UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF GEORGIA
ATLANTA DIVISION

ARBOR PHARMACEUTICALS, LLC Plaintiff, v. NORRIS W. COCHRAN IV, in his official Capacity as Acting Secretary of Health and Human Services, JANET WOODCOCK, M.D., in her official capacity as Acting Commissioner of Food and Drugs, UNITED STATES FOOD AND DRUG ADMINISTRATION, Defendants.	)	Case No. _____

COMPLAINT

Plaintiff Arbor Pharmaceuticals, LLC ("Arbor") brings this Complaint against Defendants Norris W. Cochran IV, in his official capacity as Acting Secretary of Health and Human Services; Janet Woodcock, M.D., in her official capacity as Acting Commissioner of Food and Drugs; and the United States Food and Drug Administration (collectively "FDA" or "the Agency"). In support thereof, Arbor states the following:

PARTIES

1. Plaintiff Arbor is an Atlanta-headquartered specialty pharmaceutical company which markets both branded and generic prescription drug products for the cardiovascular, neurology, hospital, and pediatric markets. Arbor is organized under the laws of the State of Delaware, and owns New Drug Application ("NDA") 203340 for its original formulation of the drug product Nymalize® (nimodipine) oral solution, 3 mg/mL ("Original Nymalize®"), and the supplemental NDA 203340/S-11 for a reformulated, double-concentrated, and improved version of Nymalize® (nimodipine) oral solution, 6 mg/mL ("Reformulated Nymalize®").

2. Defendant Norris Cochran is the Acting Secretary of Health and Human Services ("HHS") and the official charged by law with administering the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 *et seq*., including the drug-approval provisions codified at 21 U.S.C. § 355. Secretary Cochran in turn has delegated his authority under the FDCA to the Commissioner of Food and Drugs. Acting Secretary Cochran is sued in his official capacity. He maintains offices at 200 Independence Ave., S.W., Washington, DC 20204.

3. Defendant Janet Woodcock, M.D., is the Acting Commissioner of Food and Drugs and, as noted above, has been delegated authority to administer the FDCA's drug-approval provisions. Commissioner Woodcock is sued in her official

capacity. She maintains offices at 10903 New Hampshire Ave., Silver Spring, MD 20903.

4. Defendant FDA is an agency within HHS. 21 U.S.C. § 393(a). FDA is charged with overseeing, *inter alia*, the human drug approval process, including the portions of that process relevant to this case. Its headquarters are located at 10903 New Hampshire Ave., Silver Spring, MD 20903.

5. HHS and FDA are each an "agency" of the government within the meaning of the Administrative Procedure Act ("APA"). 5 U.S.C. § 701(b)(1).

JURISDICTION AND VENUE

6. This Court has subject-matter jurisdiction pursuant to 28 U.S.C. § 1331. This action arises under the FDCA, as amended *inter alia* by the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act" or "Hatch-Waxman"), Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355); the APA, 5 U.S.C. §§ 555, 702, and 706; and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

7. Venue is proper in this District pursuant to 28 U.S.C. § 1391(e)(1)(C) (providing that venue against federal defendants is proper "in any judicial district in which … the plaintiff resides if no real property is involved in the action"); *see also id*. § 1391(c)(2) (providing that "an entity with the capacity to sue and be sued in its

common name under applicable law, whether or not incorporated, shall be deemed to reside … if a plaintiff, only in the judicial district in which it maintains its principal place of business").

8. Venue is proper in this Division pursuant to LR 3.1B because Arbor resides in this Division and the activity giving rise to the cause of action occurred at least in part in this Division.

9. FDA's February 17, 2021 final decision determining that Arbor's Original Nymalize® NDA product "was not withdrawn from sale for reasons of safety or effectiveness"—published at 86 Fed. Reg. 9944 (Feb. 17, 2021), and issued as FDA's formal response (*see* Exs. A & B) to the Citizen Petitions submitted in Docket Nos. FDA-2020-P-1511 (Ex. C) and FDA-2020-P-1549 (Ex. D)—is final agency action that is subject to immediate judicial review under the APA. *See* 21 U.S.C. § 355(q)(2)(A) (expressly deeming FDA's "final decision" on a Citizen Petition to be "final agency action"); *see also* 21 C.F.R. § 10.45(d) ("[T]he Commissioner's final decision constitutes final agency action (reviewable in the courts under 5 U.S.C. 701 *et seq*. and, where appropriate, 28 U.S.C. 2201) on a petition submitted under [21 C.F.R.] § 10.25(a)").

