IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

GENUS LIFESCIENCES, INC.,
514 N. 12th Street,
Allentown, PA 18102

Plaintiffs,

v.

ALEX AZAR, Secretary of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201;

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 Independence Avenue, SW
Washington, DC 20201;

STEPHEN HAHN, Commissioner of Food and Drugs
10903 New Hampshire Avenue
Silver Spring, MD 20993; and

U.S. FOOD AND DRUG ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993,

Defendants.

Case No._____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff Genus Lifesciences, Inc. (Genus) brings this suit against Defendants Alex Azar, in his official capacity as Secretary of Health and Human Services; the U.S. Department of Health and Human Services (DHHS); Stephen Hahn, in his official capacity as Commissioner of Food and Drugs; and the U.S. Food and Drug Administration (FDA), and alleges as follows:

PRELIMINARY STATEMENT

1. Congress enacted numerous incentives in the Federal Food, Drug, and Cosmetic Act (FDCA) to reward drug sponsors who invest in the expensive, complex, and demanding scientific process for FDA drug approval. These statutory incentives included various types of market "exclusivity" for sponsors who develop and obtain approval of specific beneficial drug products—like innovative drugs, or drugs that treat rare diseases. FDA has not always seen eye-to-eye with Congress about the wisdom of that statutory scheme, and over many years has taken steps to try to limit statutory exclusivities. But courts have repeatedly rebuked FDA's efforts to thwart the statutory text establishing these exclusivities. *See, e.g.*, *Eagle Pharm., Inc. v. Azar*, 2018 WL 3838265 (D.D.C. June 8, 2018) (rejecting FDA's efforts to limit orphan drug exclusivity); *Ranbaxy Labs., Ltd. v. Leavitt*, 469 F.3d 120, 121 (D.C. Cir. 2006) (rejecting FDA effort to attach extra-statutory condition for exclusivity); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1069 (D.C. Cir. 1998) (same).

2. This case involves a statutory exclusivity known as "New Chemical Entity" exclusivity (NCEE)—an incentive to perform scientific testing and evaluation on an active ingredient that is not a component of any previously approved drug. *See* 21 U.S.C. § 355(c)(3)(E)(ii). NCEE awards five years of market exclusivity to an applicant who undertakes that effort and ultimately receives drug approval. Most forms of exclusivity under the FDCA bar FDA from *approving* a competing drug product for a particular period of time—thus allowing the competing drug product to go through the multi-year FDA review process during the exclusivity period, but prohibiting it from coming to the market until that period expires. NCEE, by contrast, provides even broader protection from competition: In addition to prohibiting approval of another drug with the same active ingredient for five years once NCEE has been granted, NCEE goes

further: NCEE also prohibits even the *submission* of another drug application for a competing drug with that same active ingredient to FDA for review during the five-year exclusivity period if the application does not contain a "paragraph IV certification" (a claim that a patent owned by the NCEE holder is invalid, unenforceable, or not infringed by the drug that is the subject of the application) and during the first four years of that period if the application contains a paragraph IV certification.

3. FDA has sought to narrow the impact of NCEE by interpreting it to only bar "submission" and not approval of a competing initial drug application once NCEE is granted. Under FDA's interpretation, because NCEE bars FDA "submissions" of applications *after* the drug eligible for NCEE has been approved, there is a possibility that, before NCEE is awarded for a particular active ingredient, multiple applications for drugs containing that ingredient could be submitted and simultaneously pending for FDA review. In that case (according to FDA), the first drug to receive approval would be awarded NCEE, but would not always block approval of the other drug whose application was pending at the time of approval (because, according to FDA, NCEE blocks "submissions" of initial applications, not approval). Under FDA's interpretation, the agency could approve a competitor's application based on materials submitted after NCEE became applicable, even if the application materials submitted before the deadline were wholly inadequate to support approval. But even under FDA's improperly narrow interpretation, for NCEE to operate consistently with Congress's intent, FDA cannot allow a competitor to thwart an innovator company's NCEE by submitting a materially incomplete, placeholder application before the agency approves the innovator's application, with the rest to be completed later. FDA's strained interpretation drastically devalues NCEE, making it less valuable than other forms of

exclusivity under the FDCA even though Congress intended NCEE to be the broadest form of exclusivity.

4. Even assuming that FDA could interpret NCEE to bar only "submission" of an initial application and not approval (which would be erroneous), FDA would still be required to faithfully apply non-arbitrary and uniform criteria governing the acceptance of "submissions" of new drug applications for filing. For instance, if an initial drug applicant who would qualify for NCEE is required to expend multiple years of effort on a series of very rigorous and necessary scientific testing over a period of years before FDA will accept its application "submission" for filing under the FDCA, FDA could not properly then make the "submission" acceptance and filing criteria materially more lenient for the second applicant, so that the second applicant could sneak in a materially incomplete "submission" before the first applicant's approval. When the first drug applicant otherwise qualifies for NCEE, FDA's leniency on the second applicant defeats the first applicant's NCEE. Likewise, here FDA cannot implicitly rely on the first applicant's studies so that the second applicant need not conduct them. Nor could FDA further undermine the statutory scheme by allowing the second applicant to bring its shoddy initial submission up to code through additional submissions made during the first applicant's five-year NCEE period. FDA's arbitrary manipulation of drug application acceptance criteria is unlawful in and of itself, but especially so when it defeats statutory rights.

