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VIA ELECTRONIC SUBMISSION
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

On behalf of Zydus Pharmaceuticals (USA) Inc. ("Zydus"), we respectfully submit this Citizen Petition pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act (the "FDCA") and 21 C.F.R. §§ 10.20, 10.25, 10.30, and 10.31 to request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application ("ANDA") for Phytonadione Tablets that references the reference listed drug ("RLD") Mephyton® (NDA No. 010104).

Phytonadione Tablets are approved for the treatment of certain coagulation disorders that are due to faulty formation of factors II, VIII, IX, and X when caused by vitamin K deficiency or interference with vitamin K activity. Because the stereochemistry of the drug substance can be impacted by the starting material and manufacturing process and controls, the phytonadione active ingredient of a generic drug product may be comprised of an isomeric mixture that differs from the isomeric mixture of the active ingredient of the RLD. Such differences may impact the bioactivity, and therapeutic equivalence, of the ANDA product. The Food and Drug Administration ("FDA") should ensure that approved and pending generics establish that their active ingredients have comparable isomeric purity to the RLD and that the quantity of *Z* isomers present are comparable to the RLD. Absent such a showing, the ANDA holder has not established that it has the "same" active ingredient as Mephyton pursuant to the FDCA.

As such, FDA should require holders of approved and pending ANDAs to demonstrate comparable isomeric purity to the active ingredient of the RLD by way of identification and quantification of isomers through validated testing with appropriate limits based on data from RLD samples. Otherwise, FDA cannot ensure that the ANDA product is pharmaceutically equivalent or therapeutically equivalent to the RLD. Further, we request that FDA change the current therapeutic equivalence ("TE") code published in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") from "AB" to "BX" for any approved ANDA product for Mephyton that has not demonstrated comparable isomeric purity unless and until sufficient information is provided to FDA from the ANDA holder.

ACTIONS REQUESTED

We respectfully request that FDA take the following actions:

(1) To establish sameness of the active ingredient in a generic product to that of the RLD, 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 ANDA absent such a showing; and

(3) Downgrade the TE code of any generic drug product currently listed as "AB" in 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.

STATEMENT OF GROUNDS

I. FACTUAL BACKGROUND

A. Mephyton and Approved Generics

Phytonadione is 2-methyl-3-phytyl-1,4-naphthoquinone, and is also known as Vitamin K_1 or phylloquinone. Vitamin K_1 has antihemorrhagic and prothrombogenic activity. Naturally-occurring Vitamin K is necessary for the production in the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). Phytonadione is also a drug substance used in the treatment of various coagulation disorders due to faulty formation of factors II, VII, IX, and X when caused by Vitamin K deficiency or interference with Vitamin K activity.

Phytonadione is approved in oral tablet and injectable dosage forms in the United States. Oral phytonadione has similar efficacy and safety to that of intravenously administered phytonadione.[1] The tablet dosage form has been marketed as Mephyton under NDA No. 010104. Phytonadione Tablets are indicated for: anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives; hypoprothrombinemia secondary to antibacterial therapy; hypoprothrombinemia secondary to administration of salicylates; hypoprothrombinemia secondary to obstructive jaundice or biliary fistulas but only if bile salts are administered concurrently, since otherwise the oral vitamin K will not be absorbed.[2]

Phytonadione Tablets are widely utilized by patients, with the tablet dosage form making up around 81% of the prescriptions dispensed for phytonadione and more than 7.5 million tablets dispensed in the last six years. Generic versions of Mephyton are now available, as shown in Table 1:

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[1] A. Lubetsky, M.D., et al., "Comparison of Oral vs Intravenous Phytonadione (Vitamin K1) in Patients With Excessive Anticoagulation: A Prospective Randomized Controlled Study," Arch Intern Med. 163(20), 2469-73 (2003), *available at* https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/216315.

[2] *See* Mephyton Prescribing Information (2004), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/010104s023lbl.pdf.

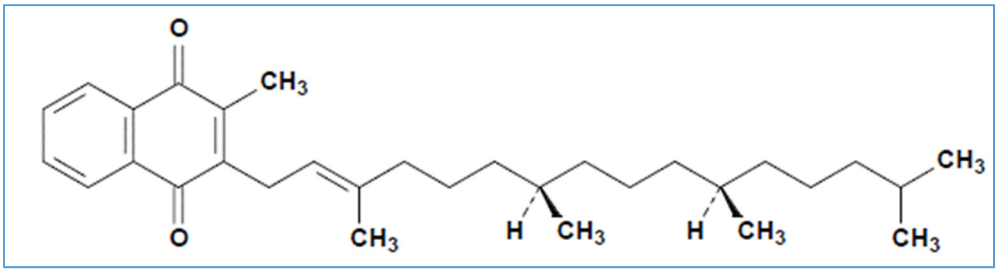
Table 1: Approved Phytonadione Tablets[3]