10. As the subject of, and as a party to, the administrative proceedings resulting in the challenged final agency action, Arbor exhausted its administrative

remedies and has standing to pursue the claims at issue in this Complaint. *See* 21 C.F.R. § 10.45(d)(1) ("It is the position of FDA except as otherwise provided in paragraph (d)(2) of this section, that: (i) Final agency action exhausts all administrative remedies and is ripe for preenforcement judicial review as of the date of the final decision, unless applicable law explicitly requires that the petitioner take further action before judicial review is available; [and] (ii) An interested person is affected by, and thus has standing to obtain judicial review of final agency action."); *see also* 21 U.S.C. § 355(q)(2)(B) (providing that dismissal for failure to exhaust administrative remedies is appropriate only where "a civil action is filed against the Secretary with respect to any issue raised in the petition ***before*** the Secretary has taken final agency action on the petition") (emphasis added).

11. An actual and justiciable controversy exists between Plaintiff and Defendants.

STATUTORY AND REGULATORY BACKGROUND

12. The FDCA establishes both the procedures and requirements for obtaining FDA's approval to market pharmaceutical products in interstate commerce. *See* 21 U.S.C. § 355.

13. To obtain FDA's approval for a new (or "brand-name") drug product, applicants must submit an NDA that contains, among other things, data from

adequate and well-controlled human clinical trials that are sufficient to establish the proposed new drug's safety and efficacy for its intended use or uses under the terms and conditions set forth in its proposed labeling. *Id*. § 355(b)(1).

14. Before Hatch-Waxman's enactment in 1984, the FDCA generally required generic drug manufacturers to conduct their own human clinical trials and submit full NDAs in order to obtain approval, even though genuine generic drugs contain the same active ingredients and can be expected to have the same safety and efficacy as their brand-name equivalents. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 612 (2011). To simplify the approval process for genuine generic drugs, Hatch-Waxman established an abbreviated approval pathway for generic copies of previously approved drugs: It allows FDA to approve a generic version of a previously approved NDA product (called the "reference listed drug" or "RLD") if the generic applicant proves that its proposed drug product is identical to its RLD in all material respects—meaning that it contains "the same" amount (or "strength") of "the same" pharmaceutically active ingredient, in "the same" dosage form, for use through "the same" route of administration as its RLD, is bioequivalent[1] to its RLD,

[1] FDA regulations define "bioequivalence" as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety

and bears "the same … labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(A)(i)-(v); *see also id*. § 355(j)(4)(C) (barring FDA from approving a generic application where it fails to meet any of the foregoing sameness requirements).

15. To support such an approval, Hatch-Waxman requires generic drug applicants to submit an Abbreviated New Drug Application ("ANDA") establishing each of the foregoing product characteristics. *Id*. § 355(j)(2)(A). Where (and only where) a proposed ANDA product satisfies each of the foregoing "sameness" requirements, its sponsor need not replicate the RLD holder's clinical trials in order to obtain FDA approval. FDA instead can approve the ANDA product based on its prior determination that the RLD is safe and effective, because two materially indistinguishable drug products usually can be expected to have materially indistinguishable safety and efficacy profiles. *See Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998).

16. Of critical importance to this case, Hatch-Waxman makes clear that certain NDA products cannot be relied upon as an RLD for purposes of submitting

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in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 C.F.R. 314.3(b).

or securing approval of an ANDA. Because post-approval developments have the potential to alter the risk/benefit profile of a previously approved NDA product, the Hatch-Waxman Act expressly precludes FDA from approving any ANDA that references a previously approved NDA product where (as relevant here) either [1] "approval under [21 U.S.C. § 355](c) of the listed drug referred to in the [ANDA] has been withdrawn or suspended for grounds described in the first sentence of [21 U.S.C. § 355](e)"[2] or [2] the NDA product remains approved, but the NDA holder has ceased marketing its NDA product and "the Secretary has determined that the

[2] The cross-referenced first sentence of 21 U.S.C. § 355(e) provides that the Agency may "withdraw approval of an application … if [FDA] finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact."

listed drug has been withdrawn from sale for safety or effectiveness reasons." 21 U.S.C. § 355(j)(4)(I).

17. FDA's regulations implement this statutory proscription by requiring that any ANDA that seeks to reference "a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons." 21 C.F.R. § 314.122(a).

18. Upon receipt of such a "Citizen Petition," the Agency "will consider the evidence in the petition and any other evidence before the agency, and determine whether the listed drug is withdrawn from sale for safety or effectiveness reasons." *Id*. § 314.122(b). FDA's regulations in turn obligate the Agency to "disapprove" an ANDA referencing any voluntarily withdrawn NDA product "unless the agency determines that the withdrawal of the listed drug was not for safety or effectiveness reasons." *Id*. § 314.122(c). FDA must publish any decision made under this section in the *Federal Register*, *id*. §§ 314.161(c), (e), and the Agency not surprisingly is obligated to render its decision "[p]rior to approving an [ANDA] that refers to [a withdrawn] listed drug." *Id*. § 314.161(a)(1).

