>48</sup> See e.g., 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>.

<sup>49</sup> See 21 CFR 314.101(a)(1).

<sup>50</sup> 21 CFR 314.101(a)(1). See also FDA draft guidance for industry *Refuse to File: NDA and BLA Submissions to CDER* (Dec. 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 FDA’s current thinking on this topic); FDA CDER , Manual of Policies and Procedures (MAPP) 6025.4, *Good Review Practice: Refuse to File*, available at <https://www.fda.gov/media/87035/download>.

<sup>51</sup> PDUFA VI Letter at 10.

decision.<sup>52</sup> 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 ANDA) if another drug qualifies for 5-year NCE exclusivity. 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.

For applications 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).<sup>53</sup> The Agency will issue a CR letter when the Agency determines that it will not approve the application in its present form.<sup>54</sup> Upon receiving a CR letter, an applicant may elect to file a resubmission, withdraw the application, or request an opportunity for a hearing.<sup>55</sup>

If the applicant decides to file a resubmission, it must address in the resubmission all deficiencies identified in the CR letter.<sup>56</sup> 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. 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.”<sup>57</sup> A resubmission is thus an amendment after a CR action to a pending, unapproved application. No filing determination is made for a resubmission to an application, because applications for which a CR action has been taken are considered filed.<sup>58</sup>

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.

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<sup>52</sup> 21 CFR 314.101(d), (e).

<sup>53</sup> 21 CFR 314.101(a)(1).

<sup>54</sup> 21 CFR 314.110(a).

<sup>55</sup> 21 CFR 314.110(b).

<sup>56</sup> 21 CFR 314.110(b)(1).

<sup>57</sup> 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>.

<sup>58</sup> Resubmission MAPP at 2.

### III. PETITIONER'S ASSERTIONS

The Petitioner presents statutory, regulatory, and policy reasons that, in its view, support its request that FDA refuse to accept any submission (including a resubmission or any other amendment) by Lannett, and withdraw any of Lannett's submissions dated after December 14, 2017, that support approval of Lannett's 505(b)(2) application for a cocaine product until the expiration of Goprelto's 5-year NCE exclusivity. The Petitioner asserts that the 5-year NCE exclusivity statutory provision "prevents the 'submission' of any 'application' that 'refers to the drug' that receives NCE exclusivity."<sup>59</sup> The Petitioner believes "Congress prohibits without qualification any NDA submissions for drugs entitled to NCE exclusivity during the pendency of the exclusivity period."<sup>60</sup> The Petitioner cites legislative history on the 5-year NCE exclusivity statutory provision, focusing on Congress's desire to encourage industry to develop new chemical entities, including those molecules whose clinical usefulness is discovered late when the patent life may be limited.<sup>61</sup> Legislative history is also cited to emphasize that 5-year NCE exclusivity bars submission, and not approval, of 505(b)(2) applications and ANDAs.<sup>62</sup>

To further support its requests, the Petitioner relies on FDA's definition of *application* in 21 CFR 314.3, which it describes "as a series of submissions during the review period, which includes all amendments and supplements supporting the approval of an NDA."<sup>63</sup> The Petitioner asserts that "an 'application' includes 'amendments and supplements.'"<sup>64</sup> According to the Petitioner, the statute precludes a second applicant like Lannett from continuing to submit an "application" (including amendments and supplements) after Genus obtained 5-year NCE exclusivity.<sup>65</sup> Under the Petitioner's theory, the Agency then "cannot accept from Lannett a 'gating QT study,' safety update reports, samples, copies of procedures, patent information, amendments, supplements, or anything else because each submission to FDA in furtherance of the approval of an application constitutes part of the 'application' for a cocaine product during the period of Goprelto's NCE exclusivity."<sup>66</sup> The Petitioner also contends that Lannett's resubmission should be barred from submission by Goprelto's 5-year NCE exclusivity because Lannett is presumably planning to resubmit its application, and by definition, a resubmission is a submission.<sup>67</sup> The Petitioner further asserts that because Lannett cannot make any submissions until December 17, 2022 (the

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<sup>59</sup> Petition at 5.

