FDA U.S. FOOD & DRUG ADMINISTRATION

Chad Landmon
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950 F Street NW
Washington, DC 20004

OCT 0 3 2019

Re: Docket No. FDA-2019-P-2240

Dear Mr. Landmon:

This letter responds to your citizen petition submitted on behalf of Zydus Pharmaceuticals (USA) Inc. ("Zydus") and received by the Food and Drug Administration (FDA or the Agency) on May 6, 2019 (Petition). In your Petition, you request that FDA take the following actions:

(1) To establish sameness of the active ingredient in a generic product to that of [the reference listed drug (RLD) Mephyton (phytonadione) Vitamin K1 tablets (new drug application (NDA) 010104)], require that manufacturers of Phytonadione Tablets (a) provide data for each isomer (geometric isomers and stereoisomers) in the phytonadione drug substance by way of identification and quantification through validated tests with appropriate limits demonstrating comparable isomeric purity to the RLD; and (b) control the level of *Z* isomers in the drug substance to be comparable to the RLD; and

(2) Refrain from approving any new [abbreviated new drug application (ANDA)] absent such a showing; and

(3) Downgrade the [therapeutic equivalence (TE) code] of any generic drug product currently listed as "AB" in the [*Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book)] to "BX" unless and until sufficient data has been provided to FDA to demonstrate the comparable isomeric purity of the active ingredient to that of the RLD.[1]

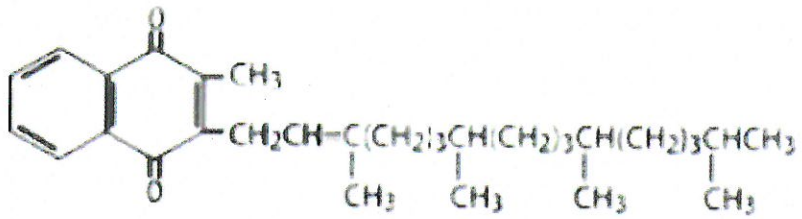
FDA has carefully considered the information submitted in your Petition and appended exhibits, as well as other relevant data identified by FDA. For the reasons explained below, we deny your request that the Agency downgrade the TE code of any generic phytonadione product. We deny the remainder of your Petition without comment on whether we will take the actions you request.

[1] Petition at 1-2.

I. BACKGROUND

A. Mephyton

Mephyton (phytonadione) Vitamin K1 tablets were first approved on September 30, 1955. Mephyton is indicated in certain "coagulation disorders which are due to faulty formation of factors II, VII, IX, and X when caused by vitamin K deficiency or interference with vitamin K activity."[2] The Prescribing Information for Mephyton provides that the empirical formula of phytonadione is $C_{31}H_{46}O_2$, and its structural formula is:



The phytonadione molecule has two geometric isomers (*E* and *Z*), with two chiral centers (C7 and C11) that each generate two enantiomers (*R* and *S*). Thus, there are eight diastereomers of phytonadione, four in the *E* configuration and four in the *Z* configuration.

Currently, there are two approved ANDAs citing Mephyton as the RLD. ANDA 209373 was approved on May 11, 2018. ANDA 210189 was approved on February 20, 2019, and is held by Zydus.

B. Statutory and Regulatory Background

1. Overview of ANDA Approval Process

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the FD&C Act to, among other things, add section 505(j), which established an abbreviated approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the proposed generic drug product.[3] Instead, an ANDA applicant relies on the Agency's previous finding that the RLD[4] is safe and effective.

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[2] Mephyton Prescribing Information (Nov. 2016), available at https://www.accessdata.fda.gov/spl/data/5ebc6430-0067-4908-b2ce-44e2bb75f662/5ebc6430-0067-4908-b2ce-44e2bb75f662.xml.

[3] *See generally* section 505(j)(2)(A) of the FD&C Act.

[4] An *RLD* is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3). A *listed drug* is "a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness" Id. RLDs are identified in the Orange Book.