19. Because FDA receives dozens of Citizen Petitions every year, spanning the full array of matters that are subject to the Agency's regulatory jurisdiction, the

Agency triages its resolution of those submissions and typically takes final agency action on a given Citizen Petition only at the point where rendering a decision on a given matter is essential. *Id.* § 10.30(e)(1) ("The Commissioner shall … rule upon each [Citizen Petition], taking into consideration (i) available agency resources for the category of subject matter, (ii) the priority assigned to the petition considering both the category of subject matter involved and the overall work of the agency, and (iii) time requirements established by statute.").

20. Consistent with that approach, where an ANDA applicant or NDA holder has asked the Agency to determine whether a previously approved NDA product was withdrawn from sale for safety or effectiveness reasons, FDA frequently defers resolution of a pending Citizen Petition until shortly before the Agency is prepared to approve the ANDAs implicated by such a petition. Indeed, FDA routinely renders such decisions either simultaneously with, or within a few days or weeks before, an ANDA approval. *See, e.g*, Docket Nos. FDA-2005-P-0003, FDA-2006-P-0019, FDA-2006-P-0331, & FDA-2006-P-0391 (Sept. 15, 2009) (determining that Zosyn® was not discontinued for safety or effectiveness reasons and approving an ANDA the same day); Docket Nos. FDA-2011-P-0339 & FDA-2012-P-0507 (Nov. 7, 2012) (determining that Acetadote® was not discontinued for safety or effectiveness reasons and approving an ANDA the same day); Docket Nos.

FDA-2009-P-0089 & FDA-2011-P-0482 (May 22, 2015) (determining that Vagifem® was not withdrawn for safety and effectiveness reasons and approving an ANDA seven days later).

FACTUAL BACKGROUND

A. Original Nymalize® (nimodipine) Oral Solution, 3mg/mL

21. On May 10, 2013, FDA approved Arbor's NDA No. 203340 for Nymalize® (nimodipine) Oral Solution, 3mg/mL, a "dihydropyridine calcium channel blocker indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V)." NDA 203340—Full Prescribing Information (the "Original Package Insert," attached as Ex. E) at 2 (May 2013 ed.). As approved, Original Nymalize® was supplied (alternatively) in 16-ounce bottles and 20 mL unit dose cups, with a recommended dose of either 20 mL (containing 60 mg of nimodipine) every four hours or 10 mL (containing 30 mg of nimodipine) for patients with cirrhosis (for whose benefit Arbor subsequently secured approval to market Original Nymalize® with 10 mL unit dose cups). *Id*. at 1. Because this product is intended for use by neurologically impaired patients in hospital settings, those alternative configurations allowed the product to be

administered either orally *via* unit dose cups (for patients who were able to swallow the solution) or by administering the product through a nasogastric or gastric tube using an oral syringe (*e.g.*, for patients with severe neurological damage who may have difficulty swallowing or are unable to do so).

B. Reformulated Nymalize® (nimodipine) Oral Solution, 6 mg/mL (NDA 203340/S-11)

22. To mitigate some of the challenges and adverse effects associated with Original Nymalize® (3 mg/mL), reduce its impurities, and extend the product's shelf-life, Arbor eventually reformulated Nymalize® and submitted supplemental NDA ("sNDA") 203340/S-11 for a significantly modified version of the product on April 5, 2019. Like Original Nymalize®, Arbor's proposed reformulation (for ease of reference, "Reformulated Nymalize®") was designed to provide patients with the same 60 mg dose of nimodipine as Original Nymalize®, but in a reduced volume of just 10 mL of solution—thereby doubling the product's concentration to 6 mg/mL from 3 mg/mL—contained within a unit dose prefilled syringe that simplifies the administration of the product for both neurologically impaired patients and their healthcare providers. NDA 203340/S-11—Full Prescribing Information (the "New Package Insert," attached as Ex. F) at 2 (Apr. 2020 ed.).

23. It would be hard to overstate the significance of the change in concentration between Original Nymalize® and Reformulated Nymalize®. Because nimodipine is known to cause hypotension—a potentially life-threatening decrease in blood pressure—the Original Package Insert included special warnings and precautions directing that patients' "[b]lood pressure should be carefully monitored during treatment with NYMALIZE," that the recommended dosage should be lowered for certain patients, and that the concomitant use of certain drugs with nimodipine "should generally be avoided because of a risk of significant hypotension." Ex. E at 2-3. But because Reformulated Nymalize® doubled the product's original concentration (again, to 6 mg/mL from 3 mg/mL), administering the same 20 mL volume of Reformulated Nymalize® that healthcare providers were accustomed to providing with Original Nymalize® would significantly increase the risk of severe hypotension: Patients would receive a double-dose of nimodipine (120 mg instead of 60 mg) with potentially fatal consequences. Accordingly, the New Package Insert for Reformulated Nymalize® required critically important modifications to its Dosing and Administration instructions that were intended to prevent these potentially catastrophic results. *Compare, e.g.*, Ex. E at 2 ("The recommended oral dosage is ***20 mL*** (60 mg) every 4 hours for 21 consecutive days")

with Ex. F at 2 ("The recommended oral dosage is ***10 mL*** (60 mg) every 4 hours for 21 consecutive days") (emphasis added).