5. Genus is the drug developer of Goprelto® (cocaine hydrochloride), which is indicated for "the induction of local anesthesia of the mucous membranes" when performing certain diagnostic procedures and surgeries. *See* Goprelto® Labeling. Prior to FDA's approval of Goprelto®, FDA had never before approved a drug with cocaine hydrochloride as an active ingredient. During the application process for Goprelto®, FDA advised Genus that it would

qualify for NCEE upon approval, but that FDA would not accept its application until a battery of time-consuming and expensive studies were performed. These studies included (1) a QT prolongation potential study ("QT study"); (2) studies in special populations, including hepatically impaired patients and geriatric patients (unless Genus could demonstrate that the special population studies were unnecessary based on publicly available scientific literature and/or included these special populations as part of its clinical trials); and (3) specific leachable studies at the time of filing to address the safety of the product's container. Genus worked to complete each of those time-consuming studies, including on the relevant special patient populations as no applicable literature was available to obviate the need for studies. FDA accepted Genus's application on November 23, 2016, approved it on December 14, 2017, and notified Genus in February 2018 that it had been awarded NCEE. The length of Genus's NCEE for Goprelto® is determined based on its approval date, so the NCEE extends until December 14, 2022.

6. After FDA accepted Genus's application for review but before Goprelto®'s approval, the Agency was also in discussions with Genus's competitor Lannett Company, Inc. (Lannett) regarding the scientific support needed to accept Lannett's application for a substantially similar cocaine hydrochloride drug. Rather than hold Lannett to the same intensive acceptance standard it applied to Genus, FDA materially altered that standard, and agreed to and did accept Lannett's application without all of the dedicated scientific submissions that FDA had deemed essential for Genus. For example, while Genus was required to perform a dedicated QT study prior to the filing of its NDA to demonstrate the safety of Goprelto®, FDA did not require Lannett to do so prior to acceptance of Lannett's application submission. Likewise, Lannett was not required to perform the same pre-acceptance studies on patients with hepatic deficiencies that were required of Genus, even though FDA knew by this time from Genus's studies that safety

precautions were necessary for hepatically impaired patients and that Lannett's filing included an erroneous attempt to justify that there was no need to perform studies on hepatically impaired patients due to low systemic absorption. Lannett also included an inadequate number of patients over the age 65 in its safety and efficacy study, and FDA permitted reliance on this inadequate number of geriatric patients to determine the effect of Lannett's product on geriatric patients, rather than requesting Lannett to increase the number of geriatric patients. Finally, FDA accepted Lannett's application notwithstanding that the leachable studies Lannett included were plainly inadequate to justify the safety of Lannett's container closure system.

7. FDA admits that the two companies submitted substantively different information in their initial applications, and that Genus's submission contained multiple scientific studies that Lannett's lacked. FDA's argument is instead that: (1) it has *discretion* to hold Lannett to a different, more lenient filing standard, and (2) it could continue to review and *approve* Lannett's application even after it granted Genus NCEE. But FDA lacks the discretion to manipulate the filing standard when doing so would thwart Congress's statutory exclusivities. Had FDA required Lannett to perform these studies prior to accepting Lannett's submission, Lannett could not have completed that work before December 14, 2017, when Genus's NCEE period began. In other words, even under FDA's erroneous interpretation of the NCEE provision, Genus's NCEE would have barred FDA from accepting Lannett's application until 2022 had FDA not materially and arbitrarily applied more lenient acceptance criteria for Lannett's application. Compounding that error, FDA then allowed Lannett to attempt to plug the many holes in its initial submission by amending and *even resubmitting its application* while Genus's NCEE was in effect. If, after accepting an application for drug approval, FDA ultimately determines that the application is materially incomplete, it issues a Complete Response Letter (CRL) explaining that the application

cannot be approved as submitted. *See* 21 C.F.R. § 314.110(a). If the applicant decides that it will attempt to remedy the deficiencies in the application, it can agree to try to solve those shortfalls by "*resubmit[ting]*" the application, this time including all the additional studies and other information FDA has identified as necessary for review and approval. *See id*. § 314.110(b)(1). The *resubmission* of an application following a CRL triggers a new FDA review period under FDA regulations and the Prescription Drug User Fee Act performance goals (PDUFA). *See* 21 C.F.R. § 314.110(b)(1); PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, https://www.fda.gov/media/99140/download. And the new review cycle triggered by a *resubmission* begins only if FDA determines that the "resubmission constitutes a complete response that addresses the deficiencies in the complete response letter." *See* MAPP 6020.4 Rev. 2, "Classifying Resubmissions of Original NDAs, BLAs, and Efficacy Supplements in Response to Complete Response Letters," https://www.fda.gov/media/72727/download.

8. Here, FDA arbitrarily accepted Lannett's materially incomplete application on November 29, 2017—mere weeks before Goprelto® was approved and Genus's NCEE period commenced. Unsurprisingly, FDA reviewers decided seven months later that the application Lannett submitted before the NCEE deadline was so incomplete that it could not be approved. FDA accordingly issued Lannett a CRL on July 20, 2018. Lannett was then required to undertake substantial, time-consuming efforts, including conducting new scientific studies, to remedy the shortfalls with its application identified in the CRL. The additional work required by FDA's CRL was so extensive that Lannett did not *resubmit its application* until nearly a year after the CRL was issued. *See* FDA Letter to Philip J. Perry at 20, Docket No. FDA-2019-P-3855 at 1 (Jan. 10, 2019) (Response to Second Genus Citizen Petition) (attached as Exhibit A). By contrast, Genus

was required to perform such studies ***prior to*** FDA acceptance of its application and ***was never issued a CRL***.