<sup>60</sup> Petition at 5-6.

<sup>61</sup> Petition at 9.

<sup>62</sup> Petition at 9.

<sup>63</sup> Petition at 11.

<sup>64</sup> Petition at 15.

<sup>65</sup> Petition at 15.

<sup>66</sup> Petition at 12.

<sup>67</sup> Petition at 13.

expiration of Goprelto’s 5-year NCE exclusivity period), “FDA should withdraw Lannett’s 505(b)(2) application” in accordance with § 314.110(c).<sup>68</sup>

The Petition restates the Agency’s preamble statements in the Proposed Rule that a 505(b)(2) application submitted to FDA before the approval of another NDA that qualifies for 5-year NCE exclusivity is not affected by that exclusivity provision.<sup>69</sup> The Petitioner cites case law and administrative law principles to assert that policy statements and interpretive rules are not binding, and the Agency should depart from the policy announced in the preamble to the Proposed Rule.<sup>70</sup> Genus states that “[w]hen FDA published its final rules on October 3, 1994 — which became effective on November 2, 1994 — FDA did not promulgate a final rule dealing with dueling applications. FDA’s 1989 interpretation has never undergone the due process requirements of agency rule-making.”<sup>71</sup> The Petitioner also claims that FDA’s interpretation conflicts with the 5-year NCE exclusivity statutory provision, which states that “no application . . . may be submitted.”<sup>72</sup> According to Genus, application of FDA’s policy would result in “five year NCE exclusivity [being] less valuable to an applicant compared to the three year new clinical investigation exclusivity. For example, if Genus had a three-year new clinical investigation exclusivity, Lannett’s application (although submitted and reviewed) would not be approvable before December 17, 2020.”<sup>73</sup>

#### IV. DISCUSSION

We have carefully considered the Petitioner’s assertions and requests. Consistent with the relevant statutory provisions, regulations, and policies on approving safe and effective drugs and on promoting competition, we conclude that any amendment, including any resubmission, submitted to Lannett’s pending 505(b)(2) application may continue to be accepted by the Agency for review and consideration notwithstanding Goprelto’s 5-year NCE exclusivity. Therefore, the Agency is denying Genus’s Petition. Because we will not grant the Petitioner’s requests that FDA refuse to accept any amendments from Lannett and treat as withdrawn any amendments submitted after Goprelto’s NCE exclusivity commenced, we will not withdraw Lannett’s 505(b)(2) application.

According to the 5-year NCE exclusivity statutory provision, no 505(b)(2) application (or ANDA) can be submitted for 5 years after the approval of an application for “a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any

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<sup>68</sup> Petition at 13-14.

<sup>69</sup> Petition at 14.

<sup>70</sup> Petition at 16.

<sup>71</sup> Petition at 15.

<sup>72</sup> Petition at 15, citing section 505(c)(3)(E)(ii) of the FD&C Act.

<sup>73</sup> Petition at 15.

other application under subsection (b).”<sup>74</sup> When the Agency issued the preamble to the Proposed Rule, FDA recognized this provision is ambiguous with respect to the treatment of concurrent 505(b)(2) applications that have been submitted and are seeking approval of a drug with the same active moiety. As explained below, the Agency’s interpretation, as embodied in its regulations at § 314.108(b)(2), is that the submission of a 505(b)(2) application seeking approval of the exclusivity-protected NCE is barred during the 5-year period. If, however, a 505(b)(2) NDA has already been submitted before the commencement of the 5-year exclusivity for the NCE recognized for another company’s drug, then FDA’s regulations do not contemplate withdrawal or termination of FDA’s review of that 505(b)(2) application; the applicant can continue to file amendments to its application, with a single, specific exception codified by regulation.