Drug products that meet the approval requirements under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) generally will be considered by FDA to be therapeutically equivalent to the RLD.[5] The Orange Book contains TE codes for approved multisource prescription drug products.[6] According to the preface to the Orange Book, TE codes starting with "A" are assigned to drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products that share the same TE code (for example two products with the code "AB"), and TE codes starting with "B" are generally assigned to drug products that FDA considers not to be therapeutically equivalent to other pharmaceutically equivalent products.[7]

2. Active Ingredient Sameness

Section 505(j)(2)(A)(ii)(I) of the FD&C Act states that, for a single active ingredient drug product, an ANDA must contain information to show that the active ingredient of the generic drug product is the "same" as that of the listed drug. FDA regulations at 21 CFR 314.3(b) provide that:

> *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

FDA has broad discretion with respect to the information FDA may consider in making a finding on the "sameness" of an active ingredient.[8]

C. Section 505(q) of the FD&C Act

Section 505(q) of the FD&C Act (21 U.S.C. 355(q)) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993), which was signed into law on July 9, 2012. Section 505(q) of the FD&C Act, as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that the Agency take any form of action relating to a pending

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[5] FDA regulations at § 314.3(b) provide that "[t]herapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." The Orange Book contains TE evaluations for approved multisource prescription drug products.

[6] The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[7] Orange Book Preface, 39th edition, section 1.7.

[8] See generally *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319-21 (D.C. Cir. 1998); *Sanofi-Aventis U.S. LLC v. FDA*, 842 F Supp. 2d 195, 212-13 (D.D.C. 2012).

application submitted under 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, the Agency must take final Agency action on a petition not later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

The Petition asserts that, "to establish sameness of the active ingredient in a generic product to that of [Mephyton,] the RLD, [FDA must] require that" an ANDA applicant "provide data for each isomer . . . in the phytonadione drug substance" "through validated tests with appropriate limits demonstrating comparable isomeric purity to the RLD" and "control the level of Z isomers in the drug substance to be comparable to the RLD."[9] The Petition requests that FDA "[r]efrain from approving any new ANDA absent such a showing."[10] Further, the Petition asks FDA to downgrade the TE code of any approved ANDA currently listed as AB-rated to the RLD to a BX TE code "unless and until sufficient data has been provided to FDA to demonstrate the comparable isomeric purity of the active ingredient to that of the RLD."[11] These arguments are discussed below.

A. Comparable Isomeric Purity to the RLD

The Petition argues that "to meet the statutory and regulatory requirements for 'sameness,' the active ingredient in the proposed generic product must be identical to the active ingredient contained in the RLD."[12] To establish that a proposed generic version of Mephyton has the same active ingredient as the RLD, the Petition asserts that that "FDA should ensure that applicants demonstrate . . . comparable chirality between the proposed generic and the RLD with respect to *each* of the isomers present in the drug substance," with "[a]t a minimum," "suitably validated testing for the presence of each isomer" and "acceptance criteria based [on] the isomeric purity of the RLD."[13]

The Petition also argues that to satisfy the sameness requirement, "FDA should tighten the control of Z isomers in the drug substance to be comparable to the RLD, rather than simply meeting the USP monograph" and require ANDA applicants to meet that tighter level.[14] The Petition states that the current USP "monograph for phytonadione drug substance sets an upper

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[9] Petition at 1-2.

[10] Id. at 2.

[11] Id.

[12] Id. at 6.

[13] Id.

[14] Id.

limit for the presence of Z isomers as NMT 21.0%."[15] According to the Petition, "there are currently no established standards around each of the phytonadione isomers" that may be present in the drug substance.[16]

The Petition states that "chirality is an important consideration for phytonadione because the [*Z*] analogs lack biological activity, whereas the [*E*] analogs are bioactive."[17] Further, it states that, "[a]lthough limited literature suggests that the prothrombogenic activities of the four stereoisomers of the [*E*] configuration . . . are nearly identical, no human studies confirm this."[18] The Petition also asserts that "the effect of different quantities (ratios) of each of the inactive [*Z*] isomers on the drug's safety or efficacy is not understood." The Petition concludes that "it is critical that the quantity of [each of the eight phytonadione] diastereomers [potentially present] in the drug [is] tightly controlled."[19]

