CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 210189

Name: Phytonadione Tablets, 5mg

Sponsor: Zydus Pharmaceuticals Inc

Approval Date: February 20, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA210189Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210189

APPROVAL LETTER

ANDA 210189

ANDA APPROVAL

Zydus Pharmaceuticals (USA) Inc.
U.S. Agent for Zydus Worldwide DMCC
73-B Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President and Head of RA and QA - North America

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 3, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Phytonadione Tablets USP, 5 mg.

Reference is also made to the complete response letter issued by this office on August 6, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Phytonadione Tablets USP, 5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mephyton Tablets, 5 mg, of Valeant Pharmaceuticals International.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at: http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Heidi Lee

Digitally signed by Heidi Lee
Date: 2/20/2019 09:19:35AM
GUID: 52795fe90009070673e7de063d080d1f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210189

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	210189	
Drug Product Name	Phytonadione Tablets, USP	
Strength(s)	5 mg	
Applicant Name	Zydus Worldwide DMCC	
Applicant Address	Unit No. 908, Armada Tower 2, Plot No. JLT-PH2-P2A, Dubai, United Arab Emirates (UAE) 340100	
US Contact Name and US Mailing Address	Srinivas Gurram (Srini), Vice President & Head of Regulatory Affairs Zydus Pharmaceuticals (USA) Inc., 73 Route 31 North Pennington, New Jersey 08534 gsrinivas@zydususa.com	
US Contact's Telephone Number	609-730-1900; (b) (6)	
US Contact's Fax Number	609-730-1999	
Original Submission Date(s)	01/03/2017	
Submission Date(s) of Amendment(s) Under Review	12/08/2017- Applicant's response to Complete Response Letter [CRL])	
Primary Reviewer	Dapeng Cui, Ph.D.	
Secondary Reviewer	Tao Bai, Ph.D.	
Tertiary Reviewer	N/A	
Study Number(s)	765-15	766-15
Study Type(s)	Fasting (pivotal)	Fed (pivotal)
Strength(s)	5 mg	5 mg
Clinical Site	Lambda Therapeutic Research Ltd.	Lambda Therapeutic Research Ltd.
Clinical Site Address	Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India.	7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector-15, CBD Belapur, Navi Mumbai-400 614, Maharashtra, India.
Analytical Site	(b) (4)	
Analytical Site Address		

Study Number(s)	763-15		
Study Type(s)	Fasting (pilot)		
Strength(s)	5 mg		
Clinical Site	Lambda Therapeutic Research Ltd.		
Clinical Site Address	Plot No. 38, Near Silver Oak Club, S.G. Highway, Gota, Ahmedabad-380 061, Gujarat, India.		
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete**	
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☒ **N/A**		
QC Dissolution	☐ **Pending** ☒ **Adequate** ☐ **Inadequate**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Deficiency Classification	☐ **Major (Deficiencies to be communicated by CR)** ☐ **Minor** ☒ **N/A (Review is Adequate)**		
Major Deficiency Theme	**N/A**		
Justification for Major Designation	**N/A**		
Overall Review Result	☒ **Adequate** ☐ **Inadequate**		
Date of Product Specific Recommendation Referenced in Review	***Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)*** ☒ **Recommended/Latest Revision Date:** on January 2016 **RLD Number: 010104** https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**

1, 2, 3, 7	**Pivotal fasting**	**5 mg**	**☒ Adequate ☐ Inadequate**
1, 2, 3, 7	**Pivotal fed**	**5 mg**	**☒ Adequate ☐ Inadequate**
1, 2, 3, 7	**Pilot fasting**	**5 mg**	**☐ Adequate ☐ Inadequate ☒ N/A (information only)**
1, 2, 3, 7	**Waiver, (Dissolution)**	**5 mg**	**☐ Adequate ☐ Inadequate ☒ N/A**

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

This is a review of a study amendment dated 12/08/2017.

The applicant's original submission was found inadequate per the bioequivalence (BE) review dated 09/29/2017[1] due to the deficiencies in the method validation studies and pivotal fasting and fed studies. The BE deficiencies were communicated to the applicant in a Complete Response Letter (CRL) dated 10/20/2017[2].

In the current amendment submission dated 12/08/2017, the applicant satisfactorily responded to all deficiencies (please see discussions in Section **3**).

The dissolution-only review was pending at the time of the original BE review dated 09/29/2017, and was completed and deemed adequate on 10/19/2017[3]. As the test product has one strength (5 mg) only and there is no waiver request, the dissolution section is not relevant from a bioequivalence perspective.

The formulation of the test product is acceptable per the original BE review dated 09/29/2017.xx

As previously stated in the original BE review dated 09/29/2017**,** the Office of Study Integrity and Surveillance (OSIS) inspection status for the current ANDA 210189 is **complete.**

The application is **adequate**.

[1] GDRP ANDA-210189-ORIG-1, Documents, *A210189N000DB_N01032017_09222017.docx*, dated 09/29/2017
[2] GDRP ANDA-210189-ORIG-1, Documents, *A210189N000DPM-CompleteResponse01*, dated 10/20/2017
[3] GDRP ANDA-210189-ORIG-1, Documents, *ANDA 210189-ORIG-1 Phytonadione Tabs Biopharm Review Final_AP*, dated 10/19/2017

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3 REVIEW OF SUBMISSION

Deficiency #1:

The recovery of the trans-phytonadione QC samples and cis-phytonadione QC samples in the method validation (Report #MV(I)-221-16, Submit Date: January 3, 2017) for the fasting BE study (Study #765-15) were substantially lower than that in the method validation (Report #MV(I)-226-16, Submit Date: January 3, 2017) for the fed BE study (Study #766-15). For example, in the fasting method validation (Report #MV(I)-221-16), the average recovery of Trans-Phytonadione ranged 39.2% - 43.9% in normal human plasma and ranged 39.0% - 41.6% in UV light exposed human plasma; whereas in the fed method validation (Report #MV(I)-226-16), the average recovery of Trans-Phytonadione ranged 66.8% - 74.5% in normal human plasma and ranged 58.2% - 70.7% in UV light exposed human plasma. Please explain the difference in the recovery of QC samples between the fasting and fed method validation reports and the relevant impact it might have on fasting and fed study results.

Applicant's Response to Deficiency #1:

We understand the Agency's concern about the differences of the recovery of the QC samples in method validation of fasting (Study No. 765-15) and fed (Study No. 766-15) BE studies. In regards to the same would like to clarify that; significant difference in the Cmax concentration of fast and fed studies was anticipated, hence it was not possible to develop a single method to cover the concentration data of both the studies in one linearity range. And thus the plasma sample of fasting BE study and fed BE study were analyzed using separate validated bio-analytical methods. The linearity range for the Trans and Cis Phytonadione considered in the bio-analytical methods are summarized in below table:

Table 1: Details of Linearity range for study # 765-15 and 766-15

Project No.	*Method validation No.*	*Method SOP*	*Linearity range*	
			Trans-Phytonadione K1	*Cis-Phytonadione K1*
765-15 (Fasting)	*MV(I)-221-16*	(b) (4)	*0.401 to 100.235 ng / mL*	*0.300 to 25.000 ng/mL*
766-15 (Fed)	*MV(I)-226-16*		*1.002 to 501.625 ng / mL*	*1.001 to 99.137 ng/mL*

(b) (4)

Table-2: Major difference in Bioanalytical methods used for fasting and fed study sample analysis

(b) (4)

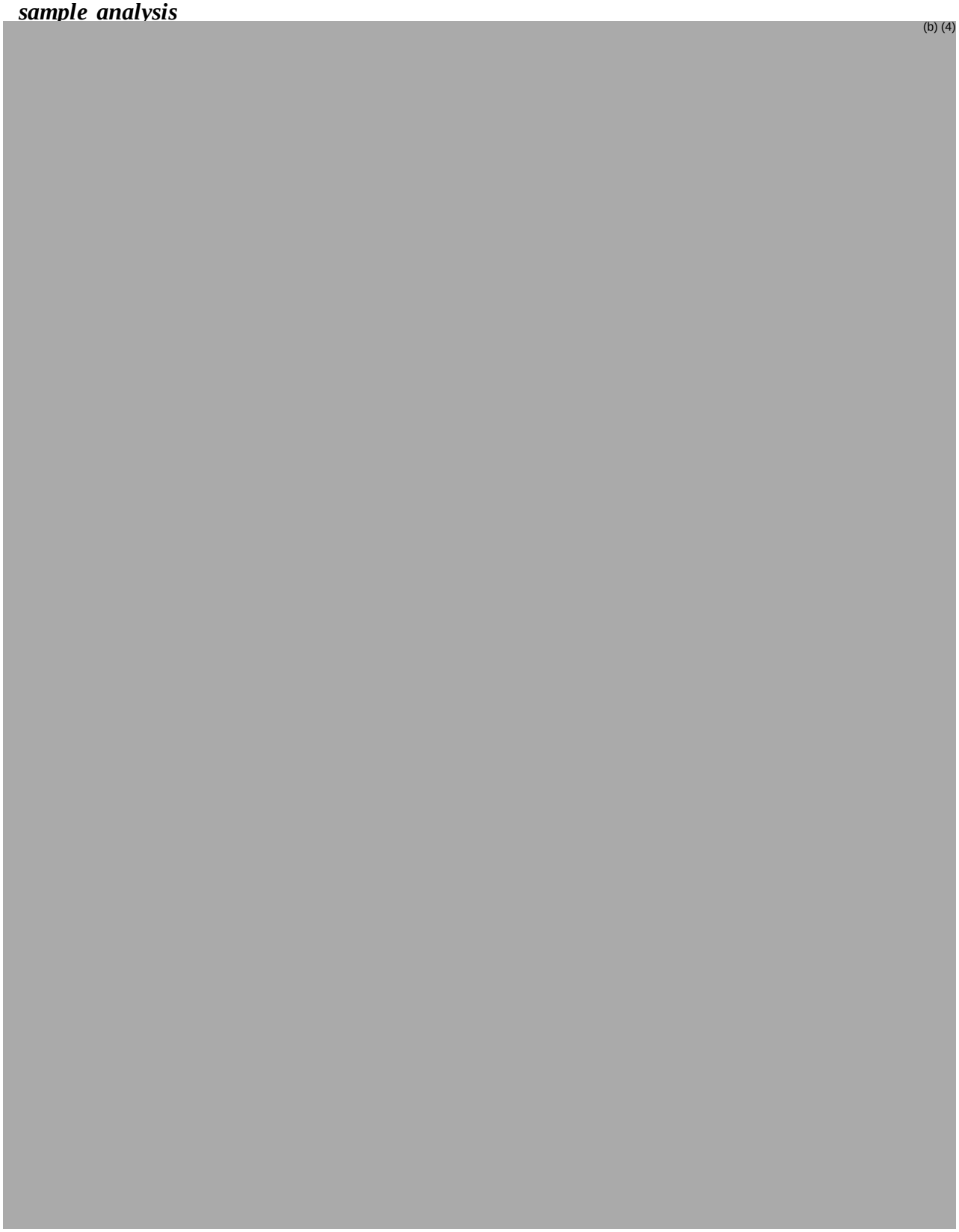
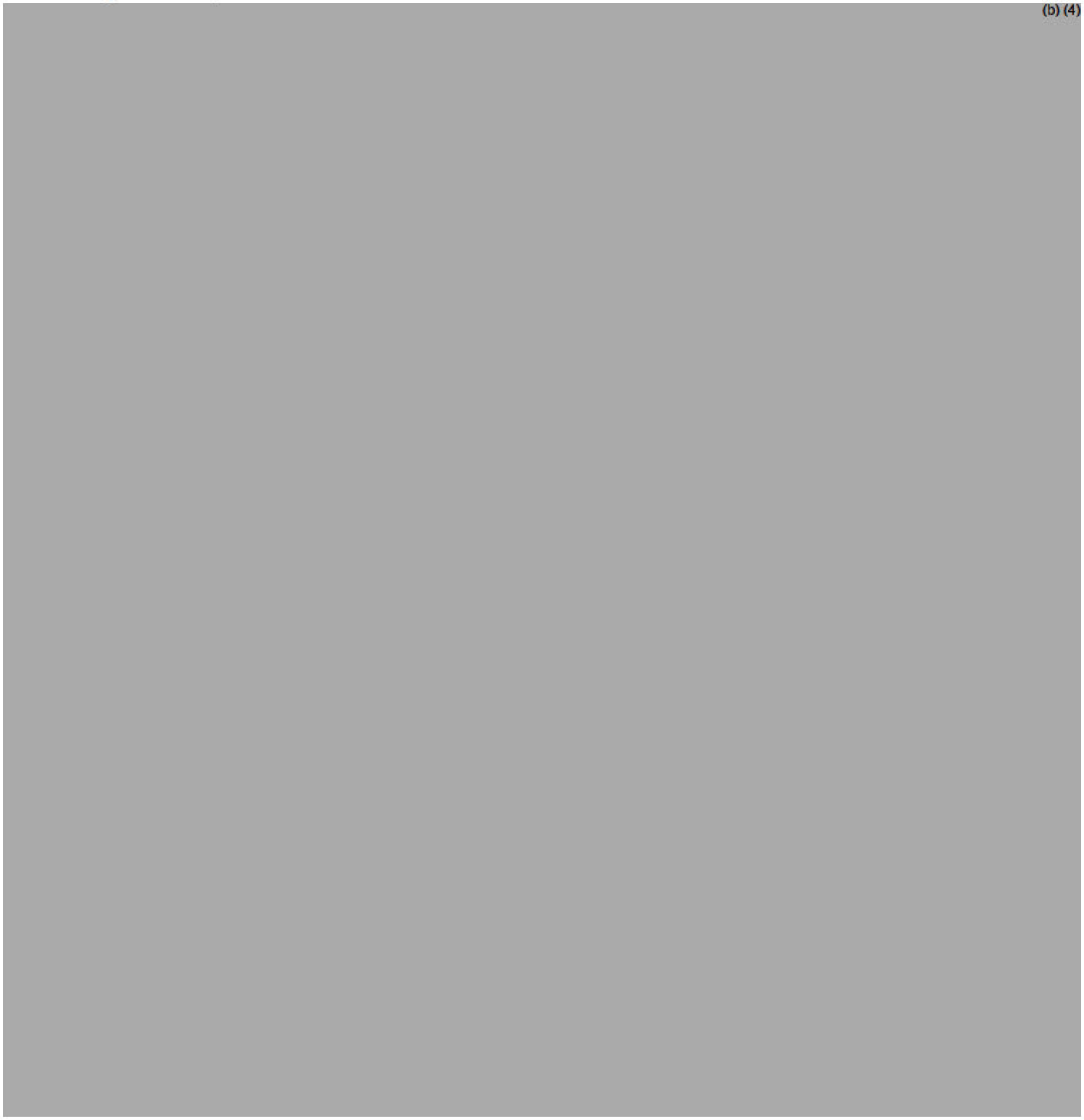


Table 3B: Details of recovery for method validation #MV(I)-226-16 (Applicable for study #766-15)



Reviewer's comments on applicant's response to deficiency #1 - Adequate

The applicant stated that due to the significant different Cmax under the fasting and fed conditions, separate bioanalytical methods were developed for the fasting and fed BE studies with different extraction procedure and chromatographic conditions, which led to the different % recovery in the two methods. The applicant also stated that the bioanalytical data generated from both methods were reproducible, accurate and precise because the % recovery was consistent across different QC levels, both methods were

fully validated, and the incurred sample reproducibility (ISR) experiments met the acceptance criteria in both BE studies.

The reviewer confirmed that the concentrations of both trans- and cis-phytonadione were substantially higher in the fed study compared to the fasting study. For example, for baseline uncorrected trans-phytonadione of the Test product, the mean Cmax was 16.998 ng/mL and most subject samples ranged from 1 to 25 ng/mL in the fasting study, whereas in the fed study the mean Cmax was 236.083 ng/mL and most subject samples ranged from 5 to 400 ng/mL[4]. Consequently, the applicant developed separate analytical methods with different linear ranges for the subject sample assay of the two BE studies. The extraction procedure (b) (4) and chromatographic conditions ((b) (4) are different between the two methods. The reviewer agrees that these differences, especially the extraction procedure, likely resulted in different % recovery. The reviewer considers that the different % recovery had no impact on study results of fasting and fed studies based on the below facts:

- Both methods were fully validated with all experiments meeting method validation acceptance criteria. The applicant has submitted method validation SOP (b) (4) and method SOPs (b) (4) for fasting study #765-15 and SOP (b) (4) 0 for fed study #766-15, respectively).

- Although the % recovery was different for both analytes between the fasting and fed method validations, the % recovery was consistent across QC samples of each analyte and its internal standards (IS) within each method validation.

- For both fasting and fed BE studies, the subject sample assay and ISR met all acceptance criteria and there was no issue in the repeat analysis.

The applicant's response to deficiency #1 is **acceptable**.

Deficiency #2:

Please provide the potencies of each phytonadione isomer (trans- and cis-) in the test (lot# EE60280) and reference products (lot# 14A094P) used in the fasting (#765-15) and fed (#766-15) BE studies.

Applicant's Response to Deficiency #2:

We wish to inform the Agency that the analytical method for determination of isomers of Phytonadione in the drug product is not available; we have adopted the drug substance's USP analytical method for Assay. This compendia analytical method was validated by the drug substance manufacturer and verified at the drug product manufacture site. Please refer method verification report (MVR/220) provided in Module 3.2.S.4.3 of the original submission.

[4] GDRP ANDA-210189-ORIG-1, Documents, *A210189N000DB_N01032017_09222017*, dated 09/29/2017

In order to extend the same methodology for the determination of isomers of Phytonadione in the drug product, we have verified this analytical method. The method verification study report (MDR/17/685-00) is provided in Module 3.2.P.5.3 of this amendment.

As the analytical methodology has been found suitable for determination of potencies of each phytonadione isomer (trans- and cis-) in the drug product, we have analyzed the test (lot# EE60280) and reference products (lot# 14A094P) used in the fasting (#765-15) and fed (#766-15) BE studies.

The test results are provided in below table for the Agency's ready reference.

Analyte	Test product (B. No. EE60280)	Reference product (B. No. 14A094P)
Cis-Isomer (Z-isomer)		(b) (4)
Trans-Isomer (E-isomer)		

From the results it is inferred that potencies of each phytonadione isomer (trans- and cis-) in the test and reference products are very similar.

Reviewer's comments on applicant's response to deficiency #2 - Adequate

Per control reviewer of 110232[5] which led to the revision of Draft Guidance on Phytonadione Tablets, "*The biological activity of cis-vitamin K1 is far less than that of trans-vitamin K1. Therefore, the assay used for the determination of phytonadione levels in plasma should be specific to trans-isomer of vitamin K. The firm is advised to determine the potencies (in terms of each isomer) of the lots of the test and reference drug products to be used in the study. It is recommended that the potency for the lot of the reference product be within 5% of that for the test product.*" Therefore, the applicant was requested to provide potency of each phytonadione isomer (trans- and cis-) in the test and reference products.

In the current amendment dated 12/08/2017, the applicant submitted method development report for determination of isomers of Phytonadione in the drug product (report #MVR/220 in Module 3.2.P.5.3) and provided potencies of each phytonadione isomer in the test and RLD lots that were used in the fasting and fed BE studies (please see table above).

The potencies of trans- and cis-phytonadione for bio-lot of test product (Lot #EE60280) were (b) (4) respectively, and the potencies of trans- and cis-phytonadione for the RLD (Lot #14A094P) were (b) (4) respectively, which was within 5% of those for the test product.

[5] V:\DIVISION\BIO\Guidance reviews\Phytonadione Tabs 010104.pdf

The USP monograph of phytonadione[6] states that "*phytonadione is a mixture of E- (trans phytonadione) and Z-isomers (cis phytonadione) containing NLT 97.0 % - NMT 103.0% of phytonadione isomers. It contains NMT 21.0% of the zisomer"*. Both RLD and test products comply with the USP specification.

The applicant's response to deficiency #2 is **acceptable**.

Deficiency #3:

For the fasting study (Study #765-15), our statistical analysis using the reference scaled average BE approach shows that the 95% upper confidence bounds for (μT - μR)2 - θs2WR for AUCinf of baseline corrected cis-phytonadione is greater than 0. Therefore, the statistical analysis shows that the test product has higher bioavailability than the reference product for cis-phytonadione. The data for cis-phytonadione are therefore, not considered supportive of the trans-phytonadione analysis. Please explain how these findings affect your conclusion for bioequivalence of the test product to the reference product under fasting conditions.

Applicant's Response to Deficiency #3:

We agree with the assessor's observation that 95% upper confidence bounds for (μT - μR)2 - θs2WR for AUCinf of baseline corrected cis-phytonadione is found greater than 0 (i.e. 0.0308). We would like to clarify that it was erroneously reported as -0.0308 in summary statistics (i.e. Table no. 14.2.3.1 of CSR) however, the correct value was provided with SAS output in the submission (i.e. appendix 16.1.9.8 of CSR). Summary statistics and SAS output of baseline corrected data of Phytonadione (Z isomer (cis-configuration)) with correct value of 95% upper bound of AUCinf has been provided in attachment. Refer Attachment # 3a for summary statistics and Attachment # 3b for SAS output and provided in Module 5.3.1.2 of this amendment. Additionally note to file is generated with mentioning respective sections in the fasting study report, where erroneously 95% upper confidence bounds for AUC0-inf of baseline corrected cis-phytonadione reported as -0.0308 in place of 0.0308. Please refer Attachment # 4 for the same which is provided in Module 5.3.1.2 of this amendment.