9. FDA's issuance of the CRL to Lannett, and Lannett's resubmission of its application a year later is critical here in at least two respects. First, that series of events leaves no doubt that Lannett's application as submitted was significantly less complete than Genus's at the outset, and should not have been accepted by FDA if the agency were applying a uniform, non-arbitrary standard for acceptance of new drug application submissions. Second, those events constitute other independent FDA violations of law: Genus's NCEE, which applied in full force by this time, prohibited Lannett from "submit[ting] a 505(b)(2) application [the exact application Lannett submitted] . . . for a drug product that contains" cocaine hydrochloride "for a period of 5 years from the date of approval of the first approved [new drug application]." 21 C.F.R. § 314.108(b)(2). That statute barred Lannett from filling in the gaps in the deficient application that it filed *before* FDA's approval of Goprelto® by making additional submissions of information necessary for approval *during* the NCEE period. At a minimum, the statute certainly barred Lannett's effort to "*resubmit [its] application*" under 21 C.F.R. 314.110(b)(1) following FDA's determination that the application could not be approved as originally submitted (emphasis added). Yet this is exactly what FDA allowed. As the term "resubmission" itself suggests, Lannett's *resubmission of its application* following the CRL was the submission of "an application" statutorily barred by NCEE until December 2022. But in order to sidestep NCEE, FDA reinterpreted the term "resubmission" and "application" in a manner inconsistent with the statutory scheme and FDA's own regulations. Under the statute and FDA's regulations, Lannett's *resubmission of its application* in response to the CRL was prohibited; FDA could not legally accept that resubmission without violating Genus's NCEE.

10. In short, FDA acceptance of Lannett's initial materially incomplete application shortly before Genus's NCEE period commenced was arbitrary, capricious, and otherwise not in accordance with law. And FDA was required by law, at a minimum, not to accept Lannett's *resubmission of its application* following FDA's CRL and could not approve that application prior to expiration of Genus' NCEE. Either way, Genus's NCEE should have barred FDA from accepting and approving any Lannett application for the five year duration of Genus's NCEE, which ends on December 14, 2022. FDA nevertheless did unlawfully accept both the initial submission and the resubmission and, contrary to law and Genus's statutory rights, approved Lannett's application for its cocaine hydrochloride product Numbrino on January 10, 2020.[1]

11. Genus is entitled to relief in the form of (i) a declaration declaring FDA's approval of Lannett's drug Numbrino unlawful, (ii) a vacatur setting aside FDA's approval of Numbrino, and (iii) appropriate declaratory and preliminary and permanent injunctive relief prohibiting FDA from approving Numbrino or any application for a drug that violates Genus's NCEE.

PARTIES

12. Plaintiff Genus Lifesciences, Inc. is the owner of New Drug Application No. 209963 for Goprelto®. Genus is a specialty pharmaceutical company with its principal place of business at 514 N. 12th Street, Allentown, PA 18102. Genus advertises, sells, and distributes its drug products in this District and nationwide.

13. Alex Azar is the Secretary of Health and Human Services and the head of DHHS. In this capacity, Secretary Azar has ultimate responsibility for activities at DHHS, including the actions complained of herein. His governmental activities occur nationwide.

[1] Lannett's wholly owned subsidiary, Cody Laboratories, Inc., is the NDA holder for this drug. This complaint uses Lannett throughout for simplicity.

14. DHHS is a department of the United States. Its headquarters and principal place of business are at 200 Independence Avenue, S.W., Washington, D.C. 20201. Its governmental activities occur nationwide.

15. Stephen Hahn is the Commissioner of Food and Drugs and the head of FDA. His governmental activities occur nationwide.

16. FDA is an agency of the United States and a division of DHHS. FDA's headquarters and principal place of business are at 10903 New Hampshire Avenue, Silver Spring, MD 20903. Its governmental activities occur nationwide.

JURISDICTION, VENUE, EXHAUSTION, AND FINAL AGENCY ACTION

17. This Court has jurisdiction pursuant to 28 U.S.C. § 1331. This action arises under the APA, 5 U.S.C. §§ 701-06. Plaintiffs' prayers for a declaratory judgment and preliminary and permanent injunctive relief are authorized by the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; the APA, 5 U.S.C. §§ 701-06; and 28 U.S.C. § 1361.

18. Venue is proper in this District under 28 U.S.C. § 1391(e) because at least one Defendant is an officer or agency of the United States and resides in this District.

19. FDA's approval of Numbrino is a final agency action reviewable under the APA. 5 U.S.C. § 704.

20. There is no statutorily mandated requirement that Genus seek relief from the agency before bringing suit in this Court. There is also no regulatory pathway to challenge the approval under which the approval would remain "inoperative" during the period of agency review. *See* 5 U.S.C. § 704 (providing that this is a mandatory condition for any agency rule seeking to compel agency review before judicial challenge). Thus, administrative exhaustion is not a prerequisite to suit.

21. In any event, immediate judicial review is warranted because Genus has made exhaustive efforts to obtain relief from FDA. Specifically, Genus raised the issues presented by this suit in two citizen petitions to the agency pursuant to the process at 21 C.F.R. §§ 10.20, 10.30, 10.31, 314.150(a)(2)(iv), and the agency denied those petitions. Review is also appropriate because Genus faces significant and irreparable harm from FDA's action, and Genus has no other adequate remedy.

BACKGROUND

A. Statutory and Regulatory Framework for New Drug Approvals and Market Exclusivity

22. Regardless of whether another drug is presently enjoying statutory exclusivity, generally *no* "new drug" may enter the market without first obtaining FDA approval. 21 U.S.C. § 355(a).

23. The principal pathway for premarket approval is through a full New Drug Application (NDA) submitted pursuant to section 505(b) of the FDCA. *Id*. § 355(b)(1). This NDA must contain, among other things, complete reports of investigations of the safety and effectiveness of the product candidate gathered through expensive clinical trials. *Id.* "Such reports rely in large measure on clinical trials with human subjects." *Abigail All. for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 697 (D.C. Cir. 2007). And "before a sponsor can even begin human testing, it must" separately "submit for the FDA's approval an" investigational new drug application (IND). *See id.*; 21 U.S.C. § 355(i)(1). A drug that obtains approval with an active ingredient that is not part of any other approved drug is commonly referred to as a "pioneer drug." *See, e.g.*, *Schering Corp. v. FDA*, 51 F.3d 390, 391 n.1 (3d Cir. 1995).