FDA’s governing regulation states that “. . . no person may submit a 505(b)(2) application . . . for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application . . .”<sup>75</sup> Because the Agency recognized the ambiguity in the 5-year NCE exclusivity statutory provision for concurrently pending 505(b) NDAs, FDA issued a regulation that specifically addresses amendments and resubmissions to unapproved NDAs. As stated in the preamble to the Proposed Rule and 1992 Final Rule, any 505(b) application submitted to FDA before the approval of another NDA that qualifies for 5-year NCE exclusivity would not be affected by that exclusivity.<sup>76</sup> We then proposed to create a single exception to that policy — when an applicant seeks to amend the unapproved NDA to include a published report of an investigation that was conducted or sponsored by the NDA holder entitled to exclusivity for the drug without obtaining a right of reference.<sup>77</sup> In such cases, the Agency would deem the pending application to be withdrawn.<sup>78</sup>

In 1992, the Agency codified the exception by regulation in § 314.60(b) (now codified in § 314.60(c)). When the rule was finalized, FDA reiterated in the preamble that for concurrently pending, unapproved NDAs, any 505(b)(2) application submitted to FDA before the approval of another NDA that qualifies for 5-year NCE exclusivity is generally “not affected by” the first approved application’s exclusivity because the statute prohibits the submission of 505(b)(2) applications, but not the approval of such applications.<sup>79</sup> Thus, the Agency envisioned that such already-submitted but unapproved 505(b) NDAs could be amended, notwithstanding another drug’s 5-year NCE exclusivity. Specifically, the regulation anticipates that such unapproved applications, including 505(b)(2) NDAs, could be amended during the first NDA’s 5-year NCE

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<sup>74</sup> Section 505(c)(3)(E)(ii) of the FD&C Act; see also, section 505(j)(5)(F)(ii) of the FD&C Act. The statute contains a single exception, which is limited to 505(b)(2) and 505(j) applications that contain a Paragraph IV certification, and states that such applications “may be submitted” after 4 years of the 5-year NCE exclusivity period.

<sup>75</sup> 21 CFR 314.108(b)(2).

<sup>76</sup> Proposed Rule at 28901; 1992 Final Rule at 17955.

<sup>77</sup> Proposed Rule at 28901; see also 21 CFR 314.60(c)(1)(ii).

<sup>78</sup> Proposed Rule at 28901.

<sup>79</sup> 1992 Final Rule at 17955.

exclusivity period, so long as the pending application is not amended to include a published investigation that was conducted by or for the holder of the first approved NDA unless a right of reference to that investigation was obtained. Therefore, the only way FDA's regulations in § 314.108(b)(2) (which bars the submission of a 505(b)(2) application seeking approval of the exclusivity-protected NCE) and § 314.60(c) (which permits an already-submitted but unapproved NDA for a drug containing the exclusivity-protected NCE to be amended) can be read harmoniously and without rendering § 314.60(c) superfluous is if the term "application" in § 314.108(b)(2) refers to the original 505(b)(2) application. Therefore, the Agency considers that under § 314.108(b)(2), only original 505(b)(2) applications are barred from submission during a 5-year NCE exclusivity period; if an original 505(b)(2) application has been submitted but has not been approved before the commencement of another drug's 5-year NCE exclusivity period, the unapproved application can be amended and supplemented as long as the amendments are consistent with § 314.60. Because Lannett's original 505(b)(2) application was submitted before the commencement of Goprelto's 5-year NCE exclusivity, FDA will not refuse to file any amendments to Lannett's application.

In its Petition, Genus fails to address FDA's regulation in § 314.60(c) and the rulemaking process to codify that regulation. Contrary to the Petitioner's claim that the Agency did not undergo rulemaking on its policy for concurrently pending NDAs and 5-year NCE exclusivity, FDA's regulation in § 314.60(c) subsumes this policy; contemplates that an already submitted but unapproved 505(b)(2) NDA for a drug containing an exclusivity-protected NCE can continue to be amended; and, as stated above, establishes an exception for when a pending NDA, including a 505(b)(2) NDA, can be deemed withdrawn in light of a prior drug's 5-year NCE exclusivity.