We would like to inform agency that the fasting BE study (#765-15) was conducted as per USFDA product specific bio-recommendation guidance for Phytonadione Tablets, 5 mg published by OGD (dated Jan 2016) and refer Attachment# 2 of bio-recommendation guidance provided in Module 5.4 of this amendment. As per the guidance, bioequivalence is based on (90%CI) of Phytonadione (E isomer (trans-configuration)) only. In addition, Z isomer (cis-configuration) data (individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax) needs to be provided as supportive evidence of comparable therapeutic outcome.

The statistical analysis for Z-isomer was performed additionally and submitted in our study report as supportive information.

[6] USP-NF Online, USP Monograph, accessed on 12/21/2017

We would like to confirm the agency that though the Z-isomer is biologically inactive, its T/R ratios for Cmax and AUC were well within 80-125% in fasting study indicating that test product behaves similar to reference product.

T/R ratio for Baseline corrected Phytonadione Z isomer (cis-configuration) in vivo Fasting Bioequivalence study	
Cmax	102.4
AUCt	111.5
AUCI	112.5

Further, we would like to inform agency that the test and reference product were tested for Z- isomer content. The results of the same are provided below:

Z-isomer potency		
Test (B. No. EE60280)	**Ref (B. No. 14A094P)**	**Ratio (% T/R)**
12.4%	11.2%	110.7

The T/R ratio for the PK parameters of Z isomer (cis-configuration) is directly correlated with potency of Z-isomer observed in test and reference products.

The higher bioavailability observed with the baseline corrected Z isomer (cis-configuration) does not have therapeutic significance considering that Phytonadione E isomer (trans- configuration) which is biologically active meets all the predefined bioequivalence criteria. In addition, Z isomer (cis-configuration) which is biologically inactive also shows T/R ratio in range of 80-125%.

Reviewer's comments on applicant's response to deficiency #3 - Adequate

The original BE review[7] found that for AUCi of baseline corrected cis-phytonadione in the fasting study, the 95% upper confidence bounds for $(\mu T - \mu R)^2 - \theta s^2_{WR}$ was 0.0415557 (i.e., > 0), indicating that the test product has higher bioavailability than the reference product for cis-phytonadione. The firm was requested to explain the higher bioavailability of the cis-isomer in the test product than the RLD.

In the current amendment dated 12/08/2017, the applicant stated that the higher bioavailability of cis-phytonadione observed in the fasting study was consistent with the higher potency of the cis-isomer in the test product compared to the RLD. Furthermore, the applicant stated that per the product specific guidance (PSG), bioequivalence is based on 90%CI of trans-phytonadione only, and the cis-isomer data are provided as supportive evidence of comparable therapeutic outcome.

A similar scenario was observed in another in-house ANDA of the same drug product, i.e., ANDA 209373, where the test product was found to have lower bioavailability of

[7] GDRP ANDA-210189-ORIG-1, Documents, *A210189N000DB_N01032017_09222017.docx*, dated 09/29/2017

cis-phytonadione than the RLD product in the fasting and fed BE studies (Cmax and AUCt of cis-phytonadione were outside of BE range in the fasting study, AUCt and AUCi of cis-phytonadione were outside of BE range in the fed study)[8,9]. Per the internal Office of Bioequivalence (OB) management meeting minutes dated 11/02/2017[10], *OB considers the firm's fasting and fed BE studies in ANDA 209373 are acceptable based on below reasons:*

1. *Unlike the BE criteria, at this time, OB does not enforce rigid criteria for the data considered as 'supportive evidence'.*
2. *Cis and trans Phytonadione are geometric isomers. The PK endpoint guidance specifies when it is necessary to measure the enantiomers vs. the racemate to establish BE. Therefore, the recommendations in this guidance are applicable mainly for the optical isomers, which may have different pharmacokinetic properties (absorption; distribution, biotransformation. and excretion) and quantitatively or qualitatively different pharmacologic or toxicologic effects. We do not necessarily have similar concerns for the geometric (cis/trans) isomers, especially when no interconversion between the isomers is known to occur in vivo. Cis- and trans-phytonadione are not known to interconvert, in vivo.*
3. (b) (4)
4. *Acceptability of the supporting data will be a judgement issue based on the available information and total weight of evidence, including the data for the T/R ratios (extent of deviation from ± 20%) and the contribution of each isomer to the pharmacological activity.*
5. (b) (4)
6. *Also, Phytonadione Tablets has a wide therapeutic index and is often used as antidote for vitamin K antagonists. It suggests that even though the point estimate of T/R ratio for cisisomer does not fall within* (b) (4) *range, the clinical impact is likely to be minimal.*

Instead of the lower bioavailability of cis-phytonadione in the test product compared to the RLD in ANDA 209373, a higher bioavailability of cis-phytonadione in the test product compared to the RLD is observed in current ANDA 210189. However, the principles used to justify the statistical results of cis-phytonadione in ANDA 209373 also

[8] GDRP ANDA-209373-ORIG-1, *A209373N000DB_N06292016*, dated 03/30/2017
[9] GDRP ANDA-209373-ORIG-1-AMEND-5, Documents, *A209373N000DB-Review01-Amend08232017*, dated 11/10/2017
[10] GDRP ANDA-209373-ORIG-1-AMEND-5, Documents, *A209373N000MeetingMinutes01-11022017*, dated 11/10/2017

apply to the current ANDA. The higher bioavailability of cis-phytonadione in the test product than the RLD is not considered to be an issue from bioequivalence perspective based on below:

- Per the above meeting minutes #1, the Office of Bioequivalence does not enforce rigid criteria for the data considered as "supportive evidence" stated in the product specific guidance.

- Cis- and trans-phytonadione are geometric isomers. The Guidance for Industry: Bioequivalence Studies with PK Endpoints for Drugs Submitted under an ANDA[11] specifies the necessity to measure the individual enantiomers of racemate (i.e., optical isomers) to establish BE. The recommendations in this guidance are applicable mainly for the optical isomers, which may have different pharmacokinetic properties (absorption; distribution, biotransformation. and excretion) and quantitatively or qualitatively different pharmacologic or toxicologic effects. There are no similar concerns for the geometric isomers. Per the above meeting minutes #2, cis- and trans-phytonadione are not known to interconvert in vivo.

- (b) (4)

- The T/R ratio for AUCi (1.12, calculated by the reviewer using reference-scaled average bioequivalence [SABE] approach) of baseline-corrected cis-phytonadione in the fasting study of current ANDA 210189 was within [0.8-1.25]. Per the above meeting minutes #4, *acceptability of the supporting data will be a judgement issue based on the available information and total weight of evidence, including the data for the T/R ratios (extent of deviation from ± 20%) and the contribution of each isomer to the pharmacological activity*. Considering that amount of cis-isomer is approximately 10% of total API and cis-isomer has about 10- to 100-fold lower activity than the trans-isomer[12], the T/R ratio of 1.12 for AUCi of cis-isomer is not considered to have a significant impact on the overall phytonadione activity, and can be attributed to the difference in the potency of cis-isomer between test and reference (products (see next bullet).

- (b) (4)

[11] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm377465.pdf

[12] Comparison of the activity of the cis and trans isomer of vitamin K1 in vitamin K-deficient and coumarin anticoagulant-pretreated rats. J. Pharmacol Exp. Ther., 1979, Jun; 209(3): 330-3

(b) (4)

- Additionally, Phytonadione Tablets has a wide therapeutic index and is indicated for coagulation disorders caused by vitamin K deficiency or interference with vitamin K activity. In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity[13]. The slight difference in the AUCi of cis-isomer (T/R ratio of 1.12) is unlikely to have meaningful clinical impact.

Based on above justifications, the reviewer considers that the statistical result of the applicant's fasting study is acceptable.

The applicant's response to deficiency #3 is **acceptable**.

Deficiency #4:

For the fed study (Study #766-15), the statistical analysis using unscaled average BE approach shows that the 90% CIs for least squares geometric means of AUCt and AUCinf of baseline corrected cis-phytonadione are not within the range of 80.00 - 125.00%. Therefore, the statistical analysis shows that the test product has higher bioavailability than the reference product for cis-phytonadione. The data for cis-phytonadione are therefore, not considered supportive of the trans-phytonadione analysis. Please explain how these findings affect your conclusion for bioequivalence of the test product to the reference product under fed conditions.

Applicant's Response to Deficiency #4:

We would like to inform agency that the fed BE study (#766-15) was conducted as per USFDA product specific bio-recommendation guidance for Phytonadione Tablets 5mg published by OGD (dated Jan 2016) and refer Attachment# 2 of bio-recommendation guidance provided in Module 5.4 of this amendment. As per the guidance, bioequivalence is based on (90%CI) of Phytonadione (E isomer (trans-configuration)) only. In addition, Z isomer (cis-configuration) data (individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax) needs to be provided as supportive evidence of comparable therapeutic outcome.

The statistical analysis for Z-isomer was performed additionally and submitted in our study report as supportive information.

We would like to confirm the agency that though the Z-isomer is biologically inactive, its T/R ratios for Cmax and AUC were well within 80-125% in fed study indicating that test product behaves similar to reference product.

[13] RLD label from Drugs@FDA, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/010104s023lbl.pdf

T/R ratio for Baseline corrected Phytonadione Z isomer (cis-configuration) in vivo Fed Bioequivalence study	
Cmax	110.2
AUCt	121.2
AUCI	120.9

Further, we would like to inform agency that the test and reference product were tested for Z- isomer content. The results of the same are provided below:

Z-isomer potency		
Test (B. No. EE60280)	**Reference (B. No. 14A094P)**	**Ratio (% T/R)**
12.4%	11.2%	110.7

The T/R ratio for the PK parameters of Z isomer (cis-configuration) is directly correlated with potency of Z-isomer observed in test and reference products.

The higher bioavailability observed with the baseline corrected Z isomer (cis-configuration) does not have therapeutic significance considering that Phytonadione E isomer (trans- configuration) which is biologically active meets all the predefined bioequivalence criteria. In addition, Z isomer (cis-configuration) which is biologically inactive also shows T/R ratio in range of 80-125%.

Reviewer's comments on applicant's response to deficiency #4 - Adequate

The original BE review[14] found that based on the reviewer's analysis using unscaled average BE approach, the 90% CIs for AUCt (113.00%-130.05%) and AUCi (113.22%-129.48%) of baseline corrected cis-phytonadione were outside the BE range of 80.00-125.00%) in the fed study, indicating that the test product has higher bioavailability than the reference product for cis-phytonadione. The firm was requested to explain the higher bioavailability of the cis-isomer in the test product than the RLD.

In the current amendment dated 12/08/2017, the applicant stated that the higher bioavailability of cis-phytonadione observed in the fed study was consistent with the higher potency of the cis-isomer in the test product compared to the RLD. Furthermore, the applicant stated that per the product specific guidance (PSG), bioequivalence is based on 90%CI of trans-phytonadione only, and the cis-isomer data are provided as supportive evidence of comparable therapeutic outcome.

As discussed in deficiency #3, the higher bioavailability of cis-phytonadione in the test product than the RLD is not considered to be an issue from bioequivalence perspective (please refer to reviewer's justification for deficiency #3).

The applicant's response to deficiency #4 is **acceptable**.

[14] GDRP ANDA-210189-ORIG-1, Documents, *A210189N000DB_N01032017_09222017.docx*, dated 09/29/2017

4 DEFICIENCY COMMENTS

None

5 RECOMMENDATIONS

- The Division of Bioequivalence I (DBI) finds the pivotal fasting BE study (#765-15) adequate. Zydus Worldwide DMCC conducted the fasting study on its test product, Phytonadione Tablets USP, 5 mg (Lot #EE60280), comparing it to Valeant Pharmaceuticals North America's Mephyton® (phytonadione) Tablets, 5 mg (Lot # 14A094P).

- The DBI finds the pivotal fed BE study (#766-15) adequate. Zydus Worldwide DMCC conducted the fed study on its test product, Phytonadione Tablets USP, 5 mg (Lot #EE60280), comparing it to Valeant Pharmaceuticals North America's Mephyton® (phytonadione) Tablets, 5 mg (Lot # 14A094P).

- There is only one strength of the test product and no waiver request. The applicant's dissolution testing data are for information only.

- The formulation of the test product is acceptable.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 210189

APPLICANT: Zydus Worldwide DMCC

DRUG PRODUCT: Phytonadione Tablets, USP, 5 mg

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6 *COMPLETED ASSIGNMENT FOR 210189 ID: 33480*

Reviewer: Cui, Dapeng **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Phytonadione Tablets, USP, 5 mg

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
33480	2/14/2018	BIO	ANDA Amendment [1]	1	1
33480	2/14/2018	Parallel	Study Amendment [1]	1	1
				Total:	2

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA 210189-ORIG-1
Product Name	Phytonadione Tablets
Applicant	Zydus Pharmaceuticals
Dosage Form/Strengths	Tablets, 5 mg
Route of Administration	Oral
Indication for Use (*as per product's labeling*)	It is indicated in the following coagulation disorder 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
Submission Date	1/3/2017
Review Date	10/10/5017
Primary Reviewer	Banu S. Zolnik, Ph.D.
Secondary Reviewer	Okpo Eradiri, Ph.D.
Recommendation	**ADEQUATE**

1. REVIEW SUMMARY:

Submission:
Zydus Pharmaceutical is seeking approval for Phytonadione Tablets, 5 mg for the following 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. The reference listed drug is Meyphyton® (phytonadione tablets), 5 mg approved under NDA 10104.

Review's Objective:
The objective of this review is to evaluate (1) the dissolution method and its validation, and (2) the proposed dissolution acceptance criteria for the proposed drug.

Reviewer's Assessment:
The Applicant provided adequate dissolution development data to support the proposed in-house developed dissolution method (USP II (paddle), 50 rpm, 0.1 N HCl containing 0.5% Triton X-100, 900 mL).

The Applicant's originally proposed acceptance criterion (Q= (b)(4)% in (b)(4) minutes) was deemed permissive. After the review of the Applicant's responses (Seq. 004 dated 09/05/2017, and Seq. 005 dated 09/29/2017) and the discussion during the t-con held on 09/26/2017, the Applicant's revised acceptance criterion of (Q= (b)(4)% in (b)(4) minutes) is acceptable.

Conclusion and Recommendation:
From Biopharmaceutics perspective, ANDA 210189 is recommended for Approval.

2. SUBMISSION CONTENT CHECKLIST:

	INFORMATION	YES	NO	N/A
1	**Is there a USP dissolution method?**	☐	☒	☐
2	**Did the Applicant use the USP dissolution method?**	☐	☐	☒
3	**Is there an FDA-Database dissolution method?**	☐	☒	☐
4	**Did the Applicant use the FDA-Database dissolution method?**	☐	☐	☒
5	**Did the Applicant conduct dissolution testing with a proposed in-house dissolution method?**	☒	☐	☐
6	**Did the Applicant use 12 individual units of the test (proposed) drug product in the dissolution testing?**	☒	☐	☐
7	**Did the Applicant provide complete dissolution data for the test (proposed) drug product (all raw data, range, mean, % CV, date of dissolution testing)?**	☒	☐	☐
8	**Was the dissolution/release testing and pivotal bioequivalence study conducted using an unexpired reference drug product?**	☒	☐	☐
9	**Does the proposed product (any strength) have a functional scoring?**	☒	☐	☐
10	**If there is a functional scoring, did the Applicant provide complete dissolution data for the whole vs. split tablets?**	☒	☐	☐
11	**Is there significant change in the dissolution of stability samples?** For long-term stability batch EE602237 (b) (4) (b) (4) Drug Product review requested for more information on this issue.	☒	☐	☐

3. REVIEW:

a) List Submissions being reviewed:

01/03/2017	ANDA 210189/Original submission
09/05/2017	eCTD-0004/Response to Biopharmaceutics Information Requests
09/29/2017	eCTD-0005/Response to Biopharmaceutics Information Requests

b) Concise Description of Outstanding Issues:

None

c) Dissolution method and acceptance criterion proposed by the Applicant:

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Acceptance criterion
In house	USP II (paddle)	50 rpm	0.5% Triton X-100 in 0.1 N HCl/ 37°C	900 mL	45 minutes	Q= (b) (4) % in (b) (4) min

d) In Vitro Dissolution Data

(b) (4)

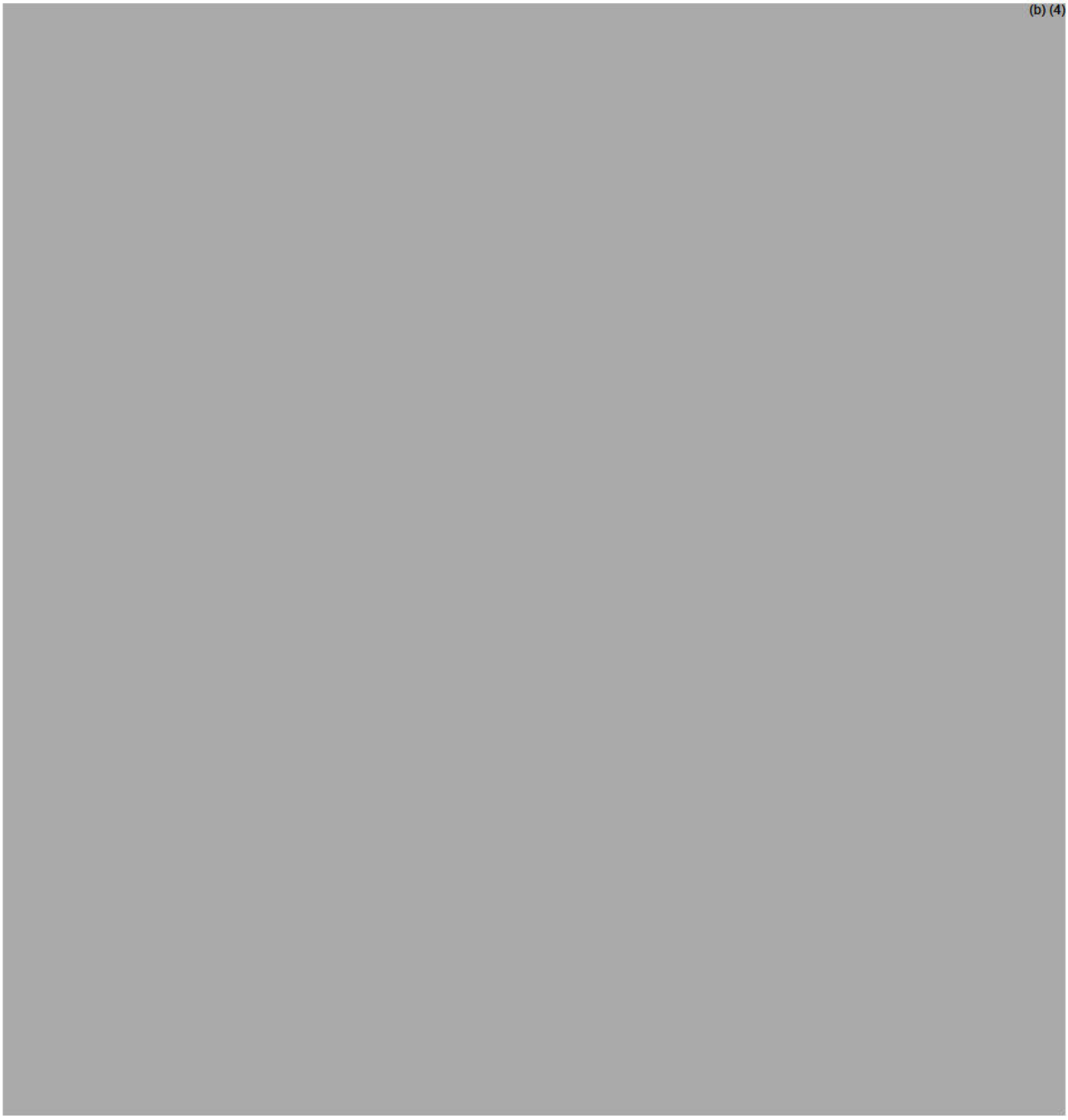
Figure 1. Summary of mean in vitro dissolution data for the proposed drug product (Bio-batch)

Refer to Appendix 1 for the tables of detailed dissolution data.

e) Dissolution Method Development

There is neither an FDA database method nor a USP method for Phytonadione tablets. The Applicant developed an in-house dissolution method for the proposed drug product.

(b) (4)



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APPENDIX 2

Biopharmaceutics Information Requests conveyed to the Applicant on 08/04/2017

Based on the submitted data, FDA recommends Q= (b) (4) *% in* (b) (4) *minutes as the dissolution acceptance criterion for Phytonadione Tablets, 5 mg. Revise the Specifications table and the stability protocol to reflect the recommended dissolution acceptance criterion. Thereafter, submit a copy of the updated drug product specifications table to the ANDA.*

Applicant's Response (Seq. 004 dated 09/05/2017)

The Applicant proposed dissolution acceptance criterion of Q (b) (4) % in (b) (4) minutes on the basis (b) (4) .

The Applicant included the table below in their response to justify their proposed acceptance criterion.

Batch no : EE60235			
Unit	% Phytonadione dissolved		
	30 min	45 min	60 min
Mean	93.6	96.4	97.4
%RSD	3.5	3.4	3.1
Minimum	(b) (4)		
Maximum			

T-con held between the Applicant and the FDA on September 26, 2017

During the t-con, the review team stated that (b) (4) (b) (4) In response to the Agency's comment, the Applicant provided additional information to justify their revised dissolution acceptance criterion. It was agreed that the Applicant submit the additional information in an amendment to support their proposal of Q= (b) (4) % in (b) (4) minutes.

Applicant's Response (Seq. 005 dated 09/29/2017)

The Applicant submitted dissolution data for additional batches shown in Table below. Although the Applicant listed various justifications in their response, additional batch dissolution data was the most compelling justification for their revised dissolution acceptance criterion.

