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BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Citizen Petition

The undersigned ("Petitioner") submits this Citizen Petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. §§ 10.25(a) and 10.30 with regard to the Food and Drug Administration ("FDA")-designated Reference Listed Drugs ("RLDs") for Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial. The current RLDs, VIBRAMYCIN (doxycycline hyclate) for Injection, 100 mg Base/Vial and 200 mg Base/Vial, approved under New Drug Application ("NDA") 050442,[1] are preventing additional generic drug competition under Abbreviated New Drug Applications ("ANDAs"). For this reason, Petitioner requests that FDA take action to maintain a pathway for ANDA submissions. Specifically, Petitioner requests that FDA designate additional (or new) RLDs for Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, and amend the Orange Book to reflect ANDA 062475—both "DOXY 100" and "DOXY 200," which are Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, respectively—approved on December 9, 1983, prior to the September 1984 enactment of the Hatch-Waxman Amendments, as RLDs for the drug products.

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[1] Both VIBRAMYCIN (doxycycline hyclate) for Injection, 100 mg Base/Vial and 200 mg Base/Vial, approved under NDA 050442 are listed in the "Discontinued Drug Product List" section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"). In 2016, FDA determined that neither drug product was withdrawn from the market for safety or effectiveness reasons. See FDA, Notice, Determination That BENEMID (Probenecid) Tablet and Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 81 Fed. Reg. 81,780, 81,781 (Nov. 18, 2016). In 2018, FDA withdrew approval for both drug products. See FDA, Notice, Concordia Pharmaceuticals, Inc., et al.; Withdrawal of Approval of 29 New Drug Applications, 83 Fed. Reg. 32,305 (July 12, 2018).

I. ACTION REQUESTED

Petitioner requests that FDA designate both Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, approved under ANDA 062475 as RLDs[2] for purposes of FDA evaluation of ANDAs for Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, containing mannitol as an excipient. Petitioner further requests that, based on the prior status of ANDA 062475 as an RLD, FDA expedite a response to this petition so that an ANDA can be submitted to FDA.

II. STATEMENT OF GROUNDS

FDC Act § 505(j) allows the marketing of generic versions of previously approved drug products. To obtain ANDA approval, the applicant must show, among other things, that with respect to a listed drug (i.e., a previously approved drug product), the generic drug product has the same active ingredient(s) in the same strength, dosage form and route of administration, has essentially identical labeling, and is bioequivalent.

A "listed drug" includes a new drug product that has an effective approval under FDC Act § 505(j), that has not been withdrawn or suspended under FDC Act §§ 505(e)(1) through (5) or (j)(5), and that has not been withdrawn from sale for reasons of safety or effectiveness. See 21 C.F.R. § 314.3. Listed drugs are identified in FDA's Orange Book. An RLD is the listed drug identified by FDA—either as "RLD" in the electronic Orange Book, or with a "+" in the paper version of the publication—as the drug product on which an ANDA applicant should rely in seeking approval of an application. The product designated by FDA as the "Reference Standard" in the Orange Book—either as "RS" in the electronic Orange Book, or with a "!" in the paper version of the publication—must be used to conduct the in vivo bioequivalence testing required for FDA approval. "If FDA has designated a listed drug as an RLD, but the potential applicant intends to refer to a different listed drug that is a pharmaceutical equivalent to the drug designated as an RLD, the potential applicant may submit a citizen petition under 21 CFR 10.25(a) and 10.30 to request that FDA designate that different listed drug as an additional RLD." FDA, *Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions,* at 5 (Jan. 2017).[3]

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[2] Petitioner acknowledges that FDA does not typically assign RLD status to an ANDA. In this case, however, ANDA 062475, approved prior to the Hatch-Waxman Amendments, previously served as a RLD for ANDA submission and approval purposes.

[3] FDA also notes the following in the draft guidance:

> The principles in this draft guidance focus on the appropriate identification of products referred to in ANDAs for generic drugs that are intended to duplicate

(continued . . .)