Drug Name	Strength	RLD	TE Code	Application No.	Company
Mephyton	5MG	Yes	AB	010104	Valeant Pharms
Phytonadione	5MG	No	AB	209373	Amneal Pharms Co
Phytonadione	5MG	No	AB	210189	Zydus

B. Phytonadione Stereochemistry and Bioactivity

Phytonadione is available from natural sources and via synthetic routes. The phytonadione molecule has two geometrical isomers (*cis*-*trans* or (*Z*)-(*E*) isomers, respectively) with two asymmetric carbon atoms (C7 and C11), each generating two enantiomers (*R* or *S*). Accordingly, there are eight diastereomers for phytonadione – four in the *trans* and four in the *cis* configurations. Vitamin K_1, the 2'-*trans*-7*R*, 11*R*-stereoisomer, is depicted in Figure 1.

Figure 1. Chemical Structure of Phytonadione (Vitamin K_1)[4]



The synthesis of phytonadione invariably forms the *cis* analogs. While phytonadione exists in nature mainly as the *trans* configuration (i.e., 2′,3′-*trans*-phytonadione),[5] synthetic phytonadione contains appreciable quantities of the *cis* configuration (2′,3′-*cis*-phytonadione).[6]

Chirality is an important consideration for phytonadione because the *cis* analogs lack biological activity, whereas the *trans* analogs are bioactive.[7] Because phytonadione is a

[3] As reported in FDA's Orange Book online, https://www.accessdata.fda.gov/Scripts/cder/ob/index.cfm (last visited March 14, 2019).

[4] European Commission Directorate-General for Health & Consumers, Scientific Committee on Consumer Safety, "Opinion on Vitamin K_1 (phytonadione)," SCCS/1313/10, 7 (March 24, 2010), *available at* https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_014.pdf.

[5] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 76, 417-486, 424 (2000) (Exhibit A).

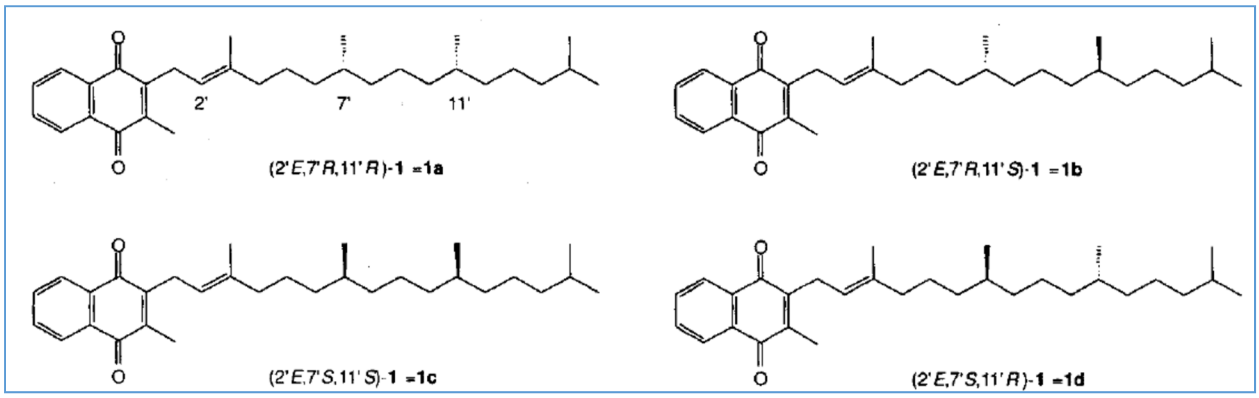
[6] *Id.* *See also* N. A. Golubkina, "Preparation Of Optically Active Vitamin K_l," Methods Of Synthesis And Production Technology Of Drugs, 126-28, 126 (1986) (Exhibit B).

[7] "Phylloquinone," Merck Index 15th ed., 1370 (2013) (Exhibit C); T. E. Knauer, "Metabolism and Biological Activity of *cis*- and *trans*-Phylloquinone in the Rat," J. Nutrition 105(12), 1519–24, 1521 (1975) (Exhibit D). FDA also recognizes the relationship between phytonadione chirality and bioactivity because it requires that the bioequivalence acceptance criteria should be based upon the 90% confidence interval of the *trans* configuration. Draft Guidance on Phytonadione Tablets (January 2016), *available at* https://tinyurl.com/y3aqmvyk.

prothrombogenic, it is critical that the quantity of the diastereomers in the drug are tightly controlled. Currently, the United States Pharmacopeia ("USP") monograph for phytonadione drug substance sets out an upper limit for the presence of *Z* isomers as "NMT 21.0%,"[8] which ANDA products are typically required to meet.