Banu Zolnik

Digitally signed by Banu Zolnik
Date: 10/10/2017 12:20:20PM
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Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 10/10/2017 02:41:02PM
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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	210189	
Drug Product Name	Phytonadione Tablets, USP	
Strength(s)	5 mg	
Applicant Name	Zydus Worldwide DMCC	
Applicant Address	Unit No. 908, Armada Tower 2, Plot No. JLT-PH2-P2A, Dubai, United Arab Emirates (UAE) 340100	
US Contact Name and US Mailing Address	Srinivas Gurram (Srini), Vice President & Head of Regulatory Affairs Zydus Pharmaceuticals (USA) Inc., 73 Route 31 North Pennington, New Jersey 08534	
US Contact Telephone Number	609-730-1900; (b) (4)	
US Contact Fax Number	609-730-1999	
US Contact Email Address	gsrinivas@zydususa.com	
Original Submission Date(s)	01/03/2017	
Submission Date(s) of Amendment(s) Under Review	02/17/2017, Firm provided pilot BE study tables per Information Request (IR) by Filing review; 06/13/2017, Firm provided responses to IR by Drug Product review and Biopharmaceutical review	
Primary Reviewer	Dapeng Cui, Ph.D.	
Secondary Reviewer	Bruce Lerman, Ph.D.	
Tertiary Reviewer	N/A	
Study Number(s)	765-15	766-15
Study Type(s)	Fasting (pivotal)	Fed (pivotal)
Strength(s)	5 mg	5 mg
Clinical Site	Lambda Therapeutic Research Ltd.	Lambda Therapeutic Research Ltd.
Clinical Site Address	Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India.	7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector-15, CBD Belapur, Navi Mumbai-400 614, Maharashtra, India.
Analytical Site	(b) (4)	
Analytical Site Address		

	Gota, Ahmedabad – 382481, Gujarat, India.		
Study Number(s)	763-15		
Study Type(s)	Fasting (pilot)		
Strength(s)	5 mg		
Clinical Site	Lambda Therapeutic Research Ltd.		
Clinical Site Address	Plot No. 38, Near Silver Oak Club, S.G. Highway, Gota, Ahmedabad-380 061, Gujarat, India.		
Analytical Site	(b) (4)		
Analytical Site Address			

OSIS status	**Backlog, Year 1 and Year 2 ANDAs** **☐ Pending** **☐ Complete** **☐ N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** **☐ To Be Determined by OSIS** **☐ Pending For Cause Inspection** **☒ Complete**
Waiver/Deem Bioequivalent	**☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A**	
QC Dissolution	**☒ Pending ☐ Adequate ☐ Inadequate**	
Formulation	**☒ Adequate ☐ Inadequate**	
Will Response to CR Result in a Reformulation?	**☐ Possibly ☒ No ☐ N/A**	
Deficiency Classification	**☐ Major (Deficiencies to be communicated by CR)** **☒ Minor** **☐ N/A (Review is Adequate)**	
Overall Review Result	**☐ Adequate ☒ Inadequate**	
Revised/New Draft Guidance Generated as Part of Current Review	**☐ YES ☒ NO**	

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 2	**Pivotal fasting**	**5 mg**	**☐ Adequate ☒ Inadequate**
1, 2	**Pivotal fed**	**5 mg**	**☐ Adequate ☒ Inadequate**
1, 2	**Pilot fasting**	**5 mg**	**☐ Adequate ☐ Inadequate** **☒ N/A (for information only)**
1, 2	**Waiver, (Dissolution)**	**5 mg**	**☐ Adequate ☐ Inadequate** **☒ N/A**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Zydus Worldwide DMCC's Phytonadione Tablets, USP, 5 mg to the corresponding reference product Valeant Pharmaceuticals' Mephyton® (phytonadione) Tablets, 5 mg. The fasting BE study was designed as a single-dose, two-treatment, two-sequence, four-period replicate crossover study in healthy male subjects. The fed BE study was designed as a single-dose, two-treatment, two-sequence, four-period replicate crossover study in healthy male subjects.

The Draft Guidance for Phytonadione Tablets recommends single-dose, two-way crossover fasting and fed studies[1].The firm's fasting four-period replicate crossover study is acceptable despite not meeting PSG recommendation. Bioequivalence is based on trans-phytonadione; cis-phytonadione data is recommended as supportive evidence (see appendix 4 for more information). Per the current draft guidance for Phytonadione tablets, *baseline correction should be based on phytonadione levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. If the baseline is stable, you may choose to do baseline correction for 24 hours rather than 48 hours*. The firm used the average levels from -48 to 0 hour as baseline. The reviewer considers that the firm's approach is appropriate because the baseline level of trans-phytonadione shows some fluctuation. The reviewer also spot checked the firm's SAS dataset and confirmed that the firm's calculation of baseline correction is correct.

The results of the pivotal fasting and fed BE studies are summarized in the tables below.

Fasting (Reference-Scaled Average BE for Baseline Corrected Trans-Phytonadione)

Phytonadione Tablets (No. of subjects completed = 32; No. of subjects included in the analysis = 31) Dose (1×5 mg) Least Squares Geometric Means, Ratio of Means and 90% ``Confidence Intervals								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT (ng.h/mL)	0.94	78.95	113.01	0.2724392	0.5219571	-0.130893	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.06	84.86	122.04	0.2560268	0.5059909	-0.116524	Scaled/PE	PASS
LCMAX (ng/mL)	0.89	73.25	108.03	0.3227386	0.5681009	-0.130079	Scaled/PE	PASS

Note: Subject (b) (6) s excluded due to Period-II predose concentration > 5% Cmax

Fed (Unscaled Average BE for Baseline Corrected Trans-Phytonadione)

Phytonadione Tablets (No of subjects completed, N = 45) Dose (1 × 5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals

[1]OGD Guidance on Phytonadione Tablets, (Recommended Feb 2010, Revised Sep 2012, Jan 2016), available at: https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT (ng.h/mL)	1135.99	1030.68	1.10	102.29	118.77
LAUCI (ng h/mL)	1188.32	1076.96	1.10	102.65	118.60
LCMAX (ng/mL)	217.11	215.38	1.01	92.81	109.48

Fasting (Reference-Scaled Average BE for Baseline Corrected Cis-Phytonadione)

Phytonadione Tablets (No. of subjects completed = 32; No. of subjects included in the analysis = 31) Dose (1×5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	1.11	91.33	133.84	0.3938131	0.6275453	-0.183471	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.12	87.13	125.17	0.1091161	0.3303272	0.0415557	Scaled/PE	FAIL
LCMAX (ng/mL)	1.00	85.61	117.96	0.184873	0.4299686	-0.096923	Scaled/PE	PASS

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Fed (Unscaled Average BE for Baseline Corrected Cis-Phytonadione)

Phytonadione Tablets (No of subjects completed, N = 45) Dose (1 × 5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT (ng.h/mL)	166.17	137.07	1.21	113.00	130.05
LAUCI (ng h/mL)	176.65	145.90	1.21	113.22	129.48
LCMAX (ng/mL)	32.19	29.20	1.10	101.92	119.24

The firm's fasting and fed BE studies are **inadequate** due to deficiencies in bioanalytical method validation, missing product information, and point estimates of cis-phytonadione not being supportive of bioequivalence determination based on trans-phytonadione.

The firm also submitted summary tables of a pilot fasting (Study No. 764-15) BE study comparing Batch #5-F012A of the test product to the RLD. The formulation of Batch #5-F012A is different formulation from the ANDA exhibit batch (Lot# EE60280) used in the pivotal fasting and fed studies. There is no safety concern of the test product based on the pilot study. The firm's statistical analysis of the pilot study met the BE criteria. Per current DB practice, the summary tables of the pilot fasting study are listed for information only (Please refer to **Section 4.1.3**).

Since there is only one strength of the test product and no waiver request, the firm's dissolution data are listed for information only (Please refer to **Section 4.3**).

OSIS Inspection Status

The Office of Study Integrity and Surveillance (OSIS) declined to inspect the clinical site for the pivotal fasting study (Study #765-15), Lambda Therapeutic Research Ltd (Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S.G. Highway, Gota, Ahmedabad – 382481, Gujarat, India), and the clinical site for the pivotal fed study (Study #766-15), Lambda Therapeutic Research Ltd (7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector-15, CBD Belapur, Navi Mumbai-400 614, Maharashtra, India), citing the rationale that "*OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)*" [2]. The OSIS declined to inspect the bioanalytical site for both pivotal fasting and fed studies. (b) (4) (b) (4) citing the rationale that "*Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time*" [3] . The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is considered to be complete.

The application is **inadequate**.

[2] GDRP ANDA 210189-ORIG-1, Clinical PKPD Sites,_Decline to Inspect Lambda Clin , 05/09/2017
[3] GDRP ANDA-209450-ORIG-1, Bioanalytical Site,_No-VAI to (b) (4), 05/05/2017

2 TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1 Drug Product Information[4]

Test Product	Phytonadione Tablets, 5 mg
Reference Product	Mephyton® (phytonadione) Tablets, 5 mg
RLD Manufacturer	Valeant Pharmaceuticals North America
NDA No.	010104
RLD Approval Date	September 30, 1955[5]

***Reviewer's Note:**
Mephyton® (Phytonadione) Tablets 5 mg is listed as RLD in current Orange Book. Lachman Consultant Service Inc. filed a citizen petition on 07/23/2008 for new strengths (2.5 mg, 7.5 mg, and 10 mg) according to dosage recommendation of the RLD (2.5 mg up to 25 mg daily). On 03/18/2010, FDA approved the proposal put forward in the citizen petition. (Docket: FDA-2008-P-0421)[6]. The Office of Generic Drugs will further assess whether the product specific guidance should be modified. It should be noted that the Division of Bioequivalence generally does not accept/approve a higher strength without the conductance of in vivo BE testing[7]. As of the date of completion of the current review, the product specific guidance has not been updated to reflect 2.5, 7.5, and 10 mg as waiver strengths. This will not impact the current review as the applicant has not requested a waiver for any of the aforementioned waiver strengths.

3.2 PK/PD Information[8]

Most recent RLD label (provide embedded document)[9] Please check if an NG/G/J tube study is needed.	010104s023lbl.pdf An NG tube study is not needed as per the RLD label.
Indication	MEPHYTON is indicated in the following 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. MEPHYTON tablets are indicated in: • 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.
Boxed warning	None
Bioavailability	All K vitamins are fat-soluble and are absorbed in the jejunum and ileum and

[4] Electronic Orange Book, search term "Phytonadione". Last accessed: 09/12/2017.
[5] DARRTS: NDA 10104, COR-NDAACTION-03(Approval), 9/30/1955
[6] https://www regulations.gov/document?D=FDA-2008-P-0421-0004
[7] GDRP: ANDA #209373 General BE Review Final Date: 3/28/2017
[8] PKPD information from Online Clinical Pharmacology, Last accessed on 09/12/2017, available at: http://www.clinicalpharmacologyip.com/Forms/Monograph/monograph.aspx?cpnum=487&sec=monphar&t=0
[9] RLD label from Drugs@FDA, available at: https://www.accessdata fda.gov/drugsatfda_docs/label/2004/010104s023lbl.pdf

<table>
<tr><td></td><td>require the presence of bile salts and pancreatic enzymes for absorption. Phylloquinone[10] from cooked spinach was reported to be only 4% as bioavailable as the suspension product of phylloquinone (Konakion). Absorption of vitamin K from spinach is 1.5 times slower compared to the pharmaceutical preparation. Evidence of increased concentrations of blood-coagulation factors occurs within 6-12 hours of an oral dose of phytonadione.</td></tr>
<tr><td>Food Effect</td><td>Not reported in the labeling;
From Online Clinical Pharmacology[11]: Dietary fat enhances absorption. The bioavailability of the spinach-derived phylloquinone increased 3-fold (to 13%) when butter was consumed with the spinach.</td></tr>
<tr><td>Tmax</td><td>Not reported in the labeling.
From Online Clinical Pharmacology[11]: MEPHYTON tablets generally exert their effect within 6 to 10 hours.</td></tr>
<tr><td>Metabolism</td><td>Little is known about the metabolic fate of vitamin K.</td></tr>
<tr><td>Excretion</td><td>Almost no free, unmetabolized vitamin K appears in the bile or urine. High fecal concentrations are attributable to synthesis of the vitamin by intestinal bacteria.</td></tr>
<tr><td>Half-life</td><td>Not reported in the labeling</td></tr>
<tr><td>Dosage and Administration</td><td>MEPHYTON
Summary of Dosage Guidelines
(See circular text for details)
<table><tr><th>Adults</th><th>Initial Dosage</th></tr><tr><td>Anticoagulant-Induced Prothrombin Deficiency
(caused by coumarin or indanedione derivatives)</td><td>2.5 mg-10 mg or up to 25 mg (rarely 50 mg)</td></tr><tr><td>Hypoprothrombinemia due to other causes
(Antibiotics; Salicylates or other drugs; Factors limiting absorption or synthesis)</td><td>2.5 mg-25 mg or more (rarely up to 50 mg)</td></tr></table>
Anticoagulant-Induced Prothrombin Deficiency in Adults
To correct excessively prolonged prothrombin times caused by oral anticoagulant therapy – 2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition. If, in 12 to 48 hours after oral administration, the prothrombin time has not been shortened satisfactorily, the dose should be repeated

Hypoprothrombinemia Due to Other Causes in Adults
If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, antibiotics) is suggested as an alternative to administering concurrent MEPHYTON. The severity of the coagulation disorder should determine whether the immediate administration of MEPHYTON is required in addition to discontinuation or reduction of interfering drugs.

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the</td></tr>
</table>

[10] Phytonadione is synonymous with phylloquinone and Vitamin K1. https://en.wikipedia.org/wiki/Phylloquinone Last accessed 7/17/15.
[11] http://www.clinicalpharmacology-ip.com/Default.aspx Search: mephyton Last access: 9/15/2017

	condition and response obtained. The oral route should be avoided when the clinical disorder would prevent proper absorption. Bile salts must be given with the tablets when the endogenous supply of bile to the gastrointestinal tract is deficient.
Maximum Daily Dose	100 mg (Note: 50 mg × 2 based on dosage and administration information highlighted above)

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance[12]	UCM199670.pdf (Recommended Feb 2010, Revised Sep 2012, Jan 2016) **Reviewer' note:** Per the PSG, Bioequivalence is based on (90% CI): Phytonadione (E isomer (trans-configuration)). Z isomer (cis-configuration) data are supportive evidence of comparable therapeutic outcome. For the Z isomer, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.	
Summary of OGD or DB History	Approved ANDAs:	None
	Pending ANDAs:	Yes, see below
	Controls:	Yes, see below (none from current applicant)
	Protocols:	None[13]
	Pending Citizen Petitions and other legal and regulatory issues:[14] If yes, please comment.	☐ Yes ☒ No
	Pending Developing guidance	☐ Yes ☒ No As of 9/12//2017[15]

Pending ANDA (DARRTS search as of 09/12/2017)

ANDA#	DARRTS	DARRTS	BE Review Status

[12] OGD Guidance on Phytonadione Tablets, (Recommended Feb 2010, Revised Sep 2012, Jan 2016), available at: https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf
[13] DBE Protocol Database. http://ogd fda.gov/seltrack/ProtocolGrid.ASP, Search term: phytonadione, Last accessed on 09/12/2017
[14] DLRS policy alert updates, search as of 09/12/2017, http://sharepoint fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx
[15] \\cdsnas\ogds11\Office of Bioequivalence\BE Guidances Under Development

	Status	Status Date	
(b) (4)			
210189 (Current ANDA)	Pending	1/3/2017	N/A
209373	Pending	8/23/2017	Inadequate[16]
(b) (4)			

Controls (OGD Controls Correspondence Document Database, as of 09/12/2017)

Ctl No	Title	Description	Status	From
(b) (4)				

[16] GDRP ANDA-209373-ORIG-1 Documents *A209373N000DR_N06292016.docx* 03/30/2017
(b) (4)

3.5 Pre-Study Bioanalytical Method Validation[a,b]

Method Validation for the Fasting Study

Information Requested	Data	
Bioanalytical method validation report location	**Appendix 16.5.3**	
Analyte	Trans Phytonadione and Cis Phytonadione	
Internal Standard (IS)	Trans Phytonadione D7 for Trans Phytonadione Cis Phytonadione D7 for Cis Phytonadione	
Method description	(b) (4)	
	Trans Phytonadione	Cis Phytonadione
Limit of quantitation (ng/mL)	0.401 ng/mL	0.300 ng/mL
Average recovery of drug (%) in normal human plasma (LQC, MQC and HQC)	LQC: 43.9 % MQC: 40.4 % HQC: 39.2 %	LQC: 35.4 % MQC: 36.2 % HQC: 37.2 %
Average recovery of IS (%) in normal human plasma	35.9 %	35.2 %
Average recovery of drug (%) in UV light exposed human plasma (LQC, MQC and HQC)	38.8 %, 41.6 % and 39.0 %	35.9 %, 37.5 % and 37.4 %
Average recovery of IS (%) in UV light exposed human plasma	38.7 %	38.0 %
Standard curve concentrations (ng/mL)	0.401 to 100.235 ng/mL	0.300 to 25.000 ng/mL
QC concentrations (ng/mL) in normal human plasma	LOQQC: 1.436 ng/mL LQC: 2.223 ng/mL LMQC: 12.393 ng/mL MQC: 45.017 ng/mL HQC: 78.654 ng/mL DQC: 301.509 ng/mL	LOQ QC: 0.310 ng/mL LQC: 0.887 ng/mL LMQC: 2.534 ng/mL MQC: 10.136 ng/mL HQC: 19.005 ng/mL DQC: 75.006 ng/mL
QC concentrations (ng/mL) In UV light exposed human plasma	LOQQC: 0.406 ng/mL LQC: 1.193 ng/mL LMQC: 11.363 ng/mL MQC: 43.987 ng/mL HQC: 77.624 ng/mL	LOQ QC: 0.310 ng/mL LQC: 0.887 ng/mL LMQC: 2.534 ng/mL MQC: 10.136 ng/mL HQC: 19.005 ng/mL
Precision and accuracy for normal human plasma		

QC Intraday precision range (%)	1.1 % to 10.6 %	1.0 % to 9.8 %
QC Intraday accuracy range (%)	101.7 % to 108.7 %	86.7 % to 103.5 %
QC Interday precision range (%)	2.5 % to 13.2 %	2.8 % to 15.5 %
QC Interday accuracy range (%)	102.3 % to 110.3 %	89.3 % to 104.3 %
Accuracy for UV light exposed human plasma		
QC Intraday accuracy range (%)	99.2 % to 108.3 %	91.2 % to 104.6 %
QC Interday accuracy range (%)	101.0 % to 109.1 %	96.0 % to 103.9 %
Precision for UV light exposed human plasma		
QC Intraday precision range (%)	0.5 % to 4.0 %	1.2 % to 3.2 %.
QC Interday precision range (%)	2.2 % to 11.5 %.	2.5 % to 5.0 %.
Bench-top stability (hrs) for normal as well as UV light exposed human plasma	19.0 hours (b) (4) (b) (4))	
Stock stability (days)	29 days (at -22 ± 5°C) for stock solutions and stock dilutions of both the analytes and spiking solutions at lower level of both the analytes 23 days (at -22 ± 5°C) for stock solutions of both the ISTDs	
Processed stability (hrs) for UV light exposed human plasma	199.0 hours (within 2 to 8°C) 2.0 hours (in ice-cold water bath)	
Freeze-thaw stability (cycles) for normal as well as UV light exposed human plasma	4 cycles (at -65 ± 10°C) (b) (4) (b) (4) (b) (4) eet)	
Long-term storage stability (days)	129 days at -65 ± 10°C & -22 ± 5°C (in UV light exposed human plasma) 129 days at -65 ± 10°C (in normal human plasma) 130 days at -22 ± 5°C (in normal human plasma) **Module 5.3.1.4/Method Validation Report/MV(I)-221-16 (Addendum-I)/page 24 of 182**	
Dilution integrity for normal human plasma	301.509 ng/mL diluted 5 fold	75.006 ng/mL diluted 5 fold
Selectivity	The peaks of Trans-Phytonadione (coded as 'A1'), Cis-Phytonadione (coded as 'A2'), Trans- Phytonadione-d7 (ISTD-1) and Cis-Phytonadione-d7 (ISTD-2) were free from any overlapping peaks[18].	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 4A
[b]: Module 5.3.1.4, Fasting Method Validation Report, MV(I)-221-16 and MV(I)-221-16 (Addendum-1)

Method Validation for the Fed Study

Information Requested	**Data**
Bioanalytical method validation report location	**Appendix 16.5.3**
Analyte	Trans Phytonadione and Cis Phytonadione
Internal Standard (IS)	Trans Phytonadione D7 for Trans Phytonadione Cis Phytonadione D7 for Cis Phytonadione

[18] EDR: ANDA #210189 Section 5.3.1.4 Method Validation Report Page 67 Submit Date: 1/3/2017