24. The Hatch-Waxman Amendments of 1984 added more streamlined pathways to approval, but also added exclusivity provisions designed to "reward[] a pioneer drug" and thereby

"encourage innovation in the drug industry." *See Abbott Labs. v. Young*, 920 F.2d 984, 986 (D.C. Cir. 1990).

25. This case principally concerns one specific exclusivity—NCEE—codified at 21 U.S.C. § 355(c)(3)(E)(ii). The NCEE statute prohibits the *submission* of another drug application for a competing drug with the same active ingredient either during the five-year exclusivity period or during the first four years of that period. Which time period applies depends on whether the subsequent application includes a paragraph IV certification. The statute provides that:

> "**If** an application submitted under subsection (b) for a drug, no active ingredient . . . of which has been approved in any other application under subsection (b), is approved" **then** "**no application** which refers to the drug for which the subsection (b) application was submitted and for which the investigations [required] and relied upon by the applicant for approval of the application were not conducted by or for the applicant 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 form the date of the approval of the application under subsection (b)**, **except** that such an application may be submitted under subsection (b) after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A). The **approval of such an application** shall be made effective in accordance with this paragraph …."

See 21 U.S.C. § 355(c)(3)(E)(ii) (emphasis added); *see also id.* § 355(j)(5)(F)(ii) (same for other types of follow-on drugs).

26. In other words, as FDA has explained through regulation: "If a drug product that contains a new chemical entity [i]s approved . . . in an [application] submitted under section 505(b) of the Act, no person may submit a 505(b)(2) application . . . for a drug product that contains the same active moiety[2] as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application." 21 C.F.R. § 314.108(b)(2).

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[2] *See Amarin Pharm. Ir. Ltd. v. FDA*, 106 F. Supp. 3d 196, 206 (D.D.C. 2015) ("When dealing with single molecule drugs, the 'active ingredient' and the 'active moiety' refer to the same

B. FDA Regulatory Process for Accepting and Evaluating Applications

27. By regulation and practice FDA has established a body of law governing the process of accepting submissions and resubmissions of new drug applications.

28. As relevant here, FDA's regulation at 21 C.F.R. § 314.50 codifies the voluminous material required in a new drug application. An NDA must contain "reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source." 21 C.F.R. § 314.50. Specifically, an NDA "is required to contain . . . technical sections" which must in turn "contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the NDA or whether grounds exist [under the FDCA] to refuse to approve the NDA." *Id.* § 314.50(d). And those technical sections include a "[c]hemistry, manufacturing, and controls section;" a "[n]onclinical pharmacology and toxicology section;" a "[h]uman pharmacokinetics and bioavailability section;" and a "[c]linical data section." *Id.* § 314.50(d)(1)-(3), and (5). FDA regulations define an "application" as "the application described under § 314.50, including all amendments and supplements to the application." 21 C.F.R. § 314.3(b). FDA will accept an application only after it makes a threshold determination that the application is sufficiently complete to permit a substantive review. *See* 21 C.F.R. § 314.101(a)(1). And it will "refuse to file" applications that are incomplete—meaning such applications are no longer before the agency. *See id.* § 314.101(d) and (e).

29. FDA's "expectation is that an application is complete upon submission." *See* FDA Letter to Michael J. Freno at 9, Docket No. FDA-2019-P-0538 (July 1, 2019) (Response to First

molecule and thus the distinction typically makes no difference to the Agency's exclusivity analyses.").

Genus Citizen Petition) (attached as Exhibit B). In order to ensure that this expectation is met, FDA encourages applicants to confer with the agency prior to submission of a new drug application in order to "resolv[e] questions and issues raised during the course of a clinical investigation." 21 C.F.R. § 312.47(a).[3] The "primary purpose" of a "pre-NDA" meeting:

> is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application.

Id. § 312.47(b)(2). Thus, for example, FDA can indicate during a pre-NDA filing meeting that an applicant needs to submit information regarding a clinical pharmacology study of the drug in order to comply with the regulatory requirement at 21 C.F.R. § 314.50(d)(5)(i) for a new drug application and avoid a "refuse to file" determination under 21 C.F.R. § 314.101. If the applicant nonetheless omits that study, FDA would typically consider the application incomplete and would "refuse to file" it.

30. Once an application is filed (accepted by FDA for review), FDA assesses its contents to determine whether to either approve the application or send a CRL under 21 C.F.R. § 314.110. FDA issues a CRL when it determines it cannot approve the application in its present

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[3] *See also* Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, FDA, Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development at 4 (Dec. 2017) ("Sponsors can request meetings with FDA at any time during drug development, and FDA strongly encourages sponsors to request the critical milestone meetings . . . ."); FDA Standard Operating Policy and Procedure 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products at 6 ("The purpose of the [pre-NDA] meeting is to discuss the planned content of the application with the appropriate . . . review division. Applicants are strongly encouraged to request this meeting.").

form. *Id.* § 314.110(a). Upon receipt of a CRL, an applicant only has three options: elect to "resubmit [its] application," withdraw the application, or request a hearing. *Id.* § 314.110(b). No amendments to the application are permitted after a CRL has been granted. If the applicant decides to submit its application again (a "resubmission" under the regulations), it must address in that resubmission all deficiencies identified in the CRL. *Id.* § 314.110(b)(1). Mirroring the process for reviewing the completeness of an initial application, FDA will not accept the application as resubmitted unless or until it determines that the resubmitted application is complete and addresses all deficiencies. *See* MAPP 6020.4 (FDA will "will determine whether the resubmission constitutes a complete response that addresses all deficiencies in the complete response letter" and will inform applicant of FDA's determination by "letter to the applicant within 30 calendar days").