24. At the same time, however, Reformulated Nymalize® offered significant advantages over the Original Nymalize® formulation. Because this product is intended to treat patients suffering from neurological damage associated with a brain aneurysm, reducing the product's volume and providing it in prefilled syringes significantly eased the administration of the product to its intended patient population. In addition, Arbor's Reformulated Nymalize® either removed or reduced several excipients used in the Original Nymalize® formulation—including a nearly 50% per dose reduction of Polyethylene Glycol 400, a commonly used excipient in pharmaceutical preparations that has unfortunate laxative properties—and therefore offered the potential to reduce the frequency and/or severity of diarrhea and other gastrointestinal side effects associated with this drug. Finally, Arbor's formulation changes extended the product's shelf-life and allowed for an easing of the tightly controlled storage conditions previously required to maintain Original Nymalize®. *Compare* Ex. E at 9 ("Store at 25°C (77°F)") *with* Ex. F at 9 ("Store between at 20°C to 25°C (68°F to 77°F)").

25. Following the Agency's initial review of Arbor's Reformulated Nymalize® sNDA, FDA informed Arbor that it had identified serious safety risks—

including the previously described risk of potentially fatal overdosing errors—that could be caused by introducing higher-concentration Reformulated Nymalize® at the same time Original Nymalize® remained on the market. It therefore directed the Company to conduct a comprehensive risk analysis and develop an appropriate risk mitigation strategy:

> We have determined that the introduction of your proposed concentration (6 mg/mL) into the marketplace would increase the potential for dosing errors with nimodipine oral solution. We recommend you conduct a proactive risk analysis to characterize the risks of confusion and dosing errors between the currently marketed nimodipine oral solution concentration (3 mg/mL) and your proposed concentration (6 mg/mL). Please propose risk-mitigation strategies and explain how you plan to validate that your proposed strategies will address the identified risks and mitigate the potential for errors.

NDA 203340/S-11—Information Request (the "Safety IR") at 2 (May 3, 2019).

26. In accordance with FDA's instructions, Arbor assembled a multidisciplinary team of experts in drug safety, medical practice, regulatory affairs, manufacturing operations, and the drug supply chain to: identify potential risk vectors associated with the proposed formulation change; conduct a comprehensive use-related risk analysis ("URRA") based on a Failure Modes and Effects Analysis ("FMEA") model; and recommend potential remedies for any identified issues. After a comprehensive review, Arbor's team of experts determined that the most likely sources of medication error would be associated with the pre-administration

preparation and administration of Nymalize® by pharmacists/pharmacy technicians and nurses (as opposed to the prescribing behavior of physicians) and therefore evaluated an array of potential solutions to mitigate the risks associated with potential preparation/administration errors in response to the introduction of Reformulated Nymalize®.

27. In particular, and as memorialized in Arbor's comprehensive response to the Safety IR on June 13, 2019, the Company's expert panel recommended that Arbor take five steps in order to mitigate the risk of potentially fatal medication errors, including: discontinuing the marketing of Original Nymalize® "due to the level of risk for potential dosing errors"; initiating a costly "multi-channel education program/communication process … to prepare relevant hospital health care providers and staff about the formulation and packaging change" including "emails, mail, distributor phone calls and sales representative calls that notify about the change in formulation and packaging and prompt current users to update their formularies and ordering systems"; communicating with "the Institute for Safe Medication Practices (ISMP) to notify of the upcoming formulation change after approval of the supplement and prior to product availability so they have the opportunity to communicate the change in formulation through their network of hospital health care providers"; and preparing and distributing special "instruction

cards [to] be placed in the new formulation shipment boxes." NDA 203340/S-11—Response to Information Request (the "Safety IR Response"), at 16-17 (June 13, 2019).