Method description	(b) (4)	
	Trans Phytonadione	Cis Phytonadione
Limit of quantitation (ng/mL)	1.002 ng/mL	1.001 ng/mL
Average recovery of drug (%) in normal human plasma (LQC, MQC and HQC)	68.9 %, 66.8 % and 74.5 %	63.3 %, 65.0 % and 68.0 %
Average recovery of IS (%) in normal human plasma	80.3 %	78.9 %
Average recovery of drug (%) in UV light exposed human plasma (LQC, MQC and HQC)	70.7 %, 64.8 % & 58.2 %	64.7%, 62.3% & 52.2 %
Average recovery of IS (%) in UV light exposed human plasma	77.1 %	75.2 %
Standard curve concentrations (ng/mL)	1.002 to 501.625 ng/mL	1.001 to 99.137 ng/mL
QC concentrations (ng/mL) in normal human plasma	LOQQC: 1.681 ng/mL LQC: 3.563 ng/mL LMQC: 54.272 ng/mL MQC: 206.838 ng/mL HQC: 389.668 ng/mL DQC: 1489.190 ng/mL	LOQ QC: 1.038 ng/mL LQC: 2.966 ng/mL LMQC: 12.358 ng/mL MQC: 47.529 ng/mL HQC: 79.215 ng/mL DQC: 297.058 ng/mL
QC concentrations (ng/mL) In UV light exposed human plasma	LOQQC: 1.013 ng/mL LQC: 2.895 ng/mL LMQC: 53.604 ng/mL MQC: 206.170 ng/mL HQC: 389.000 ng/mL	LOQ QC: 1.038 ng/mL LQC: 2.966 ng/mL LMQC: 12.358 ng/mL MQC: 47.529 ng/mL HQC: 79.215 ng/mL
Precision and accuracy for normal human plasma		
QC Intraday precision range (%)	0.8 % to 4.5 %	1.4 % to 4.8 %
QC Intraday accuracy range (%)	89.8 % to 99.6 %	88.7 % to 102.1 %
QC Interday precision range (%)	3.8 % to 8.9 %	3.8 % to 8.6 %
QC Interday accuracy range (%)	96.5 % to 103.7 %	93.4 % to 104.1 %
Precision and accuracy for UV light exposed human plasma		
QC Intraday accuracy range (%)	95.1 % to 103.8 %	90.7 % to 105.4 %
QC Interday accuracy range (%)	94.8 % to 103.0 %	95.3 % to 106.6 %
QC Intraday precision range (%)	1.2 % to 2.4 %	1.1 % to 2.3 %
QC Interday precision range (%)	5.1 % to 7.3 %	3.2 % to 7.4 %

Bench-top stability (hrs) for normal as well as UV light exposed human plasma	21.0 hours (b) (4) (b) (4)	
Stock stability (days)	16 days (at -22 ± 5°C) for stock solutions and spiking solutions at lower level of both the analytes 16 days (at -22 ± 5°C) for stock solutions of both the ISTDs	
Processed stability (hrs) for UV light exposed human plasma	154.0 hours (within 2 to 8°C) 2.0 hours ((b) (4) (b) (4)	
Freeze-thaw stability (cycles) for normal as well as UV light exposed human plasma	5 cycles (at -65 ± 10°C) (b) (4) (b) (4)	
Long-term storage stability (days)	138 days at -65 ± 10°C **Module 5.3.1.4/Method Validation Report/MV(I)-226-16 (Addendum-I)/page 21 of 181**	
Dilution integrity for normal human plasma	1489.190 ng/mL diluted 5 fold	297.058 ng/mL diluted 5 fold
Selectivity	The peaks of Trans-Phytonadione (coded as 'A1'), Cis-Phytonadione (coded as 'A2'), Trans- Phytonadione-d7 (ISTD-1) and Cis-Phytonadione-d7 (ISTD-2) were free from any overlapping peaks	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 4B
[b]: Module 5.3.1.4, Fed Method Validation Report, MV(I)-226-16 and MV(I)-226-16 (Addendum-1)

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No Module 5.3.1.4, Bioanalytical SOPs
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? If not, was cross validation study conducted?	☒ Yes ☐ No
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No See comments below
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☐ Yes ☒ No See comments below

Comments on the Pre-Study Method Validation: Inadequate

- The firm developed and validated analytical method that simultaneously measure the concentrations of trans-phytonadione and cis-phytonadione in human plasma (exposed to UV light) using LC-MS/MS.

- Trans-phytonadione is an endogenous molecule. (b) (4) (b) (4)

(b) (4). Per the RLD labeling, "*vitamin K1 (phytonadione) is fairly rapidly degraded by light*"[19],[20]. (b) (4)

(b) (4)

- (b) (4)

- For the fasting study method validation, the storage time for the long term stability samples (129 days at -65 ± 10°C & -22 ± 5°C in UV light exposed human plasma, 129 days at -65 ± 10°C in normal human plasma, and 130 days at -22 ± 5°C in normal human plasma) is sufficient to cover the maximum storage period of the study samples from the fasting BE study (113 days at -65ºC ± 10ºC).

- For the fed study method validation, the storage time for the long term stability samples (138 days at -65 ± 10°C in normal human plasma) is sufficient to cover the maximum storage period of the study samples from the fed BE study (137 days at -65ºC ± 10ºC).

- The recovery of trans-phytonadione QC samples and cis-phytonadione QC samples in the method validation (Report #MV(I)-221-16) for the fasting BE study (Study #765-15) were substantially lower than that in the method validation (Report # MV(I)-226-16) for the fed BE study (Study #766-15). For example, in

[19] Drugs@FDA: Mephyton Last Access: 9-16-2018
[20] Kamm et al. (1942) The Ultraviolet Absorption of Vitamin K and the Effect of Light on the Vitamin. Journal of Biochemistry.
[21] EDR: ANDA #210189 Section 5.3.1.4 Method Validation Report Page 71 Submit Date: 1/3/2017
[22] EDR: ANDA #210189 Section 5.3.1.4 Method Validation Report Page 150 Submit Date: 1/3/2017

the fasting method validation (Report #MV(I)-221-16), the average recovery of Trans-Phytonadione ranged 39.2%-43.9% in normal human plasma and ranged 39.0%-41.6% in UV light exposed human plasma; whereas in the fed method validation (Report #MV(I)-226-16), the average recovery of Trans-Phytonadione ranged 66.8%-74.5% in normal human plasma and ranged 58.2%-70.7% in UV light exposed human plasma. The firm is requested to explain the difference in recovery of QC samples between the two method validation reports.

- Per control reviewer of 110232[23], the literature data[24,25] implied that cis- and trans-phytonadione are stable and would not automatically inter-convert without enzyme. This is supported by other ANDAs submitted for this drug product[26]. The firm demonstrated acceptable stability in its inter-conversion experiment[27].

The pre-study validation for trans-phytonadione and cis-phytonadione is **inadequate**.

[23] V:\DIVISION\BIO\Guidance reviews\Phytonadione_Tabs_010104.pdf

[24] Gutnick DL, Dunphy PH, Sakamoto H, Phillips PG, Brodie AF. Cis-Trans isomerism in naphthoquinones: interconversion and participation in oxidative phosphorylation. Science 1967; 158(3807):1469-71

[25] Samuel JD and Rapoport H. The reconstitution of oxidative phosphorylation in *Mycobacterium phleiwith cis- and trans-Phylloquinone.* Evidence agains isomerization. Biochemistry 1968; 7(7):2650-2. http://pubs.acs.org/doi/pdf/10.1021/bi00847a030

[26] GDRP ANDA-209373-ORIG-1, Documents, *A209373N000DB_N06292016.docx*, 03/30/2017

[27] EDR: ANDA #210189 Section 5.3.1.4 Method Validation Report Page 171 Submit Date: 1/3/2017

3.6 In Vivo Studies

Summary of Bioavailability Studies
Baseline Corrected Phytonadione (E isomer (trans-configuration))[765-15 (Fasting)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters ± SD (%CV)						Study Report Location
					T_{max} (h)[#]	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)	$t_{½}$ (h)	λ_z (1/h)	
765-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's Test Product relative to that of Reference Product in normal, healthy, adult subjects under fasting conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, replicate, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fasting conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 32 [M-32 / F-0] Healthy Subjects Age Mean: 31.8 ± 8.38 Range:21-44	6.500 (5.000 - 13.000)	16.285 ± 18.2591 (112.1)	122.129 ± 116.8766 (95.7)	135.566 ± 120.2357 (88.7)^	3.845 ± 1.3718 (35.7)^	0.209 ± 0.0919 (44.0)^	**5.3.1.2: study-report-body Page 7 and 56 of 286**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.500 (5.000 - 13.000)	15.722 ± 14.2112 (90.4)	122.312 ± 123.9242 (101.3)	128.263 ± 127.7669 (99.6)$	3.582 ± 1.0904 (30.4)$	0.213 ± 0.0708 (33.2)$	

[#]T_{max} is represented as median (min-max) value.
^N = 59 observations and $N = 63 observations.
Note 1: Subject nos (b) (6) (Period-III), (b) (6) (period-IV) & (b) (6) period-IV) had inadequate time-points for the computation of elimination phase pharmacokinetic parameters and hence same could not be calculated.
Note 2: Subjects having AUC_%Extrap_obs > 20% are excluded from calculation of elimination phase pharmacokinetic parameters.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2A

Baseline Uncorrected Phytonadione (E isomer (trans-configuration)) [765-15 (Fasting)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters ± SD (%CV)						Study Report Location
					T_{max} (h)[#]	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{½}$ (h)	λ_z (1/h)	
765-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's Test Product relative to that of Reference Product in normal, healthy, adult subjects under fasting conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, replicate, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fasting conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 32 [M-32 / F-0] Healthy Subjects Age Mean: 31.8 ± 8.38 Range: 21-44	6.500 (5.000 - 13.000)	16.998 ± 18.4948 (108.8)	137.517 ± 124.2058 (90.3)	155.072 ± 131.0111 (84.5)^	5.210 ± 1.4327 (27.5)^	0.142 ± 0.0330 (23.3)^	**5.3.1.2: study-report-body Page 8 and 57 of 286**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.500 (5.000 - 13.000)	16.481 ± 14.6951 (89.2)	138.594 ± 136.5416 (98.5)	154.955 ± 147.8440 (95.4)[$]	5.160 ± 1.0056 (19.5)[$]	0.139 ± 0.0272 (19.5)[$]	

[#]T_{max} is represented as median (min-max) value.
^N = 60 observations and [$]N = 61 observations.
Note 1: Subject nos. (b) (6) Period-III) (b) (6) period-IV) had inadequate time-points for the computation of elimination phase pharmacokinetic parameters and hence same could not be calculated.
Note 2: Subjects having AUC_%Extrap_obs > 20% are excluded from calculation of elimination phase pharmacokinetic parameters.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2B

Baseline Corrected Phytonadione (Z isomer (cis-configuration)) [765-15 (Fasting)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters ± SD (%CV)						Study Report Location
					T_{max} (h)[#]	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng h/mL)	$t_{½}$ (h)	λ_z (1/h)	
765-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's Test Product relative to that of Reference Product in normal, healthy, adult subjects under fasting conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, replicate, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fasting conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 32 [M-32 / F-0] Healthy Subjects Age Mean: 31.8 ± 8.38 Range: 21-44	6.017 (5.000 - 8.000)	3.832 ± 3.2854 (85.7)	24.689 ± 22.4197 (90.8)	35.055 ± 24.0473 (68.6)^	4.880 ± 1.4651 (30.0)^	0.154 ± 0.0457 (29.6)^	**5.3.1.2: study-report-body Page 10 and 58 of 286**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.000 (5.000 - 8.000)	3.492 ± 2.6803 (76.7)	22.292 ± 21.3654 (95.8)	31.790 ± 23.9624 (75.4)$	4.743 ± 1.5539 (32.8)$	0.164 ± 0.0624 (38.0)$	

[#]T_{max} is represented as median (min-max) value.
^N = 45 observations and $N = 46 observations.
Note 1: Some subjects had inadequate time-points for the computation of elimination phase pharmacokinetic parameters and hence same could not be calculated.
Note 2: Subjects having AUC_%Extrap_obs > 20% are excluded from calculation of elimination phase pharmacokinetic parameters.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2C

Baseline Uncorrected Phytonadione (Z isomer (cis-configuration)) [765-15 (Fasting)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters ± SD (%CV)						Study Report Location
					T_{max} (h)[#]	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)	$t_{½}$ (h)	λ_z (1/h)	
765-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's Test Product relative to that of Reference Product in normal, healthy, adult subjects under fasting conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, replicate, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fasting conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 32 [M-32 / F-0] Healthy Subjects Age Mean: 31.8 ± 8.38 Range: 21-44	6.017 (5.000 - 8.000)	3.833 ± 3.2877 (85.8)	24.713 ± 22.4831 (91.0)	35.105 ± 24.1606 (68.8)[^]	4.883 ± 1.4648 (30.0)[^]	0.154 ± 0.0457 (29.7)[^]	**5.3.1.2: study-report-body Page 11 and 59 of 286**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.000 (5.000 - 8.000)	3.496 ± 2.6891 (76.9)	22.378 ± 21.6082 (96.6)	31.974 ± 24.4712 (76.5)[$]	4.763 ± 1.5606 (32.8)[$]	0.163 ± 0.0625 (38.2)[$]	

[#]T_{max} is represented as median (min-max) value.
[^]N = 45 observations and [$]N = 46 observations.
Note 1: Subject n (b) (6) Period-I) had inadequate time-points for the computation of elimination phase pharmacokinetic parameters and hence same could not be calculated.
Note 2: Subjects having AUC_%Extrap_obs > 20% are excluded from calculation of elimination phase pharmacokinetic parameters.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2D

Baseline Corrected Phytonadione (E isomer (trans-configuration))[766-15 (Fed)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					T_{max} (h)*	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)	$t_{½}$ (h)	λ_z (1/h)	
766-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product in normal, healthy, adult subjects under fed conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fed conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 45 [M-45 / F-0] Healthy Subjects Age Mean: 29.9 ± 5.94 Range: 19-43	6.000 (3.000 - 7.500)	235.806 ± 94.6625 (40.1)	1272.022 ± 601.5546 (47.3)	1324.481 ± 618.0486 (46.7)	6.385 ± 2.6240 (41.1)	0.123 ± 0.0422 (34.2)	**5.3.1.2: study-report-body Page 6 and 49 of 218**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.000 (2.517 - 8.000)	231.987 ± 92.9100 (40.0)	1154.068 ± 593.8904 (51.5)	1202.072 ± 605.7201 (50.4)	5.963 ± 2.0809 (34.9)	0.132 ± 0.0497 (37.6)	

*T_{max} is represented as median (min-max) value.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2E

Baseline Uncorrected Phytonadione (E isomer (trans-configuration))[766-15 (Fed)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					T_{max} (h)*	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{½}$ (h)	λ_z (1/h)	
766-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product in normal, healthy, adult subjects under fed conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fed conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 45 [M-45 / F-0] Healthy Subjects Age Mean: 29.9 ± 5.94 Range: 19-43	6.000 (3.000 - 7.500)	236.083 ± 94.8214 (40.2)	1278.366 ± 606.3961 (47.4)	1335.031 ± 626.2007 (46.9)	6.543 ± 2.7095 (41.4)	0.121 ± 0.0419 (34.7)	**5.3.1.2: study-report-body Page 7 and 49 of 218**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.000 (2.517 - 8.000)	232.323 ± 93.1511 (40.1)	1161.694 ± 600.8988 (51.7)	1213.664 ± 616.2205 (50.8)	6.084 ± 2.1167 (34.8)	0.129 ± 0.0487 (37.6)	

*T_{max} is represented as median (min-max) value.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2F

Baseline Corrected Phytonadione (Z isomer (cis-configuration))[766-15 (Fed)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					T_{max} (h)*	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{½}$ (h)	λ_z (1/h)	
766-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product in normal, healthy, adult subjects under fed conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fed conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 45 [M-45 / F-0] Healthy Subjects Age Mean: 29.9 ± 5.94 Range: 19-43	6.000 (3.000 - 7.500)	34.661 ± 13.3227 (38.4)	185.800 ± 87.5721 (47.1)	196.038 ± 89.8738 (45.8)	5.064 ± 2.3946 (47.3)	0.165 ± 0.0699 (42.3)	**5.3.1.2: study-report-body Page 8 and 50 of 218**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.000 (2.517 - 8.000)	31.272 ± 12.2546 (39.2)	153.527 ± 79.2297 (51.6)	162.576 ± 81.4551 (50.1)	4.683 ± 2.3839 (50.9)	0.186 ± 0.0880 (47.3)	

*T_{max} is represented as median (min-max) value.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2G

Baseline Uncorrected Phytonadione (Z isomer (cis-configuration))[766-15 (Fed)][a]

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					T_{max} (h)*	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{½}$ (h)	λ_z (1/h)	
766-15	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product in normal, healthy, adult subjects under fed conditions and to assess the bioequivalence. **Safety:** To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fed conditions.	**Test Product-T:** Phytonadione Tablets, USP 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Batch No.: EE60280	N = 45 [M-45 / F-0] Healthy Subjects Age Mean: 29.9 ± 5.94 Range: 19-43	6.000 (3.000 - 7.500)	34.661 ± 13.3227 (38.4)	185.800 ± 87.5721 (47.1)	196.038 ± 89.8738 (45.8)	5.064 ± 2.3946 (47.3)	0.165 ± 0.0699 (42.3)	**5.3.1.2: study-report-body Page 9 and 50 of 218**
			Reference Product-R: MEPHYTON® (Phytonadione) Tablets 5 mg Dose: 5 mg Dosage Form: Tablet Route: Oral Lot No.: 14A094P		6.000 (2.517 - 8.000)	31.272 ± 12.2546 (39.2)	153.527 ± 79.2297 (51.6)	162.576 ± 81.4551 (50.1)	4.683 ± 2.3839 (50.9)	0.186 ± 0.0880 (47.3)	

*T_{max} is represented as median (min-max) value.

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 2H

3.7 OSIS Status

3.7.1 Clinical Site

Office of Study Integrity and Surveillance (OSIS) declined to inspect the clinical site for the fasting study (Study #765-15), Lambda Therapeutic Research Ltd (Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S.G. Highway, Gota, Ahmedabad – 382481, Gujarat, India), and the clinical site for the fed study (Study #766-15), Lambda Therapeutic Research Ltd (7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector-15, CBD Belapur, Navi Mumbai-400 614, Maharashtra, India), citing the rationale that "*OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)*" [28], also shown below:

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Lambda Therapeutic Research, Ltd.	Plot No. 38, Near Silver Oak Club, Sarkhej-Gandhinagar Highway, Gota, Ahmedabad, Gujarat, India
Clinical	Lambda Therapeutic Research, Ltd.	7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector-15, CBD Belapur, Navi Mumbai, Maharashtra, India

3.7.2 Analytical Site

The OSIS declined to inspect the bioanalytical site, [redacted] citing the rationale that "*Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time*", [29] also shown below:

[28] GDRP ANDA 210189-ORIG-1, Clinical PKPD Sites,_Decline to Inspect Lambda Clin , 05/09/2017
[29] GDRP ANDA-209450-ORIG-1, Bioanalytical Site,_No-VAI [redacted],

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
		(b) (4)

In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer.

The OSIS inspection status for the clinical and analytical sites of the current ANDA are considered to be complete and adequate

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Pivotal Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information[a]

Study Number	765-15
Study Title	An open label, balanced, randomized, two-treatment, two-sequence, four period, replicate, crossover, single dose, oral bioequivalence study of Phytonadione Tablets 5 mg of Cadila Healthcare Ltd., India comparing with MEPHYTON® (Phytonadione) Tablets 5 mg of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 in normal, healthy, adult subjects under fasting condition
Study Type	☑ *In-vivo* BE ☐ *In-vitro* BE ☐ Permeability ☐ Other
Submission Location:	
Study Report:	location, ex: 5.3.1.2
Validation Report:	location, ex: 5.3.1.4
Bio-analytical Report:	location, ex: 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India. Tel. No.: +91-79-40202020 Fax. No.: +91-79-40202021
Principal Clinical Investigator (Name, Email)	Dr. Tarak Parikh, MD. tarakparikh@lambda-cro.com
Dosing Date[b]	Period-I : 27 June 2016 to 01 July 2016 Period-II : 04 July 2016 to 08 July 2016 Period-III : 11 July 2016 to 15 July 2016 Period-IV : 18 July 2016 to 22 July 2016
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Principal Analytical Director	
Analysis Dates[c]	
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	113 days (30 June 2016 to 21 October 2016) At -65 ± 10 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	129 days at -65 ± 10°C & -22 ± 5°C (in UV light exposed human plasma) 129 days at -65 ± 10°C (in normal human plasma) 130 days at -22 ± 5°C (in normal human plasma)

LTSS Data Location	Module 5.3.1.4/Method Validation Report/MV(I)-221-16 (Addendum-I)/page 24 of 182

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 10 (A)
[b]: Module 5.3.1.4, Fasting Study 765-15, Study Report Body
[b]: Module 5.3.1.4, Fasting Study 765-15, Bioanalytical Report

4.1.1.1.2 Product (Bio-batch) Information[a]

Product	Test	Reference
Treatment ID	T	R
Product Name	Phytonadione Tablets, USP 5 mg	MEPHYTON® (Phytonadione) Tablets 5 mg
Manufacturer	Cadila Healthcare Limited, Matoda, India	**Manufactured By:** Valeant Pharmaceuticals, Inc. Steinbach, MB R5G 1Z7 Canada **Distributed By:** Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807
Batch/Lot No.	EE60280 (Note: Mother Batch.No: EE60235)	14A094P
Manufacture Date	May 2016	N/A
Expiration Date	N/A	July 2016
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4) Tablets	N/A
Production Batch Size	Tablets	N/A
Potency	100.9%	97.4%
Uniformity of dosage units (by weight variation) (mean, %CV)	Mean: 102.5 % CV: 0.4% AV: 2.0	N/A
Dose Administered	1 x 5 mg	1 x 5 mg
Route of Administration	Oral	Oral

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 11

Are the test and reference products expired at the time of study? **If Yes, please comment.**	☐ Yes ☒ No Dosing Date: 27 June 2016 to 22 July 2016 Test Manufacture Date: May 2016 Ref Exp: July 2016
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment.**	☒ Yes ☐ No Batch #EE60280 (Mother Batch.#EE60235) is used for both in vivo and in vitro studies.
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment.**	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%?	☒ Yes ☐ No

If No, please comment.	