31. FDA's regulations forthrightly acknowledge that a "resubmission" of an application in response to a CRL is no less a "submission" than the *initial* submission of the application. *See* 21 C.F.R. § 314.3 (defining a "[r]esubmission, in the context of a complete response letter" as a "*submission*" of the information needed for approval (emphasis added)); *compare id*. § 314.50 (governing submissions and resubmissions) *with* § 314.60 (governing amendments to a still pending application). Indeed, FDA's regulations recognize a specific distinction between what constitutes a permissible amendment of a pending application under 314.60, and the different process of resubmitting an application. *Id.* § 314.60(c)(2); *id.* § 314.50; *id.* § 314.110(b). And resubmission has significant consequences for, *inter alia*, the time required for FDA to evaluate and approve an application. When FDA receives a resubmission, a new review cycle—the time period in which FDA works to complete its review of an application—begins. 21 C.F.R. § 314.110(b)(1). The length of the new review cycle depends on the type of information included in the resubmission. *See id*. § 314.110(b)(1)(i)-(ii); § 314.3(b) (defining

Class 1 and 2 resubmissions, which trigger the beginning of two- and six-month review cycles, respectively); PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022.

C. Genus's Submission of its Application for Goprelto® and Approval

32. Goprelto® is a cocaine hydrochloride product 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." *See* Goprelto® Labeling. Medical professionals use cocaine hydrochloride while performing medical procedures, such as biopsies, endoscopies, nasal cauterization, foreign body removal, and nasal debridement, among other procedures.

33. FDA accepted for filing Genus's submission of a 21 U.S.C. § 355(b)(2) application for Goprelto® on November 23, 2016. Before accepting that application for filing, however, FDA required Genus to complete multiple, highly technical and expensive Pre-Filing Studies, as explained below.

34. First, in June 2015, FDA told Genus that "a complete clinical pharmacology package is expected at the time of NDA submission." Response to Second Genus Citizen Petition at 8. Among other things, that meant Genus had to "address all pertinent clinical pharmacology information related" to certain aspects of its drug "and the pharmacokinetics [PK] of the drug" (*i.e.*, the way the drug interacts with the patient body) in "special populations" of users. *Id.* Two aspects that FDA specifically identified are most relevant here: First, "PK and dosing" in patients with hepatic impairment and in geriatric patients, *i.e.*, whether the drug would have a special effect on these user populations. *Id*. And second "**QT prolongation** potential," *i.e.*, effect on patients' heart. *Id.* (emphasis added).

35. Genus responded to FDA that it believed there would be no need to conduct dedicated studies for these issues and that, instead, either existing literature or information already

in Genus's possession fully satisfy any concerns FDA may have. As to QT prolongation potential, Genus stated that it "ha[d] not observed cardiovascular safety problems in [its] clinical trial." *Id.* at 8. As to "special population studies" (*i.e.*, for hepatically impaired patients and geriatric patients), Genus expressed that dedicated studies would be unnecessary because Genus believed the drug would primarily be applied topically via the intranasal route of administration and because it is designed to have "minor systemic exposure." *Id.* at 8. Genus asked FDA to confirm that "studies conducted in special populations are not relevant . . . and do not need to be conducted." *Id.* at 9. And Genus also told FDA that, if it *were* necessary, Genus would consider conducting a dedicated PK study to fill in any gaps in its application. *Id.*

36. FDA and Genus met a few days later to discuss these issues. FDA did not agree that "special population studies are not relevant" or that Genus could avoid conducting further studies or analysis on the issue. Instead, FDA stated unequivocally that Genus "must provide evidence of low systemic exposure levels using data from [a] PK study" in order to relate that PK study to literature on patients with hepatic impairment. And it even specifically defined the parameters for that study: "The PK study must be of adequate sample size, and include validated analytical assays for cocaine and its metabolites." *Id*. FDA "*also* recommended" that Genus include information from "literature sources" as "additional evidence." *Id* (emphasis added).

37. Over the course of the next several months, Genus, and consultants operating on Genus's behalf, interfaced with FDA about precisely what dedicated studies it would need to perform. Ultimately, FDA conveyed that Genus would need to conduct both **QT prolongation** and **hepatic impairment** studies before it would accept Genus's application for filing, and Genus agreed. For example, on July 5, 2016, a Senior Regulatory Health Project Manager at FDA emailed Genus's regulatory consultant requesting for clarification on the status of Genus's hepatic

impairment studies. And on a July 14, 2016 teleconference, FDA specifically indicated Genus would have to submit both a QT prolongation study and the hepatic impairment studies when Genus submitted its NDA.

38. FDA also repeatedly stated that, before Genus could submit its application, it would have to complete risk assessments regarding potential leachables throughout the stability time period.[4] In August 2013, FDA indicated that Genus's "NDA submission **must** contain information on potential leachables and extractables from the drug container closure system, unless specifically waived by" the agency. August 20, 2013 Pre-IND Meeting Request – Written Responses from FDA to Genus at 7. Then, in June 2015, FDA reiterated this position and emphasized that Genus should "evaluate *at least* three batches of [its] drug product over the course of [its] stability studies and base [its] final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration." June 15, 2015 Meeting Preliminary Comments from FDA to Genus at 9.[5] FDA expressly rejected Genus's

[4] Certain drug formulations and container closure systems present a risk that compounds from the container may "leach" from the container to the drug as a result of direct contact. Studies can be performed to determine whether a specific *combination* of drug product formulation and container closure system presents risks of these leachables by testing for relevant compounds. *See* U.S. Pharmacopeia <1663> and <1664>.