As discussed in detail below, there is a sound basis for selecting ANDA 062475 as a new (or additional) RLD.

The Orange Book ("Prescription Drug Product List" section) currently identifies both Product Nos. 001 and 002 approved under ANDA 062475 as RSs for Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, and both Product Nos. 001 and 002 (in the "Discontinued Drug Product List" section) approved under NDA 050442 as RLDs for Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial. These listings appear as follows:

Prescription Drug Product List[4]

DOXYCYCLINE HYCLATE						
CAPSULE;ORAL						
VIBRAMYCIN						
AB	+!	PFIZER	EQ 100MG BASE	N050007	002	
INJECTABLE;INJECTION						
DOXY 100						
AP	!	FRESENIUS KABI USA	EQ 100MG BASE/VIAL	A062475	001	Dec 09, 1983
DOXY 200						
AP	!	FRESENIUS KABI USA	EQ 200MG BASE/VIAL	A062475	002	Dec 09, 1983
DOXYCYCLINE						
AP		MYLAN LABS LTD	EQ 100MG BASE/VIAL	A091406	001	Aug 21, 2012
AP	!	WEST-WARD PHARMS INT	EQ 100MG BASE/VIAL	A062569	001	Mar 09, 1988
AP		ZYDUS PHARMS	EQ 100MG BASE/VIAL	A207757	001	Sep 28, 2017
AP			EQ 200MG BASE/VIAL	A207757	002	Sep 28, 2017

(continued . . .)

listed drugs approved after enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub.L. 98-417), commonly referred to as the Hatch-Waxman Amendments. If an applicant is seeking approval of an ANDA that is intended to duplicate a listed drug approved prior to enactment of the Hatch-Waxman Amendments, the applicant may consult the Agency if it has questions regarding appropriate identification of products.

FDA, *Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions*, at 4, n. 19 (Jan. 2017).

[4] Orange Book, Prescription Drug Product List, at 3-151 (Mar. 20, 2020 Ed.).

Discontinued Drug Product List[5]

DOXYCYCLINE HYCLATE

INJECTABLE;INJECTION				
DOXYCHEL HYCLATE				
RACHELLE	EQ 100MG BASE/VIAL		A061953 001	
DOXYCYCLINE				
WEST-WARD PHARMS INT	EQ 100MG BASE/VIAL		A062450 001	Oct 27, 1983
	EQ 200MG BASE/VIAL		A062450 002	Oct 27, 1983
	EQ 200MG BASE/VIAL		A062569 002	Mar 09, 1988
DOXYCYCLINE HYCLATE				
WEST-WARD PHARMS INT	EQ 100MG BASE/VIAL		A062992 001	Feb 16, 1989
	EQ 200MG BASE/VIAL		A062992 002	Feb 16, 1989
VIBRAMYCIN				
+ PFIZER	EQ 100MG BASE/VIAL **		N050442 002	
+	EQ 200MG BASE/VIAL **		N050442 001	

Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, was approved under ANDA 062475 on December 9, 1983, prior to the enactment of the Hatch-Waxman Amendments, and thus prior to FDA's contemporary ANDA regulations that prohibit the submission and approval of an ANDA for a parenteral drug product that differs from the brand-name NDA formulation other than in preservative, buffer or antioxidant. See 21 C.F.R. § 314.94(a)(9)(iii) and § 314.127(a)(8)(ii)(B).[6] The drug products approved under ANDA 062475 differ in formulation vis-à-vis VIBRAMYCIN Injection (NDA 050442). Specifically, the drug products approved under ANDA 062475 contain mannitol (300 mg), which functions as a bulking agent—a non-exception excipient use in a parenteral drug product—in the drug product formulation, whereas VIBRAMYCIN Injection (NDA 050442) does not contain mannitol. Doxycycline for Injection is supplied as a sterile powder in a cake. Without mannitol in the drug product formulation, the cake easily crumbles, making reconstitution difficult and raising questions about drug product quality.