28. On August 2, 2019, FDA responded to Arbor's Reformulated Nymalize® sNDA by issuing a Complete Response Letter ("CRL") informing the Company that FDA had "determined that we cannot approve this application in its present form." NDA 203340/S-11—CRL at 1 (Aug. 1, 2019). As relevant here, the Agency's CRL expressly rejected the adequacy of Arbor's proposed safety program—despite recognizing that the Company's proposed discontinuation of Original Nymalize® and accompanying communication and labeling plan "appear[ed] reasonable"—and directed the Company to consider whether still-further steps were required to reduce the obvious safety risks associated with simultaneously marketing two different product concentrations of Nymalize®:

> While your risk mitigation plan appears reasonable, we note that your use-related risk analysis (URRA) does not evaluate the risks of potential prescribing errors because you determined that "the ordering by the physicians will not change because the electronic ordering systems have options by strength... and will not stipulate product volumes or concentrations." ***However, we do not agree and we are concerned that the introduction of the proposed new concentration is vulnerable to prescribing errors. Not all hospitals utilize Computerized Provider Order Entry (CPOE) systems. Furthermore, CPOE systems are not standardized and may vary widely between hospitals (e.g., some CPOE systems may allow prescribers to order by***

> ***volume (mL) instead of strength).*** Thus, we recommend you consider the risks of potential errors occurring during the prescribing phase of the medication use process. Please update your URRA to evaluate the potential risks, and revise your mitigation plan, as needed, to address risks of prescribing errors.

Id. at 2-3 (emphasis added; footnote omitted). Finally, FDA recommended that Arbor (1) distribute a "Dear Healthcare Provider" (or "DHCP") letter informing healthcare providers of the transition to Arbor's double-concentrated Reformulated Nymalize® product, and (2) marking the new product's outer packaging with the words "New Concentration" for six months. *Id*. at 3.

29. After FDA informed Arbor of its determination that the Company's Reformulated Nymalize® sNDA could not be approved because its proposed risk-mitigation plan was not sufficient to remediate the identified safety risks, Arbor's multidisciplinary team of experts returned to the drawing board and revised the Company's original proposal to better address the Agency's remaining concerns regarding prescriber-level errors. That process culminated in the submission of a revised risk-mitigation plan on December 13, 2019, which continued to propose the withdrawal of Original Nymalize® and supplemented Arbor's previously proposed risk-management plan by committing the Company to disseminating a DHCP letter and augmenting Reformulated Nymalize®'s proposed product labeling to

prominently note that the product was for a "New Concentration." NDA 203340/S-11—Post-CRL Quality Information Amendment at 17, 19 (Dec. 13, 2019).

30. On April 8, 2020, FDA completed its review of Arbor's amended sNDA and approved Reformulated Nymalize®. NDA 203340/S-11—Approval Letter (Apr. 8, 2020, attached as Ex. G). The Agency's previously released and publicly available review documents in turn reflect that FDA expressly approved the Company's risk mitigation strategies, including Arbor's proposal that "[t]he current concentration (3 mg/mL) will no longer be marketed," and concluded: "Considering the totality of Arbor's risk mitigation strategies, we find the residual risk to be mitigated to an acceptable level." NDA 203340/S-11—Label and Labeling Review (attached as Ex. H), at 3 (Mar. 11, 2020).

C. Post-Approval Regulatory Proceedings

31. On or about June 6, 2020, the Indian generic drug manufacturer Annora Pharma Private Limited ("Annora") submitted a Citizen Petition asking FDA to determine that Original Nymalize® had not been withdrawn from sale for safety or effectiveness reasons "in order to enable action on an ANDA referring to [Original Nymalize®] as the Reference Listed Drug." Ex. C at 3. As its sole basis for claiming that Original Nymalize® had not been withdrawn for safety and effectiveness reasons, the Annora Citizen Petition asserted only that "[t]here are no published state

or federal court decisions relating to product liability arising out of the use of the NYMALIZE (nimodipine) oral solution 3 mg/ mL (NDA# 203340)" and claimed Arbor "withdrew NYMALIZE (nimodipine) oral solution 3 mg/ mL for voluntary reasons unrelated to the product's safety or effectiveness." *Id*. at 2-3.

32. On or about June 10, 2020, the law firm of Windels Marx Lane & Mittendorf, LLP—which frequently represents ANDA applicants in patent litigation arising under the Hatch-Waxman Act—submitted its own Citizen Petition "on behalf of a client" that likewise asked FDA to determine that Arbor had not withdrawn Original Nymalize® for safety or effectiveness reasons. Ex. D at 2. Despite expressly referencing the publicly available Reformulated Nymalize® review and approval documents reflecting that Original Nymalize® had been discontinued as part of a risk-mitigation plan that specifically was designed to reduce the risk of potentially fatal dosing errors, *id*. at 2 & n.1; *but see supra* ¶ 30 (discussing FDA's publicly available Label and Labeling Review), the Windels Marx Citizen Petition asserted that it "is not aware of any information indicating that the withdrawal was made for safety or effectiveness reasons and believes the discontinuation of Nymalize® (Nimodipine) Oral Solution, 3 mg/mL strength under NDA 203340 was only due to commercial considerations." Ex. D at 2.