[5] *See id*. ("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 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 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. . . . 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."); *id*. at 9-11 (noting that the Agency may refuse to file Genus's NDA if "the submission lacks an adequate extractable/leachable risk assessment.").

request to omit these studies from its application. *See* July 10, 2015 Response to Preliminary Comments from Genus to FDA at 8; July 14, 2015 Meeting Minutes from FDA to Genus at 14.[6]

39. As required, Genus conducted these studies and included the results of these studies in its NDA submission. *See* Goprelto® Summary Review at 2. Genus also conducted a thorough literature search for relevant, well-controlled studies including patients with hepatic impairments, but found none. Based on the results of the pharmacokinetic studies in hepatically impaired patients, FDA ultimately concluded patients with hepatic impairment could safely use Goprelto®. *See id*. at 12. However, due to Genus's discovery of certain safety issues in studies, FDA recommended that subjects with hepatic impairment not receive the product more than once in 24 hours. Goprelto Labeling § 8.7 ("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."). With the inclusion of all of this information (and much more), FDA finally accepted Goprelto®'s NDA submission for filing on November 23, 2016. It then approved the application on December 14, 2017, and awarded Goprelto® NCEE under section 505(c)(3)(E)(ii), 21 U.S.C. 355(c)(3)(E)(ii). *See* Goprelto® Approval Letter (attached as Exhibit C). Goprelto®'s NCEE expires on December 14, 2022. *See* Goprelto® Orange Book Listing (attached as Exhibit D).

[6] *See id*. (FDA stating that the toxicology 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.").

D. FDA Unlawfully Accepts Lannett's Numbrino Submission for Filing and Approves Numbrino in Violation of Goprelto®'s NCEE

40. Like Goprelto®, the active ingredient in Lannett's Numbrino is cocaine hydrochloride.

41. FDA received Lannett's first 505(b)(2) application for Numbrino on September 21, 2017.[7] *See* Response to Second Genus Citizen Petition at 9. Because Goprelto® was not yet approved and, as a result, had no patents listed in FDA's "Orange Book," Lannett's application did not include a paragraph IV certification.

42. On November 29, 2017—mere weeks before FDA approved Goprelto®, triggering the applicability of Goprelto®'s NCEE—FDA accepted Lannett's application for filing. *See* Response to Second Genus Citizen Petition at 1 n.3. Subsequent events, however, reveal that FDA arbitrarily subjected Lannett to a far more lenient standard than Genus in determining whether to accept Lannett's submission.

43. First, Lannett was able to file its NDA without conducting a dedicated QT prolongation study. Instead, Lannett submitted "data" on QT prolongation from its broader *clinical* trials. *See* Response to Second Genus Citizen Petition at 20. Although FDA allowed Lannett to file its application with only this data (and not the new study required of Genus), the data proved wholly inadequate. And FDA issued a CRL to Lannett on July 20, 2018 "instruct[ing] Lannett to conduct a dedicated QT study." *Id.*

[7] From 2008 to 2019, Lannett sold an unapproved cocaine hydrochloride drug. In 2012, Lannett asked FDA whether it could legally market its unapproved cocaine hydrochloride drug. FDA denied that request in 2015, stating that Lannett had no legal basis to market its unapproved cocaine hydrochloride product based on the information provided by Lannett. Despite this statement, FDA did not stop Lannett from distributing its unapproved drug until August 15, 2019. Lannett supplied the market with larger than normal amounts of product prior to August 15, in the hope that its product would remain in the market until it was approved by FDA.

44. Lannett also *never* conducted dedicated studies on patients with hepatic impairment (neither before filing nor afterwards). *Id.* at 17-19. Instead, FDA accepted Lannett's application for filing on the basis of "literature" that Lannett identified which allegedly supported the premise that that there would be no issues with patients with hepatic impairment. This option was not an option available to Genus. And FDA knew at the time of Lannett's filing that the claim was inaccurate, based on FDA's review of the studies Genus had performed on patients with hepatic impairment. *Id*. And FDA ultimately reached the same conclusion regarding Lannett's literature as it did for Genus: It could not support approval. But, *unlike* with Genus, FDA *never* required Lannett to conduct hepatic studies, instead, it allowed Lannett simply to add a provision to its drug label suggesting that the drug "should be avoided" *entirely* by "patients with hepatic impairment." Numbrino Labeling §§ 8.6, 8.7. This labeling option—sidestepping the studies required of Genus—was never offered by FDA to Genus as an option.

45. Geriatric patients were a mere 1.6% out of all of the patients who participated in Lannett's study to determine safety and efficacy. "[H]ypertension was observed in **all** geriatric" patients who received Numbrino during the study, and Lannett's label states, "Special precaution should be given when determining the dose of NUMBRINO for geriatric patients, commensurate with their age and physical status." Numbrino Labeling § 8.5 (emphasis added).

46. Lannett also initially submitted leachable studies and a toxicological risk assessment as part of its initial submission, but they were so deficient that FDA later found them inadequate to justify the safety of Lannett's container closure system—forcing Lannett to conduct new studies. *See* Response to Second Genus Citizen Petition at 20-21.

47. Following FDA's CRL for Lannett's Numbrino, and Lannett's resubmission of its Numbrino application roughly a year later, FDA ultimately approved Numbrino on January 10,

2020.[8] In addition to the unlawful acceptance of Lannett's initial application submission identified above, this approval also violated Goprelto®'s statutory NCEE in multiple additional ways.