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study[a]

Number of Subjects	Enrolled: 38 Dosed: Period-I (38); Period-II (34); Period-III (32); Period-IV (32); Completed: 32 Samples Analyzed: 32 Statistically Analyzed: 32
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	The venous blood samples were to be withdrawn at -48.000, -42.000, -36.000, -30.000, -24.000, -18.000, -12.000, -6.000, pre-dose (0.000 hour), 1.500, 3.000, 4.000, 5.000, 6.000, 6.500, 7.000, 7.500, 8.000, 9.000, 10.000, 11.000, 12.000, 13.000, 16.000, 20.000 and 24.000 hours following drug administration in each period.
IRB Approval	☒ Yes Date: 29 March 2016 ☐ No
Informed Consent	☒ Yes Date: 29 March 2016 ☐ No
Length of Fasting	Dosing was carried out in the morning after an overnight fast of at least 10 hours. Fasting continued for 4 hours post-dose.
Length of Confinement	Subjects will be housed in the clinical facility at least 60 hours before administration of the dose and will continue to remain in the clinical facility for at least 24 hours after administration of the investigational medicinal product in all the periods.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

[a]: Data in the table are from Module 5.3.1.2, Fasting Study 765-15, Study Report Body and Module 5.3.1.2, Fasting Study 765-15, Study Protocol

Comments on Study Design: Inadequate

- Per the RLD labeling, "*vitamin K1 (phytonadione) is fairly rapidly degraded by light*". According to the description of dosing, PK blood sample collection and sample processing in study report Section 9.4.1 and Section 9.5.4, (b) (4) (b) (4)

- Per control reviewer of 110232[30], "*The biological activity of cis-vitamin K1 is far less than that of trans-vitamin K1. Therefore, the assay used for the determination of phytonadione levels in plasma should be specific to trans-isomer of vitamin K. The firm is advised to determine the potencies (in terms of each isomer) of the lots of the test and reference drug products to be used in the study. It is recommended that the potency for the lot of the reference product be within 5% of that for the test product.*" The potency for the test product batch (Batch #EE60280 [Mother Batch.#EE60235]) is 100.9%, which is within 5% of that for the reference product (97.4% for Lot #14A094P). However, the firm did not provide the potencies of each phytonadione isomer (trans- and cis-) in the test and RLD product drug lots used in the study. The firm will be asked to provide the above mentioned information.

- The Draft Guidance on Phytonadione Tablets[31] recommends that the applicant measure baseline phytonadione levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. The firm's collection of pre-dose plasma sample is consistent with the guidance.

- Tmax and half-life of trans- and cis-phytonadione are not reported in the RLD label[32]. (b) (4) (b) (4) (b) (4) The sampling scheme in the fasting study is sufficient to accurately capture Cmax and Tmax of trans-phytonadione and cis-phytonadione (refer PK results to **Section 4.1.1.4**).

The fasting study design is **inadequate**.

[30] V:\DIVISION\BIO\Guidance reviews\Phytonadione_Tabs_010104.pdf
[31] OGD Guidance on Phytonadione Tablets, (Recommended Feb 2010, Revised Sep 2012, Jan 2016), available at: https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf
[32] RLD label from Drugs@FDA, available at: https://www.accessdata fda.gov/drugsatfda_docs/label/2004/010104s023lbl.pdf

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects[a]

Study No. 765-15			
Parameters		**Treatment Groups**	
		Test Product N = 32	**Reference Product N = 32**
Age (years)	Mean ± SD	31.8 ± 8.38	31.8 ± 8.38
	Range	21-44	21-44
Age Groups	< 18	0 (0%)	0 (0%)
	18-40	26 (81.25%)	26 (81.25%)
	41-64	06 (18.75%)	06 (18.75%)
	65-75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	32 (100%)	32 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	32 (100%)	32 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	21.477 ± 2.0168	21.477 ± 2.0168
	Range	18.57-24.87	18.57-24.87
Other Factors		NA	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 7 (A)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information[a]

Study No. 765-15					
Subject No.	**Reason for dropout / Replacement**		**Period**	**Replaced?**	**Replaced with**
(b) (6)	The subject reported to the facility with complaint of dog bite near his left ankle joint. Hence, he was withdrawn from the study on medical grounds.		II	No	N/AP
	Time and date of last	**Last IMP administered**			

Study No. 765-15					
Subject No.	**Reason for dropout / Replacement**		**Period**	**Replaced?**	**Replaced with**
	IMP administered				
	08:16 hours 30 June 2016	Reference Product-R			
(b) (6)	The subject did not report to the facility for Period-II check-in. He was tried to be contacted telephonically. However, he was not traceable. Hence, he was considered to have discontinued from the study on his own accord.		II	No	N/AP
	The subject did not report to the facility for Period-II check-in. He was tried to be contacted telephonically. However, he was not traceable. Hence, he was considered to have discontinued from the study on his own accord.		II	No	N/AP
	The subject did not report to the facility for Period-II check-in. He was tried to be contacted telephonically. However, he was not traceable. Hence, he was considered to have discontinued from the study on his own accord.		II	No	N/AP
	The subject did not report to the facility for Period-III check-in. He was tried to be contacted telephonically. However, he was not traceable. Hence, he was considered to have discontinued from the study on his own accord.		III	No	N/AP
	The subject did not report to the facility for Period-III check-in. He was tried to be contacted telephonically. However, he was not traceable. Hence, he was considered to have discontinued from the study on his own accord.		III	No	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 12 (A)

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

Reviewer Comments on Dropout Subject:

The reviewer checked the record from the firm's case report form (CRF, Module 5.3.1.2) and confirmed that the dropout reasons documented in CRF for the 6 subjects are consistent with the table above. One subject was withdrawn on medical grounds and the other 5 subjects were considered to have discontinued from the study on the subjects' own accord. The dropouts are consistent with the study protocol Section 10.3, Withdrawl Criteria, and therefore these dropouts are acceptable.

Per the fasting study protocol (Version 01, 04Feb2016) Section 8.10.2: *Samples of subjects completing at least 2 treatment periods (having one Test and one Reference) will be analyzed. In case of dropouts, samples of such subjects will not be taken for analysis* [i.e. final statistical analysis]. The Period-I and Period-II PK samples of Subjects (b) (6) (b) (6) were analyzed; PK samples of the other 4 dropout subjects were not analyzed

(fasting bioanalytical report Section 7.1). The handling of sample assay for dropout subjects is consistent with the study protocol.

Per the Fasting Study Protocol (Version 01, 04Feb2016) Section 11.1.4:

> *In case of Scaled Average Bioequivalence Approach (SABE), statistical analysis will be performed on the data obtained from subjects completing all the treatment periods, however the subject completing at least three treatment periods with two reference will be included for calculation of within-subject standard deviation with respect to Reference Product but will not be included for the statistical analysis. In case of Average Bioequivalence Approach, subjects who have one evaluable test period and at least one evaluable reference period will be included in the statistical analysis.*

Per the fasting study report Section 11.1 and Section 11.4, only the 32 subjects completing all four periods were included in the scaled average bioequivalence analysis.

The firm's handling of dropout is acceptable.

4.1.1.2.3 Study Adverse Events[a]

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. 765-15	
	Test Product	Reference Product
Body as a whole	0%	0%
Cardiovascular	0%	0%
Gastrointestinal	0%	0%
Other organ system		
Animal bite	0%	01 (2.70%)
Blood creatinine increased	0%	01 (2.70%)
Total	**0 (0.00%)**	**02 (5.40%)**

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 8 (A)

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No

If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

Reviewer Comments on Adverse Event:

There were no serious AE. Two (2) adverse events (AEs) were reported by two (2) subjects during the conduct of the study and both were after administration of the Reference product. Both AEs were mild in nature. One AE was significant but the causality assessment was judged as unrelated (animal bite) and the other AE was judged as unlikely.

The AE profile observed during the pivotal fasting bioequivalence study is considered comparable for the test and reference products.

4.1.1.2.4 Protocol Deviations[a]

Study No. 765-15		
Type	**Subject #s (Test T)**	**Subject #s (Ref. R)**
Pre-dose sample volume As per the protocol, each of 3.5 mL of blood sample volume was to be collected from each subject in each period. However, for the subjects due to inattentiveness of study personnel, 4.0 mL of blood sample volume was collected at -24.000 hours time point in Period-I.	(b) (6)	-
Pre-dose housing As per the protocol, the subjects were to be housed in the clinical facility for at least 60 hours before administration of IMP. However, deviations were observed in this regard due to check-in related logistics reason in Period-I and subjects came late in Period-III & IV. Refer Appendix No. 16.2.2 of Clinical Study Report for details.	(b) (6)	
End study laboratory assessment As per the protocol, laboratory tests for hematology, biochemistry (except random glucose, sodium, potassium and chloride) and coagulation tests (APTT and PT) were to be performed at the end of the study to assess the post-study safety of the subjects. However, post-study laboratory assessment was not performed for the Subject No (b) (6) as he did not report to the clinical facility in spite of several follow-ups. Hence, he was considered as lost to follow-up.	-	-

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 13 (A)

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Reviewer's Comments on Protocol Deviations

- The deviations in the pre-dose blood volume collection and check-in time will not impact study outcome.

- The deviation of not conducting end of study laboratory assessment of Subject (b) (6) will not impact study outcome because this subject dropped out after Period-I (refer to Section **4.1.1.2.2 Dropout Information**).

- Per study protocol Section 8.9.1, *all post dose blood samples will be collected within ± 02 minutes from schedule time….Post dose samples not collected within this time frame from scheduled time will be documented as sampling deviations*. The firm did not report any PK sample time deviations in its protocol deviation list. However, the reviewer noticed that two samples (Subject (b) (6) Period-II_1.5h and Subject (b) (6) Period-II_9h) were collected 3 minutes later than the nominal time per the firm's fasting SAS dataset. As these deviations are marginal and are not expected to impact study outcome, the reviewer will not pursue this issue.

Reviewer's Overall Comments on Dropout/Adverse Events/Protocol Deviations:

- The handling of dropouts in the statistical analysis was consistent with the protocol.

- The AE profiles are comparable between the test and RLD treatment.

- Protocol deviation did not compromise the integrity of the study.

The clinical results of the fasting study are **adequate**.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Preparation of calibration curve and quality control samples and defining analytical run organization and its acceptance criteria
		Repeat analysis and acceptance of results
		Chromatography acceptance criteria, re-injection, integration and reintegration on HPLC and LC-MS/MS data analysis
		Incurred sample reproducibility

All necessary SOPs submitted?	☒ Yes ☐ No

Reviewer's Note:

All above SOPs are provided in Module 5.3.1.4 Bioanalytical SOPs.

4.1.1.3.2 Sample Analysis Calibration and Quality Control[a]

Trans Phytonadione [765-15 (Fasting)]

Bioequivalence Study No. 765-15 Analyte Name: Trans Phytonadione								
Parameter	**Standard Curve Samples**							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng / mL)	0.401	0.801	5.009	15.043	50.143	75.177	90.212	100.235
Inter day Precision (% CV)	1.7	3.2	1.5	1.4	1.6	1.5	1.4	2.9
Inter day Accuracy (% Actual)	99.3	101.4	101.0	100.6	100.9	101.4	96.7	98.8
Linearity	0.9935 to 0.9999							
Linearity Range (ng /mL)	0.401 ng / mL to 100.235 ng / mL							
Sensitivity/ LOQ (ng / mL)	0.401 ng / mL							

Bioequivalence Study No. 765-15 Analyte Name: Trans Phytonadione						
Parameter	**Quality Control Samples**					
Quality Control Sample Ids	HQC	MQC	LMQC	INT QC	LQC	LQC(UV)
Concentration (ng / mL)	78.654	45.017	12.393	3.237	2.223	1.193

Inter day Precision (% CV)	3.4	3.7	4.7	5.5	5.1	4.9
Inter day Accuracy (% Actual)	101.0	103.7	103.6	108.8	108.1	108.2

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 14 (A)

Cis Phytonadione [765-15 (Fasting)]

Bioequivalence Study No. 765-15 Analyte Name: Cis Phytonadione								
Parameter	**Standard Curve Samples**							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng / mL)	0.300	0.600	1.249	3.752	12.506	18.722	22.500	25.000
Inter day Precision (% CV)	2.1	3.9	2.2	1.9	1.6	1.5	1.5	2.7
Inter day Accuracy (% Actual)	101.3	95.7	102.3	100.7	99.5	99.4	98.8	102.0
Linearity	0.9938 to 0.9997							
Linearity Range (ng /mL)	0.300 ng / mL to 25.000 ng / mL							
Sensitivity/ LOQ (ng / mL)	0.300 ng / mL							

Bioequivalence Study No. 765-15 Analyte Name: Cis Phytonadione						
Parameter	**Quality Control Samples**					
Quality Control Sample Ids	HQC	MQC	LMQC	INT QC	LQC	LQC(UV)
Concentration (ng / mL)	19.005	10.136	2.534	1.507	0.887	0.887
Inter day Precision (% CV)	4.6	3.4	5.0	5.7	6.0	5.0
Inter day Accuracy (% Actual)	102.2	100.7	100.5	102.0	90.9	100.6

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 14 (B)

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No Concentration data are in Compliance and Drug Concentration Data, Module 5.3.1.2, Appendix 16.2.5. **Baseline uncorrected trans-phytonadione**, Most subject samples are within 1.0 to 25 ng/mL (calibration rage: 0.401 ng/mL to 100.235 ng/mL) and QCs are well

	distributed (LQC 2.223 ng/mL, INT QC 3.237 ng/mL, LMQC 12.293 ng/mL, MQC 45.017 ng/mL, and HQC 78.654 ng/mL); **Baseline uncorrected cis-phytonadione:** Most subject samples are within 0.3 to 10 ng/mL (calibration rage: 0.3 ng/mL to 25 ng/mL) and QCs are well distributed (LQC 0.887 ng/mL, INT QC 1.507 ng/mL, LMQC 2.534 ng/mL, MQC 10.136 ng/mL, and HQC 19.005 ng/mL). Therefore the calibrators and QCs used in the study covered the entire concentration range.
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No See comments below on repeat assay
Were 20% of chromatograms included?	☒ Yes ☐ No (For both trans- and cis-phytonadione)
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No(For both trans- and cis-phytonadione)
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No(For both trans- and cis-phytonadione)
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No (For both trans- and cis-phytonadione)

Reviewer's Comments on Bioanalytical Results:

The firm provided the complete (100%) numerical raw data, incurred sample reanalysis (ISR) results, and 20% chromatograms in its submission Module 5.3.1.4 (bioanalytical report, chromatographic-data-1, and chromatographic-data-2).

4.1.1.3.3 Reanalysis of Study Samples[a]

765-15 (Fasting) (Trans Phytonadione)

Study No. 765-15, Trans Phytonadione Additional information in Module 5/ Section 5.3.1.4/ Sample Analysis Report/ Page 22 of 152		
Reason why assay was repeated	**Number of samples reanalyzed**	**Number of recalculated values**

					used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic [1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Subject sample analysis did not meet the analytical run acceptance criteria, as more than 20 % of LLOQ area response was obtained at the RT of drug in Standard Blank sample.	52.0	52.0	3.0 %	3.0 %	52.0	52.0	3.0 %	3.0 %
Subject sample analysis did not meet the analytical run acceptance criteria, as more than 20 % of LLOQ area response was obtained at the RT of drug in Standard Blank & Standard Zero samples.	52.0	52.0	3.0 %	3.0 %	50.0	50.0	2.9 %	2.9 %
Subject sample analysis did not meet the analytical run acceptance criteria as both the INTQC failed to meet the acceptance criteria.	2.0	2.0	0.1 %	0.1 %	2.0	2.0	0.1 %	0.1 %
Significant variation in response of internal standard	21.0	20.0	1.2 %	1.2 %	21.0	19.0	1.2 %	1.1 %
Poor chromatography	3.0	4.0	1.7 %	0.2 %	2.0	3.0	0.1 %	0.2 %
Concentration above highest standard	3.0	1.0	1.7 %	0.1 %	3.0	1.0	0.2 %	0.1 %
Processing error (less than 5% of mean ISTD area response of CC and QC samples of that particular run was obtained)	0.0	1.0	0.0 %	0.1 %	0.0	1.0	0.0 %	0.1 %
Processing error (No ISTD area response was obtained)	1.0	0.0	0.1 %	0.0 %	1.0	0.0	0.1 %	0.0 %
Abnormal high concentrations were obtained for both the analytes in the sample, as compared to its preceding samples. Such concentration in last time-point was not obtained for any other subject. Upon investigation it was concluded that, some sample specific contamination occurred during any step of sample processing might be the reason for such abnormal concentration. Since the obtained concentration was under doubt, sample was taken for reanalysis.	1.0	0.0	0.1 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Total	135.0	132.0	10.9%	7.7 %	131.0	128.0	7.6 %	7.5 %

[1] If no repeats were performed for pharmacokinetic reasons, insert “0.0”.
Total assay for Test Product (T): 1716 and Total assay for Reference Product (R):1716

[**a**]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 9(A)

765-15 (Fasting) (Cis Phytonadione)

Study No. 765-15, Cis Phytonadione Additional information in Module 5/ Section 5.3.1.4/ Sample Analysis Report/ Page 24 of 152								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic [1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %

Subject sample analysis did not meet the analytical run acceptance criteria, as more than 20 % of LLOQ area response was obtained at the RT of drug in Standard Zero sample.	52.0	52.0	3.0 %	3.0 %	49.0	51.0	2.9 %	3.0 %
Subject sample analysis did not meet the analytical run acceptance criteria as both the INTQC failed to meet the acceptance criteria.	3.0	2.0	0.2 %	0.1 %	3.0	2.0	0.2 %	0.1 %
Significant variation in response of internal standard	28.0	24.0	1.6 %	1.4 %	26.0	21.0	1.5 %	1.2 %
Poor chromatography	5.0	2.0	0.3 %	0.1 %	2.0	2.0	0.1 %	0.1 %
Processing error (No ISTD area response was obtained)	1.0	0.0	0.1 %	0.0 %	1.0	0.0	0.1 %	0.0 %
Abnormal high concentrations were obtained for both the analytes in the sample, as compared to its preceding samples. Such concentration in last time-point was not obtained for any other subject. Upon investigation it was concluded that, some sample specific contamination occurred during any step of sample processing might be the reason for such abnormal concentration. Since the obtained concentration was under doubt, sample was taken for reanalysis.	1.0	0.0	0.1 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Total	90.0	80.0	5.3 %	4.6 %	81.0	76.0	4.8 %	4.4 %

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
Total assay for Test Product (T): 1716 and Total assay for Reference Product (R):1716

[**a**]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 9(B)

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☐ Yes ☒ No See comments below
If no, is recalculation of PK parameters necessary?	☒ Yes ☐ No ☐ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☒ No ☐ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☒ Yes ☐ No ☐ N/A See comment below (cis-phytonadione is supportive data)

Reviewer's Comments on Reanalysis of Study Samples:

The summary for subject samples are provided in the Bioanalytical Report of pivotal fasting study: Module 5.3.1.4\Study 765-15\Bioanalytical Report, Section 7.1.
The summary for repeat sample analysis and re-injection are provided fasting bioanalytical report, Section 7.3. The run summaries are provided in fasting bioanalytical report, Table 01 (pages 29-31).

The 20% serially selected subjects (Subjects No (b) (6) sample chromatograms and 100% numerical raw data for the original and repeat analyses are provided in Module 5.3.1.4 Chromatographic-Data-1 and Chromatographic-Data-2.

Trans-Phytonadione

Out of the 3432 samples analyzed (from the 32 subjects who completed clinical phase successfully), a total of 267 samples were reanalyzed for trans-phytonadione.

- **Whole Batch Reanalysis**

According to Fasting Bioanalytical Report Section 7.3 and Table 06a, two runs, i.e., Run #40 (Subject (b) (6) including 104 subject samples) and Run #41 (Subject (b) (6) including 104 subject samples) failed due to not meeting the analytical run acceptance criteria, as more than 20 % of LLOQ area response was obtained at the RT of drug in Standard Blank sample (Subject (b) (6) and in both Standard Blank & Standard Zero samples (Subject (b) (6) ." Based on the raw data in Module 5.3.1.4 Chromatographic-Data-1, the reviewer confirmed that the original runs for Subjects (b) (6) did not meet the analytical run acceptance criteria in the firm's pre-established SOP ((b) (6) , (b) (6) i.e., *The interference present in the Standard Blank at the retention time of the analytes should be less than 20 % of LLOQ response for drug and/or metabolite and should be less than 5% for internal standard with respect to the mean internal standard response of CC & QC samples of the particular run….The interference present in the Standard Zero sample at the retention time of analytes should be less than 20 % of LLOQ response for drug and/or metabolite*. These two runs were appropriately identified for the whole batch repeat per firm's pre-established SOP ((b) (4) "Repeat analysis and acceptance of results").

Another run, i.e., Run #52 (Repeat No. 05, including 4 subject samples) failed due to both the INTQC failed to meet the acceptance criteria. Based on the raw data in Module 5.3.1.4 Chromatographic-Data-1, the reviewer confirmed that the original run for Repeat No. 05 did not meet the analytical run acceptance criteria in the firm's pre-established SOP (b) (4) i.e., *At least 50% of the Non-zero QC samples at each level and at least 67% of the total Non-zero QC samples (including DQC) of the run must be within 15% of their respective nominal concentration*. This run was appropriately identified for the whole batch repeat per firm's pre-established SOP ((b) (4) "Repeat analysis and acceptance of results").