33. On June 29, 2020, Arbor's outside counsel responded to the Annora and Windels Marx Citizen Petitions by explaining that "Arbor, with FDA's approval and encouragement, adopted a Risk Mitigation Plan anchored on the discontinuation of the old formulation to reduce the risk of dosing and prescribing errors" and that "FDA required Arbor to develop and validate the detailed risk mitigation strategy precisely because of FDA's concerns about the risks of prescribing and dosing errors." Ex. I at 4. Arbor's comments therefore asked "that FDA determine that the old NYMALIZE formulation was discontinued for safety reasons due to concerns about marketplace confusion leading to potential errors in dosing." *Id*.

34. On February 17, 2021, FDA responded to the Annora and Windels Marx Citizen Petitions by publishing a *Federal Register* notice, uploading parallel decisions to the underlying Citizen Petition dockets, and informing the public that "FDA has determined under [21 C.F.R.] § 314.161 that NYMALIZE (nimodipine), oral solution, 3 mg/mL, was ***not*** withdrawn for reasons of safety or effectiveness." 86 Fed. Reg. at 9944 (emphasis added); *see also* Exs. A & B. Without acknowledging that FDA itself had (1) identified the risk of potentially fatal medication errors that could result from the continued marketing of Original Nymalize®; (2) directed Arbor to develop a risk mitigation plan for the purpose of addressing that serious safety risk; (3) initially rejected the sufficiency of Arbor's

plan to discontinue the marketing of Original Nymalize®; and (4) ultimately and expressly approved the proposed discontinuation of Original Nymalize® as a condition of approving Arbor's sNDA for Reformulated Nymalize®, the Agency's *Federal Register* notice asserted that while Arbor's discontinuation had been "one" appropriate "way to reduce the risk of confusion between the two strengths," it supposedly had not been "necessary to discontinue marketing [Original Nymalize®]" because "there are other (often-used) mitigation strategies that may be employed to reduce the risk of confusion among multiple marketed strengths of a drug that could have been used by Arbor." 86 Fed. Reg. at 9945. The Agency therefore concluded that "ANDAs that refer to [Original Nymalize®] may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs." *Id.*

35. As set forth above, FDA typically defers taking final agency action on a Citizen Petition seeking a determination of whether an RLD product was withdrawn for safety or efficacy reasons until shortly before it is prepared to approve one or more ANDA products referencing that RLD. *Supra* ¶ 20 (collecting examples). Consistent with that longstanding practice, and on information and belief, Arbor fully expects FDA to imminently approve one or more ANDAs referencing the Company's discontinued Original Nymalize® NDA.

36. This Complaint follows.

CLAIMS FOR RELIEF

COUNT ONE: UNLAWFUL DETERMINATION THAT ORIGINAL NYMALIZE® WAS NOT WITHDRAWN FOR REASONS OF SAFETY OR EFFECTIVENESS (5 U.S.C. § 706(2))

37. The foregoing paragraphs 1 through 36 are incorporated by reference as though fully set forth herein.

38. The APA prohibits FDA from taking any action that is "not in accordance with law," 5 U.S.C. § 706(2)(A), or that is "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." *Id*. § 706(2)(C). FDA's final determination that Original Nymalize® was not withdrawn from sale for safety reasons and, thus, that ANDAs referencing Original Nymalize® can be received, reviewed, and approved by the Agency, flunks both tests.

39. Although the FDCA makes clear that an NDA sponsor's voluntary withdrawal of a previously marketed NDA does not necessarily preclude FDA from reviewing and approving an ANDA referencing that product, the statute strictly prohibits FDA from approving an ANDA whenever "the listed drug has been withdrawn from sale for safety or effectiveness reasons." 21 U.S.C. § 355(j)(4)(I). Accordingly, FDA cannot lawfully accept or approve ANDAs whose RLD has been

withdrawn from sale ***unless*** the RLD's withdrawal was ***not*** "for safety and effectiveness reasons." *Id*.

40. As set forth above, the record in this case makes clear that Arbor withdrew Original Nymalize® "from sale for safety and effectiveness reasons." *Id*. Indeed, the record leaves no doubt that Arbor made an objectively reasonable decision to discontinue sales of Original Nymalize®—***a discontinuation that FDA itself reviewed and expressly approved***—precisely to address the unmistakably serious safety risks that FDA itself determined were likely to result from continuing to market Original Nymalize® after Arbor introduced its double-concentrated Reformulated Nymalize® product.