48. As described, the FDCA provides that Lannett's "application" for Numbrino could not "be submitted" during the NCEE period. Here, Lannett did submit an application before the NCEE period—but *that* application was fatally flawed and could not be approved, resulting in FDA's issuance of a CRL. FDA's position that Lannett could continue submitting parts of the application during the NCEE period to cure deficiencies in its initial submission conflicts with both the statute and FDA's own regulations. As Genus has pointed out, FDA's regulations define an "application" as "the application described under § 314.50, *including all amendments and supplements to the application*." 21 C.F.R. § 314.3 (emphasis added). Were FDA correct that the NCEE bar does not apply to amendments, a competitor could easily circumvent the statutory bar by rushing to file a placeholder application and then completing the application after the deadline. Properly read, the statute thus prohibited FDA from allowing Lannett to *complete* the submission of its application during the NCEE period by filing additional information that was necessary to FDA's approval of Numbrino.

49. Regardless, at a minimum, the statute prohibited FDA from allowing Lannett to *resubmit* its application following FDA's determination in a CRL that the application could not be approved. The FDCA unambiguously prohibits *any* submission of an application during the time period in which NCEE is pending. And FDA's regulations make unambiguously clear that a

[8] Perhaps unsurprisingly given the FDA review history, Numbrino's labeling reported that up to 78% of patients taking Numbrino experienced adverse vascular events, such as hypertension. Numbrino Labeling § 6.1. The labeling also suggests that Numbrino should be avoided in patients with hepatic impairment, that special precaution should be given for geriatric patients, and that dose initiation should follow a conservative approach in patients with renal impairment. *Id*. §§ 8.5-8.7.

response to a CRL is a re-submission of the drug application. *See, e.g.*, 21 C.F.R. § 314.3 (defining "resubmission" as a "submission"); *id.* § 314.5(a) (explaining that a resubmission is a type of application); *id.* § 314.110(b)(1) (explicitly referring to a "resubmission" as the "resubmission of an application," not as an amendment to an application). Indeed, a CRL is only issued if the application would otherwise be *denied* as incomplete. 21 C.F.R. § 314.110(a) ("FDA will send the applicant a complete response letter if the agency determines that we will not approve the application . . . in its present form.") A CRL also starts an entirely new application review period. *See* 21 C.F.R. § 314.110(b)(1). It appears that Lannett received a Class 2 CRL, which triggered a fresh 6 month FDA application review period. *See* 21 U.S.C. § 355(c)(1). Because a "resubmission" is a "submission" of an "application" under FDA regulations, FDA's acceptance of Lannett's resubmission was a straightforward violation of the NCEE provision of the FDCA. So in addition to the NCEE statute barring *all amendments to a pending application*, the statute surely bars *resubmissions of the application once a CRL is issued concluding that the pending application cannot be approved as submitted*.

50. Even though Goprelto®'s five-year NCEE became effective on December 14, 2017, and even though FDA issued a CRL to Lannett indicating its initial Numbrino application was plainly deficient, FDA nevertheless permitted Lannett to resubmit its application after December 14, 2017 with additional material studies and information in violation of Goprelto®'s NCEE.

51. To escape the plain text of the NCEE statutory provision (which applies to submissions of "an application") and its own regulations (which specifically define a "resubmission" following a CRL as a submission of an "application"), FDA has made the untenable argument in response to a Genus Citizen Petition that the term "resubmission" has

different meanings in different neighboring provisions of its own regulations. Response to Second Genus Citizen Petition at 5 ("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 . . . . A resubmission is thus an amendment after a [CRL]."). But the only definitional provisions of those regulations applicable here expressly affirm that a resubmission is in fact a ***submission of an application,*** which is exactly what the NCEE statutory provision prohibits. Indeed, FDA's own longstanding regulations expressly indicate that a "resubmission" is subject to the statutory NCEE exclusivity provision. 21 C.F.R. § 314.60(c)(2). There is no non-arbitrary way to wriggle out of that plain text, and NCEE plainly applies.

52. Because FDA could not legally accept either Lannett's original submission of its application, or Lannett's resubmission of that application one year after it received a CRL, FDA is barred from accepting and reviewing Lannett's submissions until the conclusion of Genus' NCEE on December 14, 2022. It also appears, based on information available to Genus, that FDA relied on information from Genus's application when approving Lannett's application. For example, FDA appears to have relied on studies performed by Genus for Goprelto® when determining what labeling FDA could approve for Lannett's Numbrino. If Lannett's approval depended on studies performed by Genus to which Lannett did not have a right of reference, then FDA should have required Lannett to amend its application to include a paragraph IV certification with respect to Genus's Goprelto® patents. *See* 21 U.S.C. § 355(b)(2)(A). But such an amendment, which would have fundamentally changed the nature of Lannett's Numbrino application (including the length of time for which NCEE would have blocked its submission) and triggered numerous statutorily required procedures, surely would not have been permissible while the NCEE was in effect.

53. In addition, Congress also recognized that an application like Lannett's cannot be approved during the NCEE period, regardless of whether it could be properly submitted or resubmitted. This is explicit in the statutory text which refers to "approval"—directing that any approval of an application pending at the time NCEE attaches must be "made effective in accordance with this paragraph." 21 U.S.C. § 355(c)(3)(E)(ii). Even if FDA was permitted to accept Lannett's amendments to and re-submission of its application, it was therefore still barred from approving that application. *See Otsuka Pharm. Co. v. Burwell*, 302 F. Supp. 3d 375, 385 (D.D.C. 2016) (NCEE establishes bar on applications which "may be submitted (*or approved*) for five years"); *Otsuka Pharm. Co. v. Price*, 869 F.3d 987, 990 (D.C. Cir. 2017) (NCEE "confers an exclusivity period of five years, during which no abbreviated application which refers to the first-in-time drug may be approved" (alterations omitted)); *see also* 130 Cong. Rec. 24,425 (1984) (Rep. Waxman) (sponsor of Hatch-Waxman indicating that NCEE "provides a 5-year period of *exclusive market life*" (emphasis added)).