- **Significant variation in response of internal standard**

According to Fasting Bioanalytical Report Section 7.3 and Table 07a, forty-one (41) samples were reanalyzed due to significant variation in response of internal standard. The reviewer spot checked the firm's raw data and confirmed that these samples were correctly identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4, "*If the response of internal standard in a sample varies by more than 35% from the mean ISTD response of CC and QC samples of a particular run, then repeat the analysis of the sample under this code*". For example, the IS area for 1004_PI_10h was

29510 and the mean IS area of CC and QC samples is approximately 19000. The bioanalytical repeats for these 41 samples are acceptable.

- **Poor chromatography**

Seven (7) samples were reanalyzed due to poor chromatography. The firm provided chromatographs from the original and repeated runs for all 7 samples in Module 5.3.1.4 Chromatographic-Data-2. The reviewer confirmed that these samples were appropriately identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4, "*If peak shape deteriorates significantly due to base line noise, peak splitting, RT shifting, merging/almost merging of interfering peak or long runners, column performance (excessive tailing or fronting) then evaluate the peak shape appropriately for acceptance/rejection based on location specific SOP on chromatography acceptance criteria*" and the criteria in its SOP (b) (4) "Chromatography acceptance criteria, re-injection, integration and reintegration on HPLC and LC-MS/MS data analysis". Additionally, the original and repeated values for the 7 samples are similar (Table 07a) thus the repeats are not expected to impact study outcome.

- **Concentration above highest standard**

Four (4) samples were reanalyzed due to concentration above highest standard. The reviewer spot checked the 100% raw data and confirmed these samples were appropriately identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4. Additionally, the original and repeated values for the 4 samples are similar (Table 07a), and the dilution integrity has been established in the pre-study method validation. In all cases, the reported values are at least 85% of the upper limit of quantitation.

- **Processing error**

Two (2) samples were reanalyzed due to processing error (less than 5% of mean ISTD area response of CC and QC samples, or no ISTD area response). Based on the 100% raw data, the reviewer confirmed that the 2 samples were appropriately identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4.

- **Abnormal high concentrations**

One sample (Subject (b) (6) P-IV_24h) was reanalyzed due to abnormal high concentration. The firm stated below in Fasting Bioanalytical Report Section 7.3: "*Abnormal high concentrations were obtained for both the analytes in the sample, as compared to its preceding samples. Such concentration in last time-point was not obtained for any other subject. Upon investigation it was concluded that, some sample specific contamination occurred during any step of sample processing might be the reason for such abnormal concentration. Since the obtained concentration was under doubt, sample was taken for reanalysis*".

The original and repeated concentrations (baseline uncorrected) of Subject (b) (6) Period-IV (Test treatment) are presented below. Both analytes trans- and cis-phytonadione had substantially high concentration at the last timepoint (24h).

Trans-Phytonadione:

	0h	1.5h	3h	4h	5h	6h	6.5h	7h	7.5h	8h	9h	10h	11h	12h	13h	16h	20h	24h
Original	0	0	1.046	1.163	3.547	5.563	5.066	6.4	4.967	4.434	4.413	4.323	5.083	5.473	6.547	2.49	1.142	21.321
Repeated	0	0	1.046	1.163	3.547	5.563	5.066	6.4	4.967	4.434	4.413	4.323	5.083	5.473	6.547	2.49	1.142	0.698

Cis-Phytonadione

	0h	1.5h	3h	4h	5h	6h	6.5h	7h	7.5h	8h	9h	10h	11h	12h	13h	16h	20h	24h
Original	0	0	0	0	0.989	1.574	1.287	1.624	1.174	0.974	0.913	0.754	0.715	0.668	0.737	0	0	5.277
Repeated	0	0	0	0	0.989	1.574	1.287	1.624	1.174	0.974	0.913	0.754	0.715	0.668	0.737	0	0	0

It should be noted that the "original" values i ve table are from a repeated whole batch run. The actual original run for Subject (b) (6) failed due to not meeting the analytical run acceptance criteria (refer to the beginning of this section). In the failed original run, the concentrations of Subject (b) (6) P-IV_24h (0.882 ng/mL for trans-phytonadione and BLQ for cis-phytonadione, Fasting Bioanalytical Report Tables 06a and 06b) were similar compared to the final repeated values.

The reviewer agrees with the firm's investigation conclusion that the reason of the high concentration was likely sample specific contamination occurred during sample processing. However, the firm's pre-established SOP ((b) (4) "Repeat analysis and acceptance of results") did not have specific criteria for "abnormal high concentrations". Thus, the reviewer considers that the repeat is pharmacokinetic repeat in nature.

To confirm the impact of the repeat assay on the study outcome, the reviewer conducted a sensitivity statistical analysis using the original value and compared the results to the analysis using repeated value (see below tables and SAS output in Section **4.4.2**)..

Reference scaled average BE analysis of trans-phytonadione using <u>repeated value</u> of Subject (b) (6) P-IV_24h (reviewer's calculation)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.94	78.95	113.01	0.2724392	0.5219571	-0.130893	Scaled/PE	PASS
LAUCI	1.06	84.86	122.04	0.2560268	0.5059909	-0.116524	Scaled/PE	PASS
LCMAX	0.89	73.25	108.03	0.3227386	0.5681009	-0.130079	Scaled/PE	PASS

Reference scaled average BE analysis of trans-phytonadione using <u>original value</u> of Subject_ (b) (6) P-IV_24h (reviewer's calculation)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.95	79.65	114.11	0.2724392	0.5219571	-0.133951	Scaled/PE	PASS
LAUCI	1.08	86.49	124.74	0.2560268	0.5059909	-0.106553	Scaled/PE	PASS

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LCMAX	0.91	74.68	110.46	0.3227386	0.5681009	-0.139971	Scaled/PE	PASS

As shown above, the study outcome was not altered using the original value, i.e., BE criteria met for trans-phytonadione and not marginal from both analyses.

Therefore, the reviewer will not pursue the issue of repeated assay due to "abnormal high concentration".

- **Re-integration**

According to Fasting Bioanalytical Report Section 7.1, one run (Run #7 [Subject (b) (6)]) was re-integrated for both analytes trans- and cis-phytonadione because "improper integration was observed in Sample IDs (b) (6) for ISTD-1 and in Sample IDs (b) (6) for ISTD-2", and one run (Run #25 [Subject (b) (6) was re-integrated for cis-phytonadione because "peak adjacent to analyte peak was integrated for Cis-Phytonadione in Sample IDs (b) (6). The firm provided the original and re-integrated chromatograms and numerical data in Module 5.3.1.4 Chromatographic-Data-2 Section 16.5.7.5. The reviewer agrees that the re-integrations are consistent with the firm's pre-established SOP (b) (4) ("Chromatography acceptance criteria, re-injection, integration and reintegration on HPLC and LC-MS/MS data analysis") Section 6.5. Additionally, the reviewer spot checked the raw data and found that the back-calculated concentrations are similar before and after the re-integration. The re-integrations are acceptable.

Cis-Phytonadione (Supportive Data)

Out of the 3432 samples analyzed (from the 32 subjects who completed clinical phase successfully), a total of 170 samples were reanalyzed for cis-phytonadione.

- **Whole Batch Reanalysis**

According to Fasting Bioanalytical Report Section 7.3 and Table 06b, two runs, i.e., Run Run #41 (Subject (b) (6) including 104 subject samples) and Run #52 (Repeat No. 05, including 4 subject samples) failed due to not meeting the analytical run acceptance criteria. Based on the raw data in Module 5.3.1.4 Chromatographic-Data-1, the reviewer confirmed that these two runs were appropriately identified for the whole batch repeat per firm's pre-established SOP (b) (4) "Repeat analysis and acceptance of results").

- **Significant variation in response of internal standard**

Fifty-two (52) samples were reanalyzed due to significant variation in response of internal standard. The reviewer spot checked the firm's raw data and confirmed that these samples were correctly identified for repeat per the firm's pre-established SOP (b) (4).

- **Poor chromatography**

Seven (7) samples were reanalyzed due to poor chromatography. The firm provided chromatographs from the original and repeated runs in Module 5.3.1.4 Chromatographic-Data-2. The reviewer confirmed that these samples were appropriately identified for repeat per the firm's pre-established SOP (b) (4).

- **Processing error**

One (1) sample was reanalyzed due to processing error (no ISTD area response). The reviewer confirmed that this sample was appropriately identified for repeat per the firm's pre-established SOP (b) (4).

- **Abnormal high concentrations**

One sample (Subjec (b) (6) _P-IV_24h) was reanalyzed due to abnormal high concentration. Please see discussion above.

To confirm the impact of the repeat assay on the study outcome, the reviewer conducted a sensitivity statistical analysis using the original value and compared the results to the analysis using repeated value (see below tables and SAS output in Section **4.4.2**).

Reference scaled average BE analysis of cis-phytonadione using repeated value of Subject (b) (6) P-IV_24h (reviewer's calculation)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.11	91.33	133.84	0.3938131	0.6275453	-0.183471	Scaled/PE	PASS
LAUCI	1.12	87.13	125.17	0.1091161	0.3303272	0.0415557	Scaled/PE	FAIL
LCMAX	1.00	85.61	117.96	0.184873	0.4299686	-0.096923	Scaled/PE	PASS

Reference scaled average BE analysis of cis-phytonadione using original value of Subject_ (b) (6) P-IV_24h (reviewer's calculation)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.12	92.63	135.86	0.3938131	0.6275453	-0.17644	Scaled/PE	PASS
LAUCI	1.12	87.13	125.17	0.1091161	0.3303272	0.0415557	Scaled/PE	FAIL
LCMAX	1.02	87.25	120.38	0.184873	0.4299686	-0.092171	Scaled/PE	PASS

As shown above, the study outcome was not altered using the original value, i.e., SABE criteria was met for Cmax and AUCt and not met for AUCi for cis-phytonadione from both analysis.

Therefore, the reviewer will not pursue the issue of repeated assay due to "abnormal high concentration".

- **Re-integration**

Please refer to the section above for trans-phytonadione.

Reviewer's Overall Comments on Bioanalytical Results:

The firm provided the complete (100%) numerical raw data, ISR results, and 20% chromatograms in its submission Module 5.3.1.4.

The firm conducted incurred sample reanalysis (ISR) using 311 subject samples for both analytes trans- and cis-phytonadione (90.62% of the total 3432 samples analyzed) as per its SOP ([redacted](b) (4) 'Incurred Sample Reproducibility') Section 6.1.1, i.e., "*150 samples (10 % of 1500 samples) + 7.5 % of (Total samples - 1500 samples.* The ISR results are presented in Fasting Bioanalytical Report Tables 09a and 09b. 298 out of 311 samples (95.8%) for trans-phytonadione and 268 out of 311 samples (86.2%) for cis-phytonadione were found to be within ±20 % bias. Of the ISR samples, at least one sample was close to maximum concentration and another sample was close to LQC, to cover the entire concentration range for both analytes. Thus ISR were within acceptance criteria specified in its SOP [redacted](b) (4).

In summary, the firm's submitted bioanalytical results for the fasting study are **adequate**.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Trans-Phytonadione

4.1.1.4.1.1 Arithmetic Mean Pharmacokinetic Parameters

Trans-Phytonadione Baseline Corrected - Reviewer Calculated (N=32)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	122.129	95.70	8.18	540.50	122.312	101.32	11.17	786.02	1.00
AUCINF	ng hr/mL	124.975	96.86	0.00	549.61	126.259	101.19	0.00	814.16	0.99
CMAX	ng/mL	16.285	112.12	1.06	104.24	15.722	90.39	1.46	87.99	1.04
TMAX	hr	6.500	.	5.00	13.00	6.500	.	5.00	13.00	1.00
KEL	hr-1	0.193	54.35	0.00	0.57	0.210	35.81	0.00	0.42	0.92
THALF	hr	3.545	47.33	0.00	7.31	3.526	33.20	0.00	6.64	1.01

Tmax values are presented as median, range

Trans-Phytonadione Baseline Corrected - Reviewer Calculated (N=31, excluding Subject (b) (4))

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	116.746	98.24	8.18	540.50	118.339	103.17	11.17	786.02	0.99
AUCINF	ng hr/mL	119.393	99.50	0.00	549.61	122.081	103.14	0.00	814.16	0.98
CMAX	ng/mL	15.313	115.36	1.06	104.24	15.436	92.41	1.46	87.99	0.99
TMAX	hr	6.500	.	5.00	13.00	6.500	.	5.00	13.00	1.00
KEL	hr-1	0.193	55.02	0.00	0.57	0.211	35.75	0.00	0.42	0.91
THALF	hr	3.530	48.21	0.00	7.31	3.495	33.45	0.00	6.64	1.01

Note: Subject (b) (4) is excluded due to Period-II predose concentration > 5% Cmax

4.1.1.4.1.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Reference-Scaled Average BE for Baseline Corrected Trans-Phytonadione[a]

Parameter	T/R Ratio (%)	Lower 90% CI	Upper 90% CI	s2wr	S_{WR}	Criteria Bound	Method Used	Outcome
LAUCT	95.0	N/AP	N/AP	0.2819	0.5309	-0.1407	SABE	BE Met
LAUCI	106.1	N/AP	N/AP	0.2668	0.5165	-0.1249	SABE	BE Met
LCMAX	90.5	N/AP	N/AP	0.3233	0.5686	-0.1414	SABE	BE Met

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3B (1)

Unscaled Average BE for Baseline Corrected Trans-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☒Yes ☐No					
Phytonadione Tablets (No. of subjects completed = 32) Dose (1×5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Project No. 765-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio (%)**	**90% C.I.**
AUC_{0-t}	80.427	64	84.642	64	95.0	N/AP
$AUC_{0-\infty}$	90.760	59*	88.949	63*	106.1	N/AP
C_{max}	10.111	64	11.170	64	90.5	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (1)
* Per the fasting study report section 11.4.1, Subject nos. (b) (6) (Period-III), (b) (6) (period-IV) & (b) (6) (period-IV) had inadequate time-points for the computation of elimination phase pharmacokinetic parameters and hence same could not be calculated.

Reference-Scaled Average BE for Baseline Uncorrected (For Information) Trans-Phytonadione[a]

Parameter	T/R Ratio (%)	Lower 90% CI	Upper 90% CI	s2wr	S_{WR}	Criteria Bound	Method Used	Outcome
LAUCT	95.9	N/AP	N/AP	0.2188	0.4678	-0.1117	SABE	N/AP
LAUCI	101.9	N/AP	N/AP	0.1891	0.4348	-0.0959	SABE	N/AP
LCMAX	91.4	N/AP	N/AP	0.2912	0.5396	-0.1301	SABE	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3B (2)

Unscaled Average BE for Baseline Uncorrected (For Information) Trans-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☒Yes ☐No					
Phytonadione Tablets (No. of subjects completed = 32) Dose (1×5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Project No. 765-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio (%)**	**90% C.I.**
AUC_{0-t}	97.441	64	101.566	64	95.9	N/AP
$AUC_{0-\infty}$	109.035	60	112.572	61	101.9	N/AP
C_{max}	10.989	64	12.026	64	91.4	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (2)

Reviewer's Note:
The firm conducted the statistical analysis using both the reference scaled average BE (SABE) and the unscaled average BE approaches with both the baseline corrected and uncorrected concentration data.

4.1.1.4.1.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Reference-Scaled Average BE for Baseline Corrected Trans-Phytonadione (N=32)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	0.95	79.85	113.07	0.2818363	0.5308825	-0.140687	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.06	85.60	121.63	0.2667677	0.5164956	-0.124881	Scaled/PE	PASS
LCMAX (ng/mL)	0.91	74.80	109.53	0.3233599	0.5686474	-0.141426	Scaled/PE	PASS

Reference-Scaled Average BE for Baseline Corrected Trans-Phytonadione (N=31, excluding Subject (b) (6)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	0.94	78.95	113.01	0.2724392	0.5219571	-0.130893	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.06	84.86	122.04	0.2560268	0.5059909	-0.116524	Scaled/PE	PASS
LCMAX (ng/mL)	0.89	73.25	108.03	0.3227386	0.5681009	-0.130079	Scaled/PE	PASS

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Unscaled Average BE for Baseline Corrected Trans-Phytonadione (N=31, excluding Subject (b) (6)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT (ng.h/mL)	77.70	82.26	0.94	78.95	113.01
LAUCI (ng h/mL)	88.05	86.53	1.02	84.86	122.04
LCMAX (ng/mL)	9.71	10.92	0.89	73.25	108.03

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Reference-Scaled Average BE for Baseline Uncorrected (For Informational Purposes) Trans-Phytonadione (N=31, excluding Subject (b) (6)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	0.95	82.06	110.77	0.2056048	0.4534367	-0.100664	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.02	82.32	112.95	0.1716295	0.4142819	-0.084442	Scaled/PE	PASS
LCMAX (ng/mL)	0.90	74.89	107.75	0.2887984	0.5373997	-0.118906	Scaled/PE	PASS

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Unscaled Average BE for Baseline Uncorrected (For Informational purposes) Trans-Phytonadione (N=31, excluding Subjec (b) (6)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT (ng.h/mL)	94.30	98.91	0.95	82.06	110.77
LAUCI (ng h/mL)	105.89	109.81	0.96	82.32	112.95
LCMAX (ng/mL)	10.56	11.76	0.90	74.89	107.75

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

4.1.1.4.1.4 Additional Information for the Study

Root Mean Square Error	AUCt: 0.5219571 AUCi: 0.5059909 Cmax: 0.5681009 (Reference-Scaled Average BE for Baseline Corrected Trans-Phytonadione (N=31, excluding Subject (b) (6))
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No For both Test and Reference, Tmax median: 6.5 h and range: 5-13 h
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No See comment below
Are there first measurable drug concentration as	☐ Yes ☒ No

Cmax? **If yes, please comment.**	
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	57	0.95	0.81	1.00
Reference	61	0.96	0.84	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Reviewer's Comments on Statistical Analysis of Trans-Phytonadione

The reviewer conducted a confirmatory SAS analysis of trans-phytonadione using the original dataset submitted by the firm but excluded Subject (b) (6) due to Period-II predose concentration (4.807 ng/mL and 7.112 ng/mL for baseline corrected and uncorrected trans-phytonadione, respectively) > 5% Cmax (33.256 ng/mL and 35.561 ng/mL for baseline corrected and uncorrected trans-phytonadione, respectively). Subject (b) (6) was included in the firm's statistical analyses. Since the study outcome is the same with or without Subject (b) (6) (see tables of reviewer's calculation above), the reviewer will not pursue this issue.

Per the current draft guidance for Phytonadione tablets[33], *baseline correction should be based on phytonadione levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. If the baseline is stable, you may choose to do baseline correction for 24 hours rather than 48 hours*. The firm used the average levels from -48 to 0 hour as baseline. The reviewer considers that the firm's approach is appropriate because the baseline level of trans-phytonadione shows some fluctuation. The reviewer also spot checked the firm's SAS dataset and confirmed that the firm's calculation of baseline correction is correct.

According to DB's criteria, the scaled average bioequivalence approach was used when the estimated within subject variability (s_{WR}) > 0.294 (i.e. when the s^2_{WR} > 0.086436). In order to be considered bioequivalent to the reference product, the test product must pass the following two conditions[34]: 1) a 95% upper confidence bound for $(\mu T - \mu R)^2 - \theta\, s^2_{WR}$

[33] OGD Guidance on Phytonadione Tablets, (Recommended Feb 2010, Revised Sep 2012, Jan 2016), available at: https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf

[34] S. H. Haidar, B. Davit, M. L. Chen, et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products. *Pharm. Res.* **25**:237-41 (2008) and Davit et al., Implementation of a Reference-Scaled

must be ≤ 0, where s_{WR} is within reference standard deviation determined in the BE study; and 2) the point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

Per the Fasting Study Protocol (Version 01, 04Feb2016) Section 11.1.4:
Statistical Analyses will be conducted for Scaled Average Bioequivalence (SABE) for any ln-transformed primary parameter, where the within-subject standard deviation of Reference Product sWR ≥ 0.294. For any primary parameter where this within-subject standard deviation of Reference Product sWR < 0.294, the statistical analyses will be based on Average Bioequivalence Approach for baseline corrected and baseline uncorrected data of Phytonadione (E isomer (trans-configuration)) and Phytonadione (Z isomer (cis-configuration)).

The firm's criteria for using scaled- or unscaled-average BE approach are consistent with DB's criteria. For the fasting BE study, the estimated within subject variability (s_{WR}) > 0.294 for all 3 parameters AUCt, AUCi and Cmax, thus the scaled average bioequivalence (SABE) approach was used to determine bioequivalence.

In both the firm and reviewer's analyses, AUCi could not be determined for the following subjects due to inadequate time-points for the computation of elimination phase pharmacokinetic: Subjects (b) (6) (Period-IV), (b) (6) (Period-III), (b) (6) (Period-II and Period-IV), (b) (6) (Period-IV), and (b) (6) (Period-IV). The reviewer also confirmed the undeterminable elimination phase based on the individual PK profiles in Module 5.3.1.2 Appendix 16.2.6.

The results of the SABE analysis are consistent between the firm and reviewer's calculations. The calculation shows that the 95% upper confidence bounds for $(\mu T - \mu R)^2 - \theta s^2_{WR}$ for AUCt, AUCi and Cmax of baseline corrected trans-phytonadione are -0.130893, -0.116524 and -0.130079, respectively. The point estimate (test/reference geometric mean ratio) for AUCt, AUCi and Cmax of trans-phytonadione baseline corrected are 0.94, 1.06 and 0.89, respectively. Therefore, the statistical analysis for baseline corrected trans-phytonadione met the BE criteria for the reference scaled average BE analysis, and the results are not marginal.