In addition, according to the Petition, in reviewing Zydus's ANDA for phytonadione tablets, FDA "required that the release specification for the phytonadione drug substance include a suitably validated isomeric purity test for each of the isomers with acceptance limits developed from data obtained from RLD samples" and "a tighter acceptance criteria than defined in the USP monograph for the presence of *Z* isomer substance based on the *Z* isomer data from the RLD."[20] The Petition states that "FDA should require all ANDA holders to comply with the same approval standards it applied to Zydus's ANDA."[21] Finally, the Petition requests that FDA refuse to approve any ANDA that does not meet these more stringent standards.[22]

As described in section I.C of this response, section 505(q)(1)(F) of the FD&C Act requires the Agency to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding how FDA should review and make approval decisions on any ANDAs referencing Mephyton.

FDA has made no final determination on whether to approve or not approve any application referencing Mephyton. In the case of ANDAs referencing Mephyton, FDA's consideration of any currently pending or future applications will necessarily be informed by our decisions on the nature of the data and information regarding the approvability of such applications. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the

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[15] Id. at 4.

[16] Id.

[17] Petition at 3.

[18] Id. (citation omitted).

[19] Id. at 4.

[20] Id.

[21] Id. at 6-7.

[22] Id. at 2.

approvability of a specific aspect of an ANDA before taking final action on the approvability of the ANDA as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of ANDAs in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations in 21 CFR part 314 describe certain procedures by which FDA reviews an ANDA and notifies an applicant if it determines that an application is approved[23] or may not be approved,[24] or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies.[25] In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination.[26] Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process if the applicant requests such a hearing.[27] These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that by enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the process established under the FD&C Act and FDA regulations.[28] Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an ANDA when a final decision on the approvability of any such ANDA has not yet been made.[29] Accordingly, we are denying

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[23] See § 314.105.

[24] See section 505(j) of the FD&C Act; § 314.127.

[25] See § 314.110.

[26] See section 505(j)(5)(E) of the FD&C Act; § 314.103.

[27] Id.

[28] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond the descriptions provided in this response) would not be appropriate in this case because, as stated, our review of a given ANDA would inform our decisions regarding the sufficiency of the data and information needed for approval. We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

[29] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending ANDA before we have reached a final decision on whether to approve or not approve the ANDA. See, e.g., § 314.430.

without comment your requests on the requirements for approval for any ANDA referencing Mephyton.

B. TE Code for Currently Approved ANDAs Citing Mephyton as the RLD

The Petition contends that "FDA cannot maintain an A-rating for an approved ANDA where there is uncertainty regarding the sameness in identity of the active ingredients between the RLD and approved generic product."[30] The Petition states that active ingredient sameness must be established to demonstrate pharmaceutical equivalence, and products cannot be therapeutically equivalent unless they are pharmaceutically equivalent.[31] According to the Petition, "in the absence of batch-to-batch controls ensuring isomeric purity to the RLD, marketed products may contain an isomeric mixture that is not comparable to the RLD."[32] The Petition continues, "Zydus believes that this may be the case based on data generated and submitted to FDA by the holder of the Drug Master File for its ANDA, indicating that another marketed product contains certain isomers at levels that far exceed that of the RLD."[33] Consequently, the Petition states that "FDA should downgrade the TE code to 'BX' for any approved ANDA product to Mephyton unless and until it has sufficiently demonstrated comparable isomeric purity to the RLD by the methods described in this petition."[34]

At this time, FDA has not made a decision to change the TE code for any ANDAs referencing Mephyton. The Agency monitors the efficacy and safety of all drug products, including generic products, through the review of adverse event reports, medication error reports, and other available data from published literature and databases. Sources of postmarketing drug information include FDA's Adverse Event Reporting System and Drug Quality Reporting System. FDA intends to continue to consider the information submitted in your Petition and appended exhibits, as well as any other relevant information, and to take appropriate action regarding the TE code of an approved ANDA if and when FDA decides the circumstances warrant it.

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[30] Petition at 7.

[31] Id.

[32] Id.

[33] Id.

[34] Id.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

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