CLAIM I: INITIAL SUBMISSION
VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT
AGENCY ACTION THAT IS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, NOT IN ACCORDANCE WITH LAW, IN VIOLATION OF STATUTORY RIGHT
Violation of 5 U.S.C. § 706; 21 U.S.C. § 355(c)(3)(E)(ii)

54. The foregoing paragraphs are incorporated by reference as if set forth in full herein.

55. The Administrative Procedure Act prohibits Defendants from acting in any way that is arbitrary and capricious or an abuse of discretion, including by according "disparate treatment [to] functionally indistinguishable products." *See Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997); *see also Indep. Petrol. Ass'n of Am.*, 92 F.3d 1248, 1260 (D.C. Cir. 1996).

56. Goprelto® and Numbrino are similarly situated products because both drugs contain the same active ingredient and strength and are intended for the same use.

57. FDA arbitrarily accorded disparate and preferential treatment to Lannett, including by requiring Genus to submit studies before FDA would even accept its application for Goprelto® as filed that it did not require Lannett to submit with Numbrino's application.

58. As a result of this disparate treatment, Genus has been significantly prejudiced. Had FDA treated Numbrino as it had treated Goprelto®, FDA could not have accepted Lannett's initial submission of a new drug application for Numbrino because that submission would have been blocked by Genus's NCEE for cocaine hydrochloride.

59. For the foregoing reasons, FDA's approval of Numbrino is arbitrary, capricious, an abuse of discretion, not in accordance with law, and short of statutory right.

CLAIM II: AMENDMENT AND RESUBMISSION AFTER CRL VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT AGENCY ACTION THAT IS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, NOT IN ACCORDANCE WITH LAW, IN VIOLATION OF STATUTORY RIGHT
Violation of 5 U.S.C. § 706; 21 U.S.C. § 355(c)(3)(E)(ii)

60. The foregoing paragraphs are incorporated by reference as if set forth in full herein.

61. The Administrative Procedure Act prohibits Defendants from acting in any way that is not in accordance with law.

62. The FDCA provides that if a drug product that contains a new chemical entity is approved in an NDA under section 505(b), 21 U.S.C. § 355(b), then FDA may not accept for filing an NDA under section 505(b)(2) for a drug product with the same active ingredient as the new chemical entity for a period of five years from approval of the first approved NDA. *See* 21 U.S.C. § 355(c)(3)(E)(ii).

63. FDA approved Goprelto®, which contains the new chemical entity cocaine hydrochloride, under section 505(b) of the FDCA, 21 U.S.C. § 355(b), on December 14, 2017.

64. FDA has recognized that Genus has NCEE for cocaine hydrochloride, which will expire on December 14, 2022.

65. FDA nevertheless allowed Lannett to amend and even resubmit its application for Numbrino after December 14, 2017, and approved that application on January 10, 2020.

66. A resubmission of an application constitutes a submission barred by NCEE.

67. Here, Genus's statutory NCEE barred, at a minimum, Lannett's resubmission of the Numbrino application and FDA's approval of that resubmission, and any regulation, agency policy, or citizen petition decision that FDA would invoke to reach a different result is incompatible with the FDCA and so is invalid.

68. Moreover, FDA should have also refused to accept any amendments or resubmissions by Lannett because Lannett should have had to resubmit its application as an Abbreviated New Drug Application. *See* 21 C.F.R. § 314.101(d)(9).

69. For the foregoing reasons, FDA's approval of Numbrino is arbitrary, capricious, an abuse of discretion, not in accordance with law, and short of statutory right.

CLAIM III: APPROVAL OF APPLICATION DURING NCEE PERIOD VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT AGENCY ACTION THAT IS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, NOT IN ACCORDANCE WITH LAW, IN VIOLATION OF STATUTORY RIGHT
Violation of 5 U.S.C. § 706; 21 U.S.C. § 355(c)(3)(E)(ii)

70. The foregoing paragraphs are incorporated by reference as if set forth in full herein.

71. The Administrative Procedure Act prohibits Defendants from acting in any way that is not in accordance with law.

72. The FDCA provides that if a drug product that contains a new chemical entity is approved in an NDA under section 505(b), 21 U.S.C. § 355(b), then FDA may not approve another NDA filed under section 505(b)(2) for a drug product with the same active ingredient as the new chemical entity for a period of five years from approval of the first approved NDA. *See* 21 U.S.C. § 355(c)(3)(E)(ii).

73. FDA approved Goprelto®, which contains the new chemical entity cocaine hydrochloride, under section 505(b) of the FDCA, 21 U.S.C. § 355(b), on December 14, 2017.

74. FDA has recognized that Genus has NCEE for cocaine hydrochloride, which will expire on December 14, 2022.

75. FDA nevertheless approved Lannett's application for a cocaine hydrochloride product on January 10, 2020.

76. Here, Genus's statutory NCEE barred FDA's approval of Lannett's application, and any regulation, agency policy, or citizen petition decision that FDA would invoke to reach a different result is incompatible with the FDCA and so is invalid.

77. For the foregoing reasons, FDA's approval of Numbrino is arbitrary, capricious, an abuse of discretion, not in accordance with law, and short of statutory right.

REQUEST FOR RELIEF

Genus respectfully requests that the Court enter judgment in its favor and grant the following relief:

1. A declaration pursuant to 28 U.S.C. § 2201 that:

    a. Defendants' approval of Numbrino violates Plaintiff's NCEE; and

    b. Defendants' approval of Numbrino is arbitrary, capricious, an abuse of discretion, not in accordance with law, and short of statutory right.

2. An order setting aside Defendants' approval of Numbrino.

3. An order enjoining FDA from accepting the submission of an application for any cocaine hydrochloride drug, or approving any such application, prior to December 14, 2022.

4. An order awarding Genus its costs and attorneys' fees pursuant to 28 U.S.C. § 2412.

5. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

Dated: January 27, 2020

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