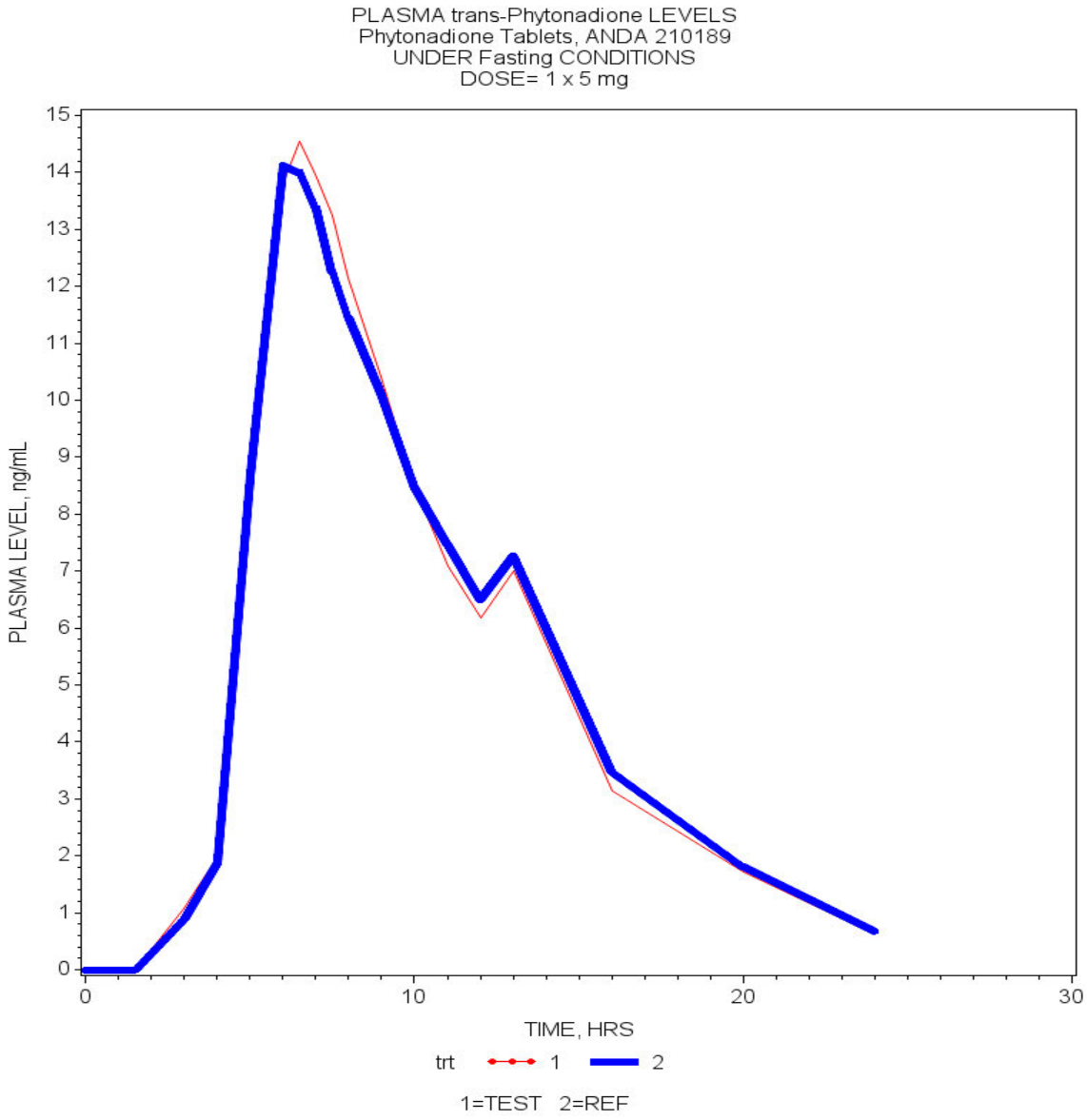
Baseline Corrected Trans-phytonadione Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Reviewer Calculated (N=31, excluding Subject (b) (6)

	Treatment A		Treatment B	
Time	**Mean (ng/mL)**	**CV%**	**Mean (ng/mL)**	**CV%**
0	0.00	.	0.00	.
1.5	0.01	703.29	0.00	.

Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. The AAPS Journal, 2012.

	Treatment A		Treatment B	
Time	**Mean (ng/mL)**	**CV%**	**Mean (ng/mL)**	**CV%**
3	1.08	149.30	0.89	225.91
4	1.96	132.52	1.88	141.34
5	8.03	93.77	8.68	81.40
6	13.79	114.97	14.12	89.28
6.5	14.54	122.07	14.00	95.39
7	13.96	122.86	13.38	103.04
7.5	13.24	121.98	12.26	102.17
8	12.15	118.89	11.44	107.04
9	10.40	114.75	10.08	119.41
10	8.52	110.87	8.47	126.54
11	7.09	104.88	7.48	136.98
12	6.17	93.73	6.50	130.39
13	7.01	81.73	7.27	105.85
16	3.15	96.61	3.47	131.87
20	1.71	91.25	1.81	99.54
24	0.63	103.63	0.68	122.83

Baseline Corrected Trans-phytonadione Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study –- Reviewer Generated



4.1.1.4.2 Cis-Phytonadione (Supportive Data)

4.1.1.4.2.1 Arithmetic Mean Pharmacokinetic Parameters

Cis-Phytonadione Baseline Corrected - Reviewer Calculated (N=32)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	24.689	90.81	0.92	117.30	22.292	95.84	0.66	135.83	1.11
AUCINF	ng hr/mL	24.648	104.58	0.00	125.40	22.849	108.77	0.00	154.32	1.08
CMAX	ng/mL	3.832	85.73	0.41	16.91	3.492	76.75	0.52	16.96	1.10
TMAX	hr	6.017	.	5.00	8.00	6.000	.	5.00	8.00	1.00
KEL	hr-1	0.108	74.36	0.00	0.27	0.118	77.29	0.00	0.38	0.92
THALF	hr	3.431	74.58	0.00	10.26	3.409	73.88	0.00	9.11	1.01

Cis-Phytonadione Baseline Corrected - Reviewer Calculated (N=31, excluding Subject (b) (6))

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	23.812	93.34	0.92	117.30	21.820	98.08	0.66	135.83	1.09
AUCINF	ng hr/mL	23.668	108.13	0.00	125.40	22.298	111.93	0.00	154.32	1.06
CMAX	ng/mL	3.658	86.91	0.41	16.91	3.464	78.35	0.52	16.96	1.06
TMAX	hr	6.025	.	5.00	8.00	6.000	.	5.00	8.00	1.00
KEL	hr-1	0.107	76.03	0.00	0.27	0.117	78.81	0.00	0.38	0.91
THALF	hr	3.392	76.23	0.00	10.26	3.351	75.52	0.00	9.11	1.01

Tmax values are presented as median, range
Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

4.1.1.4.2.2 Geometric Means and 90% Confidence Intervals - Firm Calculated Reference-Scaled Average BE for Baseline Corrected Cis-Phytonadione[a]

Parameter	T/R Ratio (%)	Lower 90% CI	Upper 90% CI	s2wr	S_{WR}	Criteria Bound	Method Used	Outcome
LAUCT	111.5	N/AP	N/AP	0.3915	0.6257	-0.1812	SABE	N/AP
LAUCI	112.5	N/AP	N/AP	0.1185	0.3442	-0.0308	SABE	N/AP
LCMAX	102.4	N/AP	N/AP	0.1831	0.4279	-0.0923	SABE	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3B (3)

Unscaled Average BE for Baseline Corrected Cis-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☒Yes ☐No					
Phytonadione Tablets (No. of subjects completed = 32) Dose (1×5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Project No. 765-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio (%)**	**90% C.I.**
AUC_{0-t}	16.715	64	14.996	64	111.5	N/AP
$AUC_{0-\infty}$	26.453	45	25.188	46	112.5	N/AP
C_{max}	2.805	64	2.740	64	102.4	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (3)

Reference-Scaled Average BE for Baseline Uncorrected (For Informational purposes) Cis-Phytonadione[a]

Parameter	T/R Ratio (%)	Lower 90% CI	Upper 90% CI	s2wr	S_{WR}	Criteria Bound	Method Used	Outcome
LAUCT	111.4	N/AP	N/AP	0.3931	0.6270	-0.1827	SABE	N/AP
LAUCI	112.3	N/AP	N/AP	0.1226	0.3502	-0.0261	SABE	N/AP
LCMAX	102.3	N/AP	N/AP	0.1836	0.4285	-0.0928	SABE	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3B (4)

Unscaled Average BE for Baseline Uncorrected (For Information) Cis-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☒Yes ☐No					
Phytonadione Tablets (No. of subjects completed = 32) Dose (1×5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Project No. 765-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio (%)**	**90% C.I.**
AUC_{0-t}	16.720	64	15.015	64	110.6	N/AP
$AUC_{0-\infty}$	26.457	45	25.233	46	120.4	N/AP
C_{max}	2.805	64	2.742	64	102.3	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (4)

4.1.1.4.2.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Reference-Scaled Average BE for Baseline Corrected Cis-Phytonadione (N=32)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	1.11	92.59	134.18	0.3914756	0.6256801	-0.181166	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.13	88.19	125.06	0.1184499	0.3441655	0.0307824	Scaled/PE	FAIL
LCMAX (ng/mL)	1.02	87.34	119.95	0.1830797	0.4278782	-0.092326	Scaled/PE	PASS

Reference-Scaled Average BE for Baseline Corrected Cis-Phytonadione (N=31, excluding Subject (b) (6))

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	1.11	91.33	133.84	0.3938131	0.6275453	-0.183471	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.12	87.13	125.17	0.1091161	0.3303272	0.0415557	Scaled/PE	FAIL
LCMAX (ng/mL)	1.00	85.61	117.96	0.184873	0.4299686	-0.096923	Scaled/PE	PASS

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Unscaled Average BE for Baseline Corrected Cis-Phytonadione (N=31, excluding Subject (b) (6))

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT (ng.h/mL)	16.20	14.66	1.11	91.33	133.84
LAUCI (ng h/mL)	25.98	24.87	1.04	87.13	125.17
LCMAX (ng/mL)	2.72	2.70	1.00	85.61	117.96

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Reference-Scaled Average BE for Baseline Uncorrected (For Information) Cis-Phytonadione (N=31, excluding Subject (b) (6))

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (ng.h/mL)	1.11	91.34	133.85	0.3936547	0.6274191	-0.183342	Scaled/PE	PASS
LAUCI (ng.h/mL)	1.12	87.14	125.19	0.1095753	0.3310216	0.0412945	Scaled/PE	FAIL
LCMAX (ng/mL)	1.00	85.61	117.97	0.184902	0.4300023	-0.096932	Scaled/PE	PASS

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

Unscaled Average BE for Baseline Uncorrected (For Information) Cis-Phytonadione (N=31, excluding Subject (b) (6))

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT (ng.h/mL)	16.21	14.66	1.11	91.34	133.85
LAUCI (ng h/mL)	25.99	24.88	1.04	87.14	125.19
LCMAX (ng/mL)	2.72	2.71	1.00	85.61	117.97

Note: Subject (b) (6) is excluded due to Period-II predose concentration > 5% Cmax

4.1.1.4.2.4 Additional Information for the Study

Root Mean Square Error	AUCt: 0.6275 AUCi: 0.3303 Cmax: 0.4299 (Reference-Scaled Average BE for Baseline Corrected Cis-Phytonadione (N=31, excluding Subject (b) (6)))
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No For both Test and Reference, Tmax median: 6 h and range: 5-8 h
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No See comment below
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	43	0.89	0.80	0.97
Reference	44	0.89	0.80	0.97
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Reviewer's Comments on Statistical Analysis of Cis-Phytonadione

The reviewer conducted a confirmatory SAS analysis of cis-phytonadione the original dataset submitted by the firm but excluded Subject (b) (6) due to Period-II predose concentration (1.263 ng/mL and 1.421 ng/mL for baseline corrected and uncorrected cis-phytonadione, respectively) > 5% Cmax (5.285 ng/mL and 5.443 ng/mL for baseline corrected and uncorrected cis-phytonadione, respectively). Subject (b) (6) was included in the firm's statistical analyses. Since the study outcome is the same with or without Subject (b) (6) (see tables of reviewer's calculation above), the reviewer will not pursue this issue.

For the fasting BE study, the estimated within subject variability (s_{WR}) > 0.294 for all 3 parameters AUCt, AUCi and Cmax of baseline corrected cis-phytonadione, thus the SABE approach was used in both the firm and reviewer's analyses.

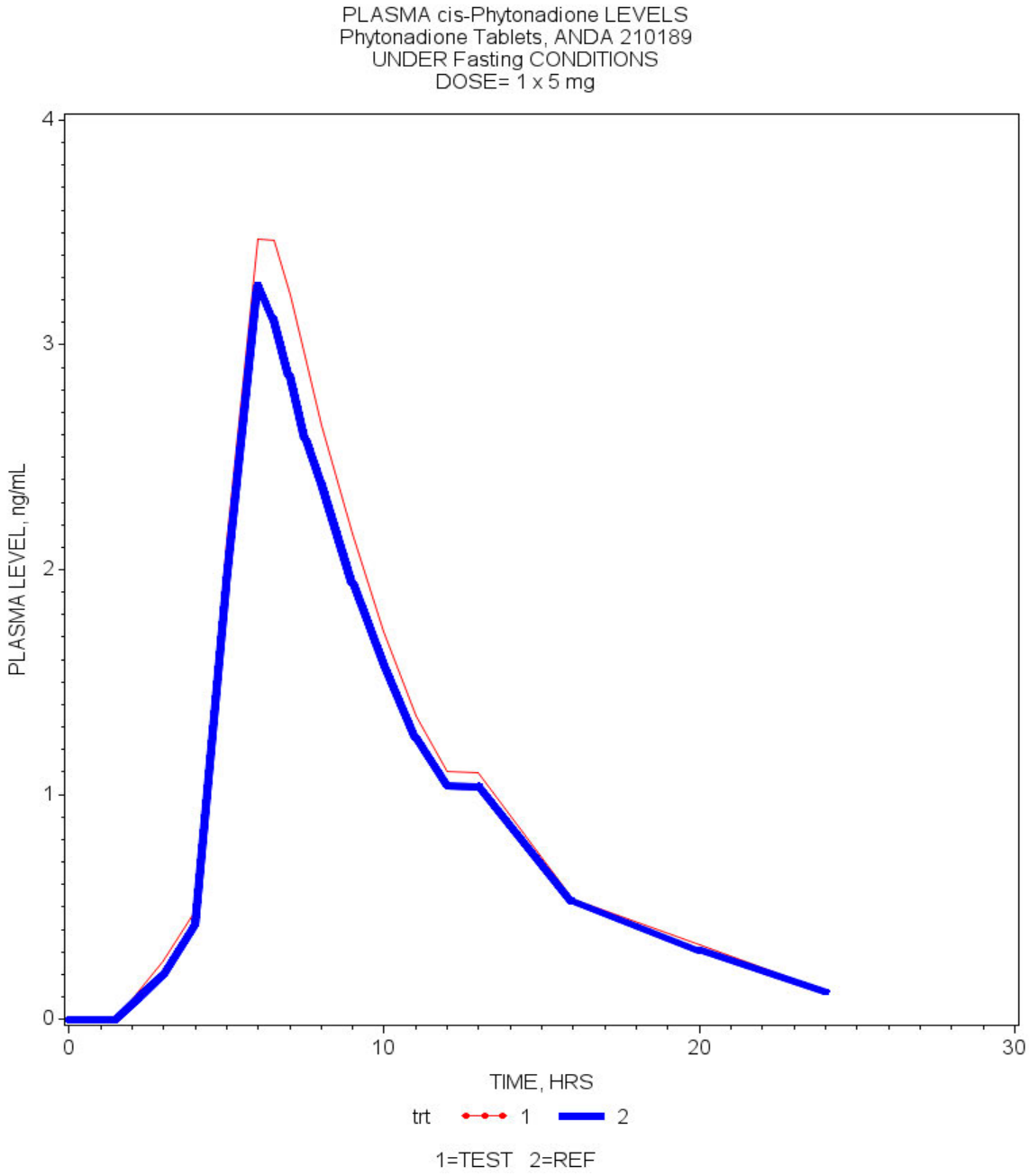
The results of the SABE analysis are consistent between the firm and reviewer's calculations. In both the firm and reviewer's analyses, there were 37 AUCi values could not be determined due to inadequate time-points (non-declining terminal phase) for the computation of elimination phase pharmacokinetic.

The calculation shows that the 95% upper confidence bounds for $(\mu T - \mu R)^2 - \theta s^2_{WR}$ for AUCt and Cmax of baseline corrected cis-phytonadione are -0.183471 and -0.096923, and the point estimate (test/reference geometric mean ratio) for AUCt and Cmax are 1.11 and 1.00, respectively. For AUCi of baseline corrected cis-phytonadione, the 95% upper confidence bounds for $(\mu T - \mu R)^2 - \theta s^2_{WR}$ is 0.0415557 (i.e., > 0). Therefore, the statistical analysis shows that the test product has higher bioavailability than the reference product for cis-phytonadione. The data for cis-phytonadione are therefore, not considered as supportive of trans-phytonadione analysis. The firm will be requested to explain why the test product shows higher bioavailability for cis-phytonadione than the reference product.

Baseline Corrected Cis-phytonadione Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Reviewer Calculated (N=31, excluding Subject (b) (6))

	Treatment A		Treatment B	
Time	**Mean (ng/mL)**	**CV%**	**Mean (ng/mL)**	**CV%**
0	0.00	.	0.00	.
1.5	0.00	.	0.00	.
3	0.26	134.43	0.20	215.39
4	0.49	113.51	0.42	134.36
5	2.13	71.31	1.94	66.72
6	3.47	86.75	3.27	72.33
6.5	3.47	92.27	3.12	77.07
7	3.22	94.66	2.87	82.98
7.5	2.95	95.38	2.58	83.94
8	2.64	95.89	2.39	102.23
9	2.16	97.18	1.94	103.92
10	1.73	102.85	1.57	107.72
11	1.35	103.73	1.25	126.02
12	1.10	100.65	1.04	126.56
13	1.10	91.77	1.04	110.04
16	0.54	117.22	0.53	139.11
20	0.33	122.07	0.31	137.85
24	0.13	193.10	0.12	235.74

Baseline Corrected Cis-phytonadione Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study –- Reviewer Generated



Was the fasting bioequivalence study acceptable? Inadequate

4.1.2 Pivotal Single-Dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information[a]

Study Number	766-15
Study Title	An open label, balanced, randomized, two-treatment, two-sequence, two period, crossover, single dose, oral bioequivalence study of Phytonadione Tablets, USP 5 mg of Cadila Healthcare Ltd., India comparing with Mephyton® (Phytonadione) Tablets 5 mg of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 in normal, healthy, adult subjects under fed condition
Study Type	☑ *In-vivo* BE ☐ *In-vitro* BE ☐ Permeability ☐ Other
Submission Location: Study Report: Validation Report: Bio-analytical Report:	 location, ex: 5.3.1.2 location, ex: 5.3.1.4 location, ex: 5.3.1.4
Clinical Site **(Name, Address, Phone #, Fax #)**	Lambda Therapeutic Research Ltd. 7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector-15, CBD Belapur, Navi Mumbai-400 614, Maharashtra, India. Tel. No.: +91-22-4125 2900 Fax. No.: +91-22-2756 2231
Principal Clinical Investigator **(Name, Email)**	Dr. Yashvant Khaire, M.B.B.S., D.A. yashvantkhaire@lambda-cro.com
Dosing Dates	Period-I : 09 July 2016 Period-II : 14 July 2016
Analytical Site **(Name, Address, Phone #, Fax #)**	(b) (4)
Analysis Dates	
Principal Analytical Investigator **(Name, Email)**	Mr. Shailendra Gupta shailendragupta@lambda-cro.com
Sample Storage : **(a) Duration (no. of days (from dosing until the last PK sample retrieval date)** **(b) Temperature Range (e.g., -20° C to -80° C)**	(a) 137 days (09 July 2016 to 23 November 2016) (b) At -65 ± 10 °C
Long-Term Storage Stability (LTSS)	138 days at -65 ± 10°C

Coverage (no. days @ temp ºC)	
LTSS Data Location	**Module 5.3.1.4/Method Validation Report/MV(I)-226-16 (Addendum-I)/page 21 of 181**

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 10 (B)

4.1.2.1.2 Product (Bio-batch) Information

Please refer to Section **4.1.1.1.2.** Please note there is a deficiency in the product information, i.e., the firm did not provide the potencies of each phytonadione isomer (trans- and cis-) in the test and RLD product drug lots used in the study. Therefor firm will be asked to provide the above mentioned information.