41. Despite conceding that Arbor's discontinuation of Original Nymalize® was in fact an appropriate "way to reduce the risk of confusion between the two strengths" of Nymalize®, FDA's ***only*** rationale for determining that Original Nymalize® "was not withdrawn for safety or effectiveness reasons" is its claim that discontinuation was not "***necessary*** … to mitigate potential confusion between the 3 mg/mL and 6 mg/mL strengths." 86 Fed. Reg. at 9945 (emphasis added).

42. That assertion is impossible to square with the plain text and structure of the statute. In contrast to scores of other provisions in the FDCA, the subsection at issue here pointedly does ***not*** require product withdrawal to have been a

"necessary" or "essential" remedy for the genuine safety risks FDA repeatedly attributed to the simultaneous marketing of multiple Nymalize® concentrations. *Cf.* 21 U.S.C. § 355(j)(3)(C)(ii) (barring bioavailability study changes unless "a substantial scientific issue ***essential to determining the safety or effectiveness of the drug*** has been identified after the testing has begun."); *id.* §§ 355(c)(3)(E)(iii), (c)(3)(E)(iv) (awarding exclusivity where a sponsor conducts "new clinical investigations … ***essential to the approval of the application***"); *id.* §§ 355(j)(5)(F)(iii), (j)(5)(F)(iv) (same).

43. Instead, the statutory subsection at issue here asks only whether the withdrawal was "***for*** safety or effectiveness reasons." *Id.* § 355(j)(4)(I) (emphasis added). The word "necessary" does not appear in this subsection, and it is not remotely synonymous with "for." *Compare* "Necessary," *Merriam-Webster Dictionary*, at https://www.merriam-webster.com/dictionary/necessary (last visited Feb. 24, 2021) (defining "necessary" as "absolutely needed" or "unavoidable") *with* "For," *id.*, at https://www.merriam-webster.com/dictionary/for (last visited Feb. 24, 2021) (explaining that the common and ordinary usage of "for" is instead "a function word to indicate purpose," "an intended goal," or "the object or recipient of a perception, desire, or activity").

44. Consistent with the ordinary usage and plain meaning of the words Congress actually used in the operative statutory subsection, the record leaves no doubt that Arbor's withdrawal of Original Nymalize® was designed, at FDA's urging, precisely ***for*** the purpose of mitigating the serious safety concerns FDA had identified—namely that the simultaneous marketplace presence of Original and Reformulated Nymalize® would have created risks of both ***overdosing*** patients (which could lead to life-threatening hypotension) and ***underdosing*** patients (which could reduce the effectiveness of this critically important medication). *See, e.g.*, Ex. H at 3 ("[T]he risk associated with potential prescribing errors is wrong dose, which could result in hypotension (overdose) or therapeutic failure (underdose).").

45. The record also confirms that withdrawing Original Nymalize® was an objectively reasonable means of remediating the FDA-identified safety risks. Indeed, the challenged FDA decision itself admits that product withdrawal was an effective means "to reduce the risk of confusion between the two strengths" and formulations of Nymalize®, 86 Fed. Reg. at 9945, and the underlying record shows that FDA repeatedly reviewed and explicitly approved Arbor's proposal to discontinue marketing of Original Nymalize® as an essential and express condition of approving Arbor's sNDA for Reformulated Nymalize®. Compl. Ex H at 3

("Considering the totality of Arbor's risk mitigation strategies, we find the residual risk to be mitigated to an acceptable level.").

46. Finally, FDA's revisionist assertion that the discontinuation of Original Nymalize® somehow was not "necessary" to remediate the serious safety issues FDA identified is belied by the record. As previously explained, Arbor's originally proposed risk-mitigation plan consisted of five steps (including the proposed discontinuation of Original Nymalize®), but FDA rejected that proposal as insufficient to remediate the serious risks FDA had identified. *Supra* ¶¶ 27-28 (describing Arbor's initial five-step proposal and FDA's rejection of that proposal as "reasonable" but ultimately insufficient). Yet the only additional changes FDA ultimately required Arbor to implement beyond withdrawing the Original Nymalize® formulation were (1) the issuance of a DHCP letter supplementing the extensive communications Arbor already planned to provide (which, again, already included "emails, mail, distributor phone calls and sales representative calls that notify about the change in formulation and packaging and prompt current users to update their formularies and ordering systems" and a formal notification to the Institute for Safe Medication Practices for dissemination to hospital healthcare providers) and (2) the addition of the words "New Concentration" on the outer packaging of Reformulated Nymalize® for six months. *Supra* ¶ 28.