It is generally understood that chirality may impact various aspects of a drug's efficacy and toxicology.[9] Although limited literature suggests that the prothrombogenic activities of the four stereoisomers of the *trans* configuration (*see* Figure 2) are nearly identical,[10] no human studies confirm this. Moreover, the effect of different quantities (ratios) of each of the inactive *cis* stereoisomers on the drug's safety or efficacy is not understood. As such, the impact of different ratios of the phytonadione isomers between the RLD and ANDAs (or across multiple batches of a single ANDA product) has not been established. Nonetheless, there are currently no established standards around each of the phytonadione isomers present in the drug substance.

Figure 2. Chemical Structure of *E* isomers of Phytonadione (Vitamin K_1)[11]



C. FDA's Review of Zydus's ANDA for Phytonadione Tablets

During review of Zydus's ANDA No. 210189, 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. FDA also required a tighter acceptance criteria than defined in the USP monograph for the presence of *Z* isomer in the drug substance based on *Z* isomer data from the RLD. FDA approved Zydus's ANDA on February 20, 2019.

II. LEGAL AND REGULATORY BACKGROUND

[8] "Phytonadione," USP43-NF48 (2019) (Exhibit E).

[9] *See* S. W. Smith, "Chiral Toxicology: It's the Same Thing. . .Only Different," 110(1) Toxicological Sciences, 4-30 (2009) (review of impact of chirality on pharmacology and toxicology) (Exhibit F).

[10] R. Schmid, "Synthesis of All Four Stereoisomers of (E)-Vitamin K_1 (Phylloquinone), Analysis of Their Diastereoisomeric and Enantiomeric Purities and Determination of Their Biopotencies," Helvetica Chimica Acta Vol. 73, 1276-1299 (1990) (Exhibit G).

[11] *Id.* at 1277.

An ANDA submitted under Section 505(j) of the FDCA is eligible for approval if it is a "duplicate of a listed drug," where the listed drug is typically the innovator product approved in a new drug application.[12] The ANDA must contain information demonstrating that the "active ingredient" of the proposed generic drug product is "the same as that of the listed drug,"[13] meaning "identical in active ingredient(s)."[14] FDA has stated that it will consider an active ingredient to be the same as the listed drug if "it meets the same standards for identity."[15]

Although the FDCA does not describe how "sameness" should be established, if a USP monograph exists for the drug substance setting forth requirements for identity, FDA typically applies those standards to the ANDA product.[16] FDA recommends that the acceptance criteria for an impurity in an ANDA be set no higher than the compendial limit set out in the USP monograph, if such a limit exists in the monograph.[17] But, FDA may "prescribe additional standards that are material to the ingredient's sameness" beyond the compendia, such as standards for "stereoisomeric mixture[s]."[18]

An ANDA must also contain information to demonstrate that it is bioequivalent to the listed drug.[19] Two drugs are bioequivalent if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[20] Bioequivalence is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[21]

If the proposed generic product has the same active ingredient, strength, dosage form, and route of administration as the RLD, the products will be considered "pharmaceutically equivalent" to one another.[22] The proposed generic must be both pharmaceutically equivalent and bioequivalent to the RLD to obtain ANDA approval. FDA considers two drug products to be "therapeutically equivalent" only if they are pharmaceutically equivalent, bioequivalent, and "can be expected to have the same clinical effect and safety profile when administered to patients

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[12] 21 C.F.R. § 314.101(d)(9).

[13] 21 U.S.C. § 355(j)(2)(A)(ii)(I).

[14] 21 C.F.R. § 314.92(a)(1).

[15] Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17959 (Apr. 28, 1992).

[16] *Id.*

[17] FDA, Guidance for Industry, ANDAs: Impurities in Drug Substances, at 3 (June 2009), *available at* https://www.fda.gov/downloads/Drugs/Guidances/UCM172002.pdf.

[18] 57 Fed. Reg. at 17959.

[19] 21 U.S.C. § 355(j)(2)(A)(iv).

[20] 21 U.S.C. § 355(j)(8)(B)(i).

[21] 21 C.F.R. § 314.3(b).