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 48 subjects Dosed: 48 subjects Completed: 45 subjects Samples Analyzed: 47 (In which, withdrawn Subject Nos. (b) (6) (b) (6) were also analyzed as per protocol requirement) Statistically Analyzed: 45 subjects
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization	☒ Yes ☐ No
Blood Sampling Times	-48 hrs, -42, -36, -30, -24, -18, -12, -6, 0 hrs, 1, 2, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 20.0, and 24 hrs post-dose.
IRB Approval	☒ Yes Date: June 28, 2016 ☐ No
Informed Consent	☒ Yes Date: June 28, 2016 ☐ No
Length of Fasting	After an overnight fast of at least 10 hours, the subjects were served high fat high calorie non-vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (5 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered in sitting posture with 240 mL of drinking water at ambient temperature.
Length of Confinement	85 hours per period
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

[a]: Data in the table are from Module 5.3.1.2, Fed Study 766-15, Study Report Body, and Fed Study Protocol

Standard FDA Meal Used?							□ Yes ☑ No
If No, then meal components and composition is listed in the tables below							
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study Study No. 766-15							
Food items	**Ingredients**	**Qty. of ingredients**	**Energy (calories)**	**Carbohydrates (Energy)**	**Fats (Energy)**	**Proteins (Energy)**	**Vit K (µg)**
Milk (sterilized flavoured)	Milk	200 mL	113.784	32.384	55.8	25.6	1.2
	Sugar	16 gm	63.68	63.616	0	0.064	0
Chicken dana	Chicken	85 gm	92.65	0	4.59	88.06	2.04
	Refined flour	30 gm	104.31	88.68	2.43	13.2	0
	Egg	30 gm	51.87	0	35.91	15.96	1.68
	Oil	20 mL	180	0	180	0	0.14
Bread butter	Bread	20 gm	49.02	41.52	1.26	6.24	0
	Butter	15 gm	109.35	0	109.35	0	1.05
Potato chaat	Potato	30 gm	29.31	27.12	0.27	1.92	0.81
	Oil	15 mL	135	0	135	0	0.105
Total			**928.974**	**253.32**	**524.61**	**151.044**	**7.025**
Total nutrients calories in percentage of total			**NA**	**27.269**	**56.472**	**16.259**	**NA**

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 16 (B)

Reviewer's Comment on Fed Study Pre-Dose Meal:

Although, the firm indicated that they did not use a standard FDA meal, the pre-dose meal used in the fed study does follow the guidelines of a standard FDA meal. The FDA recommends, *a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively*[35,36]. The firm's non-standard pre-dose meal is acceptable

[35] Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, effective date: December 2002.

[36] An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal

Comments on Study Design: The firm's fed study design is inadequate.

The Draft Guidance on Phytonadione Tablets[37] recommends that the applicant measure baseline phytonadione levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. The firm's collection of pre-dose plasma sample is consistent with the guidance.

Based on the provided concentration versus time semi-log plots for baseline corrected trans- and cis-phytonadione, there are clear absorption and elimination phases for the majority of subjects.

The firm's study design with a sampling time up to 24 hours is sufficient (>3 folds of $T_{1/2}$) to cover the entire elimination phase for both trans-phytonadione (Test: Average $T_{1/2}$=6.385h; RLD: Average $T_{1/2}$=5.963h, baseline corrected data) and cis-phytonadione phytonadione (Test: Average $T_{1/2}$=5.064h; RLD: Average $T_{1/2}$=4.683h, baseline corrected data). The washout period of 7 days (>5 folds of $T_{1/2}$) is also appropriate.

The RLD label does not make mention of food effect. The Clinical Pharmacology Database indicates that dietary fat enhances absorption of the drug[38]. For trans-phytonadione (baseline corrected), for both test and reference, Cmax, AUC increases by approximately 13% and 8.5% , respectively, due to food intake. For cis-phytonadione (baseline corrected), for both test and reference, Cmax and AUC increases by 8% and 5%, respectively, due to food intake. Therefore, it is seen that both the test and references products exhibit absorption effects due to food effect.

However, the firm's fed study design is inadequate because the firm did not provide the potencies of each phytonadione isomer (trans- and cis-) in the test and RLD product drug lots used in the study. Therefor firm will be asked to provide the above mentioned information (please refer to Section **4.1.1.1.2**)

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects[a]

Study No. 766-15			
Parameters		**Treatment Groups**	
		Test Product N = 45	**Reference Product N = 45**
Age (years)	Mean ± SD	29.9 ± 5.94	29.9 ± 5.94
	Range	19-43	19-43
Age Groups	< 18	0 (0%)	0 (0%)
	18-40	43 (95.56%)	43 (95.56%)

can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

[37] OGD Guidance on Phytonadione Tablets, (Recommended Feb 2010, Revised Sep 2012, Jan 2016), available at: https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf

[38] Clinical Pharmacology: Serach Term: phytonadione Last Access: 9/20/2017

	41-64	02 (4.44%)	02 (4.44%)
	65-75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	45 (100%)	45 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	45 (100%)	45 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	22.51 ± 2.0707	22.51 ± 2.0707
	Range	18.91-24.85	18.91-24.85
Other Factors		NA	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 7 (B)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.2.2.2 Dropout Information[a]

Study No. 766-15					
Subject No.	**Reason for dropout / Replacement**		**Period**	**Replaced?**	**Replaced with**
(b) (6)	The subject discontinued from the study on his own accord prior to dosing.		On the day of dosing for Period-I	Yes	X-1
	The subject had an episode of vomiting at approximately 11:09 hours on 09 July 2016. Hence, he was withdrawn from the study on the ground of emesis.		I	No	N/AP
	Time and date of last IMP administered	**Last IMP administered**			
	09:16 hours 09 July 2016	Reference Product-R			
	The subject had an episode of vomiting at approximately 10:50 hours on 09 July 2016. Hence, he was withdrawn from the study on the ground of emesis.		I	No	N/AP
	Time and date of last IMP administered	**Last IMP administered**			
	09:24 hours 09 July 2016	Reference Product-R			
	The subject did not report to the clinical facility on the day of check-in for Period-II. Hence, he was considered to have discontinued from the study on his own accord.		II	No	N/AP

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 12 (A)

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

Reviewer Comments on Dropout Subject:

The reviewer checked the record from the firm's case report form (CRF, Module 5.3.1.2) and confirmed that the dropout reasons documented in CRF for the 4 subjects are consistent with the table above.

One subject, Subject (b) (6), discontinued from the study on his own accord prior to Period-I dosing. This subject was replaced by Subject No (b) (6) who was later, allotted Subject No (b) (6). The replacement was consistent with the fed protocol (Version 01, 04Feb2016) Section 8.2, "*Subsequent dropouts after dosing in Period-I will not be replaced…. Note: Extra subjects if available, may be checked-in on the day of check in of period-I to compensate for any dropout prior to dosing of period-I. These subjects will be dosed if there are dropouts prior to dosing in period-I.*"

Two subjects, Subjects (b) (6) were withdrawn on the ground of emesis. The occurrence of emesis was 1 hour 53 minutes (Subject (b) (6)) and 1 hour 25 minutes (Subject 1025), respectively, following administration of the reference product in Period-I. The median Tmax was 6h. The firm's handling of the 2 subjects experiencing emesis is consistent with the fed protocol Section 10.3 Withdraw Criteria, "*Any subject experience emesis at or before reported two times of median Tmax (i.e. 08 hours) after dosing of study drug*".

One subject, Subject (b) (6), did not report to the clinical facility on the day of check-in for Period-II. Hence, he was considered to have discontinued from the study on his own accord. The firm's handling of Subject (b) (6) is consistent with the fed protocol Section 10.3 Withdraw Criteria.

The firm analyzed the PK samples from the Subjects (b) (6) who experienced emesis (samples collected up to 1 hour post dosing), and did not include the 2 subjects in the statistical analysis, which is consistent with the fasting study protocol Section 8.10.2: "*Samples of subjects completing clinical study will be analyzed. In case of dropouts, samples of such subjects will not be taken for analysis except below mentioned reason:*
• If any subject experiences emesis, samples of that subject will be analyzed."

The dropouts are consistent with the fed protocol and therefore are acceptable

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups
	Fed Bioequivalence Study

	Study No. 766-15	
	Test Product	**Reference Product**
Body as a whole	0%	0%
Cardiovascular	0%	0%
Gastrointestinal		
Vomiting	0%	02 (4.17%)
Diarrhoea	0%	01 (2.08%)
Other organ system		
Typhoid fever	0%	01 (2.08%)
Headache	01 (2.22%)	01 (2.08%)
Thrombophlebitis	02 (4.44%)	03 (6.25%)
Total	**03 (6.66%)**	**08 (16.66%)**

Subjects Experiencing Emesis (Include in eCTD)[a]

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	R	I	09-Jul-16, 09:16AM	09-Jul-16, 11:09AM	1 hour 53 minutes
	R	I	09-Jul-16, 09:24AM	09-Jul-16, 10:50AM	1 hour 25 minutes

[a]: Module 5.3.1.2, Fed Study 766-15, Appendix 16.2.7, Adverse Event Listings

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No The total number of adverse events were higher in subjects taking the RLD. The will finding will not impact the safety determination of the test product (see below for more detail).

Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

Reviewer's Comments on Adverse Events:

Eleven (11) adverse events (AEs) were reported by seven (07) subjects during the conduct of the study. Seven (07) AEs were reported in Period-I and three (03) AEs were reported in Period-II and one (01) AE was reported during post-study safety assessment of the study. Eight (08) AEs were reported in subjects after administration of Reference Product-R and three (03) AEs were reported in subjects after administration of Test Product-T. All the AEs were mild in nature. The subjects were followed up until resolution of their AEs. The causality assessment was judged as unlikely for five (05) AEs and as unrelated for six (06) AEs. There were no deaths, serious or significant AEs during the conduct of the study.

Two subjects experienced emesis following administration of the reference product, and were withdrawn per protocol. The PK samples from the 2 subjects experiencing emesis (collected up to 1 hour post dosing) were assayed but not included in the statistical analysis (refer to Section **4.1.1.2.2**).

The AE profile observed during the pivotal fed study is considered comparable for the test and reference products.

4.1.2.2.4 Protocol Deviations[a]

Study No. 766-15		
Type	**Subject #s (Test T)**	**Subject #s (Ref. R)**
Housing As per the protocol, all the subjects were to be housed in the clinical facility at least 60 hours before administration of the investigational medicinal product in each period. However, few subjects were not housed in the clinical facility 60 hours before the administration of the investigational medicinal product as their screening laboratory reports were pending at that time. Refer Appendix No. 16.2.2 of Clinical Study Report for details.	(b) (6)	
Concomitant Medication As per the protocol, no drug (including herbal remedies) other than the investigational medicinal product was to be allowed to the subjects during the study period (i.e. from 14 days prior to dosing in Period-I till the collection of last pharmacokinetic sample in Period-II). However, few subjects were given medications to treat their adverse events in particular period of the study.		

Study No. 766-15		
Type	**Subject #s (Test T)**	**Subject #s (Ref. R)**
Refer Appendix No. 16.2.2 of Clinical Study Report for details.		

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 13 (BA)

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Reviewer's Comments on Protocol Deviations

- The deviations in the housing time (late check-in) will not impact study outcome.
- The firm states that based on the information from the RLD label, the deviations of concomitant medication are not considered to impact study outcome considering the pharmacokinetics and pharmacodynamics, duration, dose and route of administration of concomitant medications and the drug under investigations. The reviewer conducted statistical analysis with the exclusion of all subjects administered concomitant medication. The fed study still met BE acceptance criteria with the exclusion of these subjects.
- Per study protocol Section 8.9.1, *all post dose blood samples will be collected within ± 02 minutes from schedule time….Post dose samples not collected within this time frame from scheduled time will be documented as sampling deviations*. The firm did not report any PK sample time deviations in its protocol deviation list. However, the reviewer noticed that two samples (Subject (b) (6)_Period-I_1h and Subject (b) (6)_Period-II_2.5h) were collected 3 minutes later than the nominal time per the firm's fed SAS dataset. As the deviation is marginal and is not expected to impact study outcome, the reviewer will not pursue this issue.

Reviewer's Overall Comments on Dropout/Adverse Events/Protocol Deviations:

- The handling of dropouts in the statistical analysis was consistent with the protocol.
- The AE profiles are comparable between the test and RLD treatment.
- Protocol deviation did not compromise the integrity of the study.

The clinical results of the fed study are **adequate**.

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Preparation of calibration curve and quality control samples and defining analytical run organization and its acceptance criteria
		Repeat analysis and acceptance of results
		Chromatography acceptance criteria, re-injection, integration and reintegration on HPLC and LC-MS/MS data analysis
		Incurred sample reproducibility

All necessary SOPs submitted?	☒ Yes ☐ No

Reviewer's Note:

All above SOPs are provided in Module 5.3.1.4 Bioanalytical SOPs.

4.1.2.3.2 Sample Analysis Calibration and Quality Control[a]

Trans Phytonadione [766-15 (Fed)]

Bioequivalence Study No. 766-15 Analyte Name: Trans Phytonadione								
Parameter	**Standard Curve Samples**							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng / mL)	1.002	2.005	25.059	75.251	250.838	376.068	451.463	501.625
Inter day Precision (% CV)	1.5	2.9	3.4	2.1	2.8	1.9	2.7	2.9
Inter day Accuracy (% Actual)	99.3	101.3	100.2	100.5	99.1	98.8	100.2	100.5
Linearity	0.9966 to 0.9998							
Linearity Range (ng /mL)	1.002 ng / mL to 501.625 ng / mL							
Sensitivity/ LOQ (ng / mL)	1.002 ng / mL							

Bioequivalence Study No. 766-15 Analyte Name: Trans Phytonadione					
Parameter	**Quality Control Samples**				
Quality Control Sample Ids	HQC	MQC	LMQC	LQC	LQC(UV)
Concentration (ng / mL)	389.668	206.838	54.272	3.563	2.895
Inter day Precision (% CV)	5.0	6.7	4.2	6.5	6.0

Inter day Accuracy (% Actual)	97.4	97.5	101.4	98.4	101.1

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 14 (C)

Cis Phytonadione [766-15 (Fed)]

Bioequivalence Study No. 766-15 Analyte Name: Cis Phytonadione								
Parameter	**Standard Curve Samples**							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng / mL)	1.001	2.003	4.945	14.850	49.499	74.323	89.223	99.137
Inter day Precision (% CV)	2.4	5.0	2.6	2.8	3.2	3.4	2.5	2.9
Inter day Accuracy (% Actual)	102.6	94.0	102.1	100.4	100.2	98.3	100.9	101.6
Linearity	0.9902 to 0.9996							
Linearity Range (ng /mL)	1.001 ng / mL to 99.137 ng / mL							
Sensitivity/ LOQ (ng / mL)	1.001 ng / mL							

Bioequivalence Study No. 766-15 Analyte Name: Cis Phytonadione					
Parameter	**Quality Control Samples**				
Quality Control Sample Ids	HQC	MQC	LMQC	LQC	LQC(UV)
Concentration (ng / mL)	79.215	47.529	12.358	2.966	2.966
Inter day Precision (% CV)	5.4	8.7	4.6	6.9	5.5
Inter day Accuracy (% Actual)	99.8	96.7	101.0	95.2	95.2

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 14 (D)

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No Concentration data are in Compliance and Drug Concentration Data, Module 5.3.1.2, Appendix 16.2.5. **Baseline uncorrected trans-phytonadione**, Most subject samples are within 5 to 400 ng/mL (calibration rage: 1.002 ng/mL to 501.625 ng/mL) and QCs are well distributed (LQC(UV) 2.966 ng/mL, LQC 3.563 ng/mL, LMQC 54.672 ng/mL, MQC 206.838 ng/mL, and HQC 389.668 ng/mL);

	Baseline uncorrected cis-phytonadione: Most subject samples are within 3 to 40 ng/mL (calibration rage: 1.001 ng/mL to 99.137 ng/mL) and QCs are well distributed (LQC 2.966 ng/mL, LMQC 12.968 ng/mL, MQC 47.529 ng/mL, and HQC 79.215 ng/mL). Therefore the calibrators and QCs used in the study covered the entire concentration range.
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No (For both trans- and cis-phytonadione)
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No(For both trans- and cis-phytonadione)
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No(For both trans- and cis-phytonadione)
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No (For both trans- and cis-phytonadione)

Reviewer's Comments on Bioanalytical Results:

The firm provided the complete (100%) numerical raw data, incurred sample reanalysis (ISR) results, and 20% chromatograms in its submission Module 5.3.1.4 (bioanalytical report and chromatographic-data).

4.1.2.3.3 Reanalysis of Study Samples[a]

766-15 (Fed) (Trans-Phytonadione)

Study No. 766-15, Trans Phytonadione Additional information in Module 5/ Section 5.3.1.4/ Sample Analysis Report/ Page 22 of 99								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic [1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %

Subject sample analysis did not meet the analytical run acceptance criteria, as all of the normal LQC & LQC (UV) samples were not within the acceptance range.	60.0	60.0	4.4 %	4.4 %	60.0	60.0	4.4 %	4.4 %
Significant variation in response of internal standard	3.0	2.0	0.2 %	0.1 %	3.0	2.0	0.2 %	0.1 %
Processing error (No ISTD area response was obtained)	1.0	3.0	0.1 %	0.2 %	1.0	3.0	0.1 %	0.2 %
Processing error (less than 5% of mean ISTD area response of CC and QC samples of that particular run was obtained)	1.0	1.0	0.1 %	0.1 %	1.0	1.0	0.1 %	0.1 %
Concentration above highest standard.	0.0	1.0	0.0 %	0.1 %	0.0	1.0	0.0 %	0.1 %
Total	65.0	67.0	4.8 %	4.9 %	65.0	67.0	4.8 %	4.9 %

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
Total assay for Test Product (T): 1349 and Total assay for Reference Product (R):1370

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 9(C)

766-15 (Fed) (Cis-Phytonadione)

Study No. 766-15, Cis Phytonadione Additional information in Module 5/ Section 5.3.1.4/ Sample Analysis Report/ Page 23 of 99								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic [1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Significant variation in response of internal standard	5.0	1.0	0.4 %	0.1%	5.0	1.0	0.4 %	0.1%
Processing error (No ISTD area response was obtained)	1.0	3.0	0.1 %	0.2 %	1.0	3.0	0.1 %	0.2 %
Processing error (less than 5% of mean ISTD area response of CC and QC samples of that particular run was obtained)	2.0	0.0	0.1 %	0.0 %	2.0	0.0	0.1 %	0.0 %
Total	8.0	4.0	0.7 %	0.3 %	8.0	4.0	5.3 %	0.3 %

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
Total assay for Test Product (T): 1349 and Total assay for Reference Product (R):1370

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 9(D)

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No See comments below
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Reviewer's Comments on Reanalysis of Study Samples:

The summary for subject samples are provided in Module 5.3.1.4\Study 766-15\Bioanalytical Report, Section 7.1. The summary for repeat sample analysis and re-injection are provided in fed bioanalytical report, Section 7.3. The run summaries are provided in fed bioanalytical report, Table 01 (pages 29-31).

The 20% serially selected subjects (Subjects No (b) (6) sample chromatograms and 100% numerical raw data for the original and repeat analyses are provided in Module 5.3.1.4 Chromatographic-Data.

Trans-Phytonadione

Out of the 2719 samples analyzed, a total of 132 samples were reanalyzed for trans-phytonadione.

- **Whole Batch Reanalysis**

According to Fed Bioanalytical Report Section 7.3 and Table 05, one run, i.e., Run #24 (Subject (b) (6) each had 60 subject samples) failed due to not meeting the analytical run acceptance criteria, as all of the normal LQC & LQC(UV) samples were not within the acceptance range (>20%). Based on the raw data in Module 5.3.1.4 Chromatographic-Data, the reviewer confirmed that the original run for Subjects (b) (6) and (b) (6) did not meet the analytical run acceptance criteria in the firm's pre-established SOP (b) (4) Section 9.0), i.e., *At least 50% of the Non-zero QC samples at each level and at least 67% of the total Non-zero QC samples (including DQC) of the run must be within + 15% of their respective nominal concentration.* This run was appropriately identified for the whole batch repeat per firm's pre-established SOP ((b) (4) "Repeat analysis and acceptance of results").

- **Significant variation in response of internal standard**

According to Fed Bioanalytical Report Section 7.3 and Table 06a, five (5) samples were reanalyzed due to significant variation in response of internal standard. The reviewer spot checked the firm's raw data and confirmed that these samples were correctly identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4, "*If the response of internal standard in a sample varies by more than 35% from the mean ISTD response of CC and QC samples of a particular run, then repeat the analysis of the sample under this code*". For example, the IS area for 1001_P-II_4.5h was 190053 and the mean IS area of CC and QC samples is approximately 70000. The bioanalytical repeats for these 5 samples are acceptable.

- **Processing error**

Four (4) samples were reanalyzed due to processing error (No ISTD area response was obtained) and two (2) samples were reanalyzed due to processing error (less than 5% of mean ISTD area response of CC and QC samples). The reviewer spot checked the 100% raw data and confirmed that the 6 samples were appropriately identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4.

- **Concentration above highest standard**

One (1) sample (Subject (b) (6)_Period-II_4.5h) was reanalyzed due to concentration above highest standard. The reviewer spot checked the 100% raw data and confirmed this sample was appropriately identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4. Additionally, this sample was not Cmax of the subject, and the dilution integrity has been established in the pre-study method validation. The reported values are within 85% of ULOQ.

- **Re-integration**

According to Fed Bioanalytical Report Section 7.1, one run (Run #21 [Subjects (b) (6), (b) (6)]) was re-integrated because excessive drug area was integrated in sample Ids 2016111, 2016129, 2016229, 2016130, 2016230, LQC-1, LQC-2, LQC-3 & LQC-4. The firm provided the original and re-integrated chromatograms and numerical data in Module 5.3.1.4 Chromatographic-Data Section 16.5.7.4. The reviewer agrees that the re-integration is consistent with the firm's pre-established SOP (b) (4) ("Chromatography acceptance criteria, re-injection, integration and reintegration on HPLC and LC-MS/MS data analysis") Section 6.5. Additionally, the reviewer spot checked the raw data and found the back-calculated concentrations are similar before and after the re-integration. Therefore, the re-integration is acceptable.

Cis-Phytonadione (Supportive Data)

Out of the 2719 samples analyzed, a total of 12 samples were reanalyzed for cis-phytonadione.

- **Significant variation in response of internal standard**

Six (6) samples