47. Without belaboring the point, it beggars belief to think (and FDA's final decision does not offer a shred of evidence to support the proposition) that these modest supplemental risk-mitigation measures would have justified jettisoning Arbor's proposed withdrawal of the Original Nymalize® formulation—that is, that FDA would have approved a risk-mitigation plan that did ***not*** include the discontinuation of Original Nymalize® ***if only*** Arbor had proposed to supplement its already-extensive direct communication plan with a DHCP letter and "New Concentration" overstamp on the Reformulated Nymalize® packaging for six months. In short, the record makes clear that withdrawing Original Nymalize® from sale was in fact "necessary" to address the serious safety issues FDA had addressed; that FDA's results-oriented, Monday morning quarterbacking is utterly irreconcilable with the actual record of its decision-making on this issue; and that Arbor is entitled to judgment even under FDA's textually unsustainable interpretation of the relevant statutory language.

48. For the foregoing reasons, FDA's final decision in this matter is both "not in accordance with the law," 5 U.S.C. § 706(2)(A), and "in excess of statutory … authority, or limitations, or short of statutory right." *Id*. § 706(2)(C).

COUNT TWO: ARBITRARY AND CAPRICIOUS AGENCY ACTION (5 U.S.C. § 706(2))

49. The foregoing paragraphs 1 through 48 are incorporated by reference as though fully set forth herein.

50. The APA prohibits FDA from taking any action that is "arbitrary, capricious, [or] an abuse of discretion," 5 U.S.C. § 706(2)(A), and that proscription in turn "requires an agency to treat like cases alike," *Westar Energy, Inc. v. FERC*, 473 F.3d 1239, 1241 (D.C. Cir. 2007), and "mandate[s] that an agency take whatever steps it needs to provide an explanation that will enable the court to evaluate the agency's rationale at the time of decision." *Pension Benefit Guaranty Corp. v. LTV Corp.*, 496 U.S. 633, 654 (1990); *see also Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) ("[T]he agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'") (quoting *Burlington Truck Lines, Inc. v. United States*, 371 U.S. 156, 168 (1962)).

51. FDA's decision in this case utterly fails to comply with that standard. As Arbor explained in the underlying administrative proceedings, *see* Ex. I at 5-6, FDA repeatedly has determined that similarly situated products—that is, drugs in varying strengths/concentrations whose simultaneous presence on the market was

associated with a risk of potentially serious medication errors—were withdrawn from the market for safety or effectiveness reasons (and indeed, that labeling changes like DHCP letters and the use of special warning stickers often are not adequate or effective means to remediate those risks). *See, e.g.*, FDA, *Determination That BREVIBLOC (Esmolol Hydrochloride) Injection, 250 Milligrams/Milliliter, 10-Milliliter Ampule, Was Withdrawn From Sale for Reasons of Safety or Effectiveness*, 75 Fed. Reg. 24,710, 24,711 (May 5, 2010, attached as Ex. J); *see also* Docket Nos. FDA-2005-P-0082 and FDA-2014-P-0142—Final Decision, at 7 (Nov. 28, 2016, attached as Ex. K) (concluding that the original formulation of Protonix I.V. was withdrawn for safety or effectiveness reasons because even "prominent statements on the Protonix I.V. labeling noting that the in-line filter supplied with the drug product must be used to remove the particulates that may form when the reconstituted drug product is mixed with intravenous solutions" were not sufficient to eliminate dosing errors).

52. Despite acknowledging these precedents, FDA's final decision here asserted only that this case "is factually distinguishable from BREVIBLOC and PROTONIX I.V." 86 Fed. Reg. at 9945. That is both incorrect and insufficient; these cases are materially indistinguishable, and FDA's bald assertion to the contrary fails in any event to discharge the Agency's most basic obligation under the APA—

to "provide an explanation that will enable the court to evaluate the agency's rationale," *Pension Benefit Guaranty Corp.*, 496 U.S. at 654, and "articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *State Farm*, 463 U.S. at 43.

53. Because FDA failed to treat these materially indistinguishable matters alike, and otherwise failed even to attempt to provide any adequate rationale for its contrary assertion, its decision is "arbitrary, capricious, [or] an abuse of discretion" and must be set aside.

REQUESTS FOR RELIEF

WHEREFORE, Arbor respectfully requests that this Court enter final judgment in its favor and:

A. **DECLARE** that FDA's final decision that Arbor's NDA for Original Nymalize® was not withdrawn from sale for safety or effectiveness reasons is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and in excess of statutory limitations;

B. **HOLD UNLAWFUL AND SET ASIDE** FDA's determination that Arbor's NDA for Original Nymalize® was not withdrawn from sale for safety or effectiveness reasons;

C. **ENJOIN** FDA from receiving, reviewing, or approving any ANDA that references as its RLD Arbor's NDA for Original Nymalize®;

D. **AWARD** Arbor its costs and attorneys' fees; and

E. **AWARD** Arbor such other relief as the Court may deem just and proper.

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Respectfully submitted,

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