In furtherance of its requests, the Petitioner focuses on FDA's general regulatory definition of *application* in § 314.50, which "include[es] all amendments and supplements to the application."<sup>80</sup> Based on this definition, the Petitioner claims that an application "includes" amendments and supplements, thereby asserting that an amendment is itself a (separate) application. Because the 5-year NCE exclusivity provisions prohibit submission of a 505(b)(2) application (or ANDA), the Petitioner argues that Lannett may not submit an amendment (which the Petitioner considers to be an application) to its pending 505(b)(2) application for a cocaine product until Goprelto's NCE exclusivity expires.

First, the Petitioner's interpretation of the general definition of "application" in the Agency's regulations that an amendment (which would include a resubmission to a CR letter) is a separate "application" that would be blocked by another drug's 5-year NCE exclusivity is not consistent with the text and structure of the statutory exclusivity provision (section 505(c)(3)(E) of the FD&C Act). Congress knew how to refer to, for example, supplements separately when it meant to do so. Indeed, the provisions governing 3-year exclusivity address "an application" (see section 505(c)(3)(E)(iii) of the FD&C Act) and "a supplement to an application" (see section 505(c)(3)(E)(iv) of the FD&C Act); similarly, for 2-year exclusivity, Congress made clear that the approval of an application or a supplement to an application during a specific time-period would lead to 2-year exclusivity (see section 505(c)(3)(E)(v) of the FD&C Act). For 5-year

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<sup>80</sup> 21 CFR 314.3(b).

NCE exclusivity, however, Congress only referred to an “application” (see section 505(c)(3)(E)(ii) of the FD&C Act). Thus, the general definition of “application” in the Agency’s regulation at § 314.50 would not be consistent with this statutory scheme if that regulation were interpreted in the way that Genus insists it should be.

Second, the structure and text of the regulatory scheme also are inconsistent with Genus’s interpretation. As to the text, FDA generally considers the word “including” to mean “comprise as a part of a whole or group,”<sup>81</sup> such that an amendment is a part of an application, but is not itself a separate application that would be blocked by a later-arising 5-year NCE exclusivity period under § 314.108(b)(2). As explained above, Genus’s interpretation is also inconsistent with the text of the regulation at § 314.60(c). Finally, when FDA announced its policy on concurrently pending NDAs and codified its regulation, the regulatory definition of application had contained the phrase “including amendments and supplements.”<sup>82</sup> Thus, when FDA’s regulation governing § 314.60 was finalized in 1992, FDA could not have considered an amendment to be a separate “application” for purposes of 5-year NCE exclusivity, which would have made § 314.60 superfluous.

The Petitioner also asserted that, in the present case, if FDA were to allow Lannett’s application to be amended and subsequently approved during Goprelto’s 5-year NCE exclusivity period, that exclusivity would be less valuable than 3-year exclusivity for a new clinical investigation, because Genus believes 3-year exclusivity would block approval of Lannett’s application, while 5-year NCE exclusivity would not. FDA believes that the Petitioner overstates the asserted hypothetical risk to the value of 5-year NCE exclusivity. First, FDA notes that more than 30 years have passed since the Hatch-Waxman Amendments became effective and more than 20 years have passed since FDA finalized the provision in § 314.60 related to dueling 505(b)(2) applications. The Petitioner itself notes that its “Citizen Petition raises an issue of first impression.”<sup>83</sup> And, indeed, the situation of concurrently pending 505(b)(2) NDAs for a previously unapproved active moiety appears to be rare.<sup>84</sup> FDA is not aware of another set of “dueling” 505(b)(2) applications since 1984.

Further, the assertion ignores certain key differences between 5-year NCE exclusivity and 3-year exclusivity. The scope of 3-year exclusivity is generally narrower than the scope of 5-year NCE exclusivity. While 5-year NCE exclusivity protects the active moiety, whether 3-year exclusivity blocks approval of another application turns on whether that application was seeking approval of the exclusivity-protected conditions of approval for that active moiety—the novel conditions for which new clinical investigations were required for approval of the product with 3-year exclusivity. Properly evaluating this assertion would thus require analysis of numerous facts not

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<sup>81</sup> See definition of “include” or “including” in Merriam-Webster, available at <https://www.merriam-webster.com/dictionary/including>.