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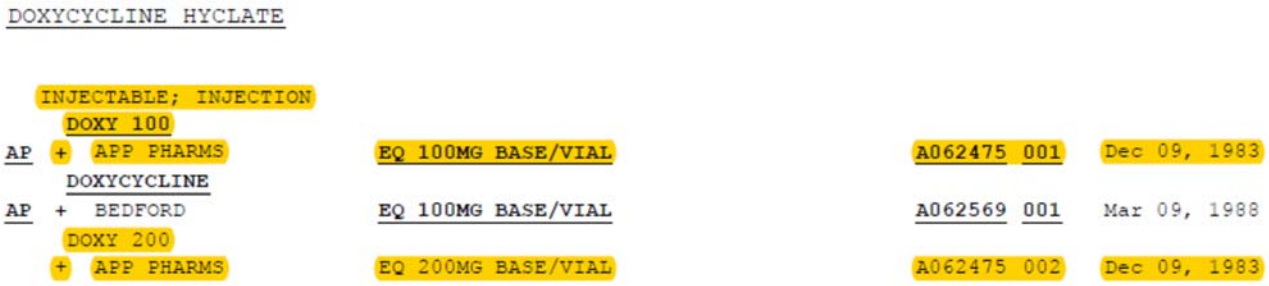
5 Orange Book, Discontinued Drug Product List, at 6-151 (Mar. 20, 2020 Ed.).

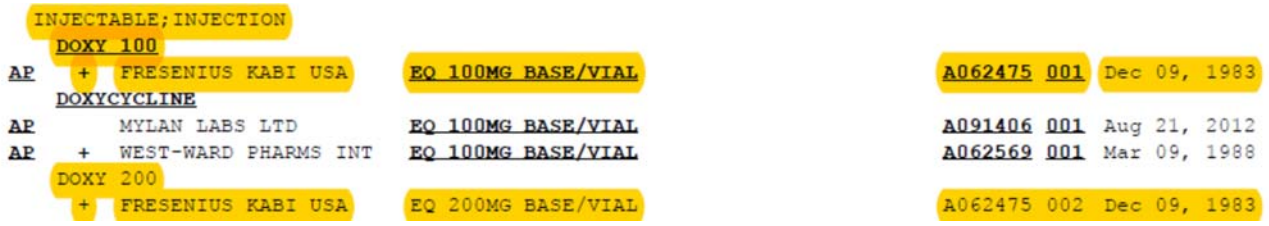
6 Instead, FDA requires the submission of a 505(b)(2) NDA. See FDA, Guidance for Industry, Determining Whether to Submit an ANDA or a 505(b)(2) Application, at 10 (May 2019) ("An applicant should consider submitting a 505(b)(2) application if the proposed drug product contains changes to its formulation that are not permissible in an ANDA. For example, a proposed parenteral drug product that contains an additional inactive ingredient not present in the RLD that cannot be considered an exception excipient would not be permitted in an ANDA under the regulations at 21 CFR 314.94(a)(9)(iii) but may be submitted in a 505(b)(2) application.").

In the past decade, FDA has approved two ANDAs that mirror the formulation approved under ANDA 062475 containing mannitol (300 mg), a non-exception excipient in Doxycycline Hyclate for Injection: (1) ANDA 091406, approved on August 21, 2012 (Doxycycline Hyclate for Injection, 100 mg Base/Vial); and (2) ANDA 207757, approved on September 28, 2017 (Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial). At the time each of these ANDAs was pending at FDA, the Orange Book reflected both Product Nos. 001 and 002 approved under ANDA 062475 as a RLD. Thus, the 2012 Orange Book[7] showed:



DOXYCYCLINE HYCLATE					
INJECTABLE; INJECTION					
DOXY 100					
AP	+	APP PHARMS	EQ 100MG BASE/VIAL	A062475 001	Dec 09, 1983
DOXYCYCLINE					
AP	+	BEDFORD	EQ 100MG BASE/VIAL	A062569 001	Mar 09, 1988
DOXY 200					
	+	APP PHARMS	EQ 200MG BASE/VIAL	A062475 002	Dec 09, 1983