[22] *Id.*

under the conditions specified in the labeling."[23] Therapeutically equivalent products are listed in the Orange Book with an "A" rating, or an "AB" rating in the case of oral products for which bioequivalence has been demonstrated.[24] If, however, FDA believes that there is insufficient evidence to assure therapeutic equivalence of the generic product to the RLD, FDA will downgrade the product's therapeutic equivalence rating to "BX" until the Agency has adequate information before it to ensure equivalence. *Id.*

III. ARGUMENT

A. FDA Should Refrain from Approving Any ANDAs for Mephyton Unless Comparable Isomeric Purity Has Been Demonstrated to the RLD

Synthetic preparations of phytonadione will invariably yield the *Z* isomer along with the *E* isomer in an isomeric mixture. The quantity of each of the diastereomers present in the synthesized drug substance will be highly dependent on the starting material used as well as the manufacturing process and controls. Synthesized phytonadione drug substances that are commercially available may have different quantities of each inactive and active isomer present, in ratios that differ from the RLD. Controlling the quantity of *each* isomer present in the drug substance is critical because the contribution of each isomer to the biological activity of phytonadione is not well understood and has not been established by human studies. Without comparable isomeric purity to the RLD, there is no assurance that a generic product will have the same clinical profile as Mephyton.

As noted above, 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. To demonstrate identity, the RLD must be adequately characterized with the active ingredient sufficiently defined, and the applicant must provide sufficient information to show that its active ingredient is the same as the active ingredient of the RLD.[25]

Therefore, FDA should ensure that applicants demonstrate that comparable chirality between the proposed generic and the RLD with respect to *each* of the isomers present in the drug substance. At a minimum, this should include suitably validated testing for the presence of each isomer in the drug substance specification of the proposed generic product, with acceptance criteria based of the isomeric purity of the RLD. Further, 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 limit. Absent that, the ANDA applicant has not satisfied the "sameness requirement," and FDA should refrain from approving the application.[26]

Moreover, FDA should apply approval requirements for the active ingredient consistently across all generic drug applications. FDA should require all ANDA holders to comply with the

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[23] *Id.*

[24] *See* Preface to Orange Book, 39th ed. (2019), *available at* https://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm.

[25] Letter from Janet Woodcock, M.D., Director, CDER, to Stuart J. Land et al., Arnold & Porter, and Nancy L. Buc, Buc & Beardsley, Docket No. 98P-0311, at 7 (March 24, 1999) ("Premarin Response").

[26] *See* Premarin Response at 10 (noting that CDER made a decision to refuse to approve generic synthetic conjugated estrogens drug products because of uncertainty around identity and sameness of the active ingredients of the RLD and proposed generics).

same approval standards it applied to Zydus's ANDA. Any other result would contravene the statutory requirements for sameness, be at odds with FDA's prior actions, and be improper. *See Bracco Diagnostics. Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) ("Government is at its most arbitrary when it treats similarly situated people differently") (internal citations omitted).

B. An Approved ANDA Cannot Maintain an "AB" TE Code Unless it Has Sufficiently Demonstrated Comparable Isomeric Purity of its Active Ingredient to that of the RLD

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.[27] Until active ingredient sameness has been sufficiently established, the ANDA product is not pharmaceutically equivalent to the RLD. If two products are pharmaceutically *in*equivalent, they cannot be therapeutically equivalent.

FDA should downgrade the TE code for any such ANDA product if the data before the Agency are insufficient to determine therapeutic equivalence.[28] Although an ANDA applicant must demonstrate bioequivalence to the RLD to obtain approval, 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. 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.

Where data before FDA are insufficient to demonstrate therapeutic equivalence, "the drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence."[29] Indeed, FDA has taken this approach with other approved generic products that it later deems have not sufficiently demonstrated therapeutic equivalence.[30] Likewise, 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.

IV. CONCLUSION

For all of the reasons described above, we respectfully request that FDA grant the actions requested in this citizen petition.

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[27] *See* Premarin Response at 10 (noting that a synthetic conjugated estrogens drug product containing different active ingredients than the RLD will not be listed as equivalent to and substitutable for the RLD in the Orange Book).

[28] *See* Preface to Orange Book, *supra* n. 24

[29] *Id.*

[30] Mallinckrodt Pharmaceuticals; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing," 81 Fed. Reg. 71737-741 (Oct. 18, 2016); "Kremers Urban Pharmaceuticals Inc.; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing," 81 Fed. Reg. 71741-745 (Oct. 18, 2016).

ENVIRONMENTAL IMPACT

The actions requested herein are subject to categorical exclusion under 21 C.F.R. § 25.31(a).

ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), the Petitioner will submit economic impact information upon request by the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: August 6, 2018. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Zydus Pharmaceuticals (USA) Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Chad A. Landmon

Exhibits