<sup>82</sup> FDA, “New Drug and Antibiotic Regulations,” Final Rule, 50 FR 7452 at 7493 (Feb. 22, 1985).

<sup>83</sup> Petition at 14.

<sup>84</sup> In the overwhelming majority of cases, a single innovator company investigates and develops a drug for a novel, previously unapproved active moiety, and subsequently submits a 505(b)(1) application for approval of that drug.

before us; this hypothetical scenario does not contain enough substance for us to reach the same conclusion as the Petitioner.

The Agency's interpretation that a pending 505(b)(2) NDA can be amended during the duration of another drug's 5-year NCE exclusivity also is consistent with FDA's goal of approving safe and effective drug products. Under the Petitioner's theory, the Agency could not accept from Lannett any amendments, including safety update reports. Therefore, if Lannett's application would have been approvable at the time of Goprelto's approval, under the Petitioner's position, Lannett would be barred from submitting any safety update reports that may otherwise cause Lannett's proposed cocaine product to be deemed unsafe and not approvable, or that could result in additional safety information in the labeling. This would be inconsistent with FDA's public health mission and conflict with and undermine the Agency's mission of approving a new drug application only after a thorough review of the available data on the safety and effectiveness of the drug.

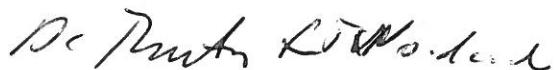
We acknowledge Representative Waxman's statement that 5-year exclusivity was to incentivize companies "to develop new chemical entities whose therapeutic usefulness *is discovered late* when little or no patent life remains . . ." In this case, the therapeutic usefulness was not discovered late; rather, the clinical usefulness of cocaine has been widely known for decades. That is why both Genus and Lannett submitted 505(b)(2) applications that rely, in part, on investigations that were not conducted by the applicant or for which the applicant did not have a right of reference. Therefore, it appears that the legislative history on the Hatch-Waxman Amendments does not necessarily support Genus's position that Lannett may not submit any amendments to its pending 505(b)(2) application.

Finally, we recognize that, in the case of concurrently pending 505(b)(2) NDAs for a previously unapproved active moiety, it is possible that the first-approved 505(b)(2) NDA will face competition from the second-approved 505(b)(2) NDA sooner than is typical for an NDA that is eligible for 5-year NCE exclusivity. We consider such a result to be consistent with the balance achieved by the Hatch-Waxman Amendments, however. The 505(b)(2) application pathway permits an applicant to rely on what is already known about a drug, thereby potentially reducing the types of studies an applicant needs to conduct or sponsor for approval of an application for a new drug. In the present case, both Genus and Lannett submitted 505(b)(2) applications for their cocaine products that relied on published studies and reports concerning cocaine's use in the nasal and sinus surgery setting. Therefore, as demonstrated in the present case, it is conceivable that more than one innovator company could develop a drug for a previously unapproved active moiety, particularly one that was historically marketed but unapproved, that has been used in medical practice in the United States or in a foreign country, and that such companies rely on published literature reports for approval. FDA's regulation at § 314.60(c) sets forth the Agency's considered approach to this scenario and balances the equities in allowing a submitted but unapproved 505(b)(2) NDA to not be withdrawn even where another, similar 505(b)(2) NDA is approved first.

**V. CONCLUSION**

Consistent with the relevant statutory provisions, regulations, and policies, we conclude that Lannett may continue to submit amendments, including a resubmission, to its already-submitted, pending 505(b)(2) application, so long as the amendment does not contain a published investigation conducted by or for Genus (without getting a right of reference to that investigation). For the reasons described above, the Petition is denied.

Sincerely,



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