And the 2017 Orange Book[8] showed:[9]



INJECTABLE;INJECTION					
DOXY 100					
AP	+	FRESENIUS KABI USA	EQ 100MG BASE/VIAL	A062475 001	Dec 09, 1983
DOXYCYCLINE					
AP		MYLAN LABS LTD	EQ 100MG BASE/VIAL	A091406 001	Aug 21, 2012
AP	+	WEST-WARD PHARMS INT	EQ 100MG BASE/VIAL	A062569 001	Mar 09, 1988
DOXY 200					
	+	FRESENIUS KABI USA	EQ 200MG BASE/VIAL	A062475 002	Dec 09, 1983

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7 Orange Book, Prescription Drug Product List, at 3-150 (32nd ed. 2012).

8 Orange Book, Prescription Drug Product List, at 3-134 (37th ed. 2017)

9 Later in 2017, FDA began to differentiate between RLD and RS Orange Book listings. FDA, *Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions*, at 6-7 (Jan. 2017) ("Prior to 2017, the column in the electronic Orange Book labeled 'RLD', and the symbol in the printed version described as identifying the RLD, at times indicated the drug product FDA selected as the reference standard and at other times indicated the RLD, contributing to the confusion about which drug is the RLD and which drug is the reference standard. Starting in 2017, FDA intends to modify the Orange Book to clarify which listed drugs are RLDs and which are reference standards, and to indicate which products in the Discontinued Section may be referred to as an RLD.").

In each case—ANDA 091406 and ANDA 207757—FDA accepted and approved the applications notwithstanding that, when compared to the current RLD, VIBRAMYCIN Injection (NDA 050442), the generic drug product formulations differed in a non-exception excipient that would ordinarily preclude ANDA submission and approval. Thus, in each case, ANDA 062475, containing mannitol (300 mg), served as the RLD.

Without the re-listing of ANDA 062475 as a RLD (in addition to the current RS listing), a generic drug manufacturer submitting an application today for a drug product formulation containing mannitol would be forced to submit a 505(b)(2) NDA citing VIBRAMYCIN Injection (NDA 050442) as the listed drug, and thus be required to pay a substantial application user fee. But such applicant is in the same position as those companies that submitted and obtained approval of ANDA 091406 and ANDA 207757, and should not be treated differently. After all, the Agency would be treating two similarly situated parties in a dissimilar manner, which is a clear violation of the Administrative Procedure Act,[10] particular with respect to FDA-regulated products.[11]

Accordingly, the undersigned requests that FDA designate in the Orange Book Doxycycline Hyclate for Injection, 100 mg Base/Vial and 200 mg Base/Vial, approved under ANDA 062475 as new (or additional) RLDs.

III. ENVIRONMENTAL IMPACT

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. § 25.31.

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[10] See, e.g., Huntington Hosp. v. Thompson, 319 F.3d 74, 75-76 (2d Cir. 2002) citing Independent Petroleum Ass'n of America v. Babbitt, 320 U.S. App. D.C. 107, 92 F.3d 1248, 1260 (D.C. Cir. 1996) ("The treatment of cases A and B, where the two cases are functionally indistinguishable, must be consistent. That is the very meaning of the arbitrary and capricious standard."); see also, Plunkett v. Castro, 67 F. Supp. 3d 1, 21-22 (D.D.C. 2014) citing Etelson v. Office of Pers. Mgmt., 684 F.2d 918, 926, 221 U.S. App. D.C. 396 (D.C. Cir. 1982) ("Government is at its most arbitrary when it treats similarly situated people differently.").

[11] See Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 28 (D.D.C. 1997) (FDA may not "permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason.").

IV. ECONOMIC IMPACT

In accordance with 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. Petitioner hereby commits to promptly provide this information, if so requested.

V. CERTIFICATION

Petitioner certifies that, to the best knowledge and belief of Petitioner, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Sincerely,

Kurt R. Karst

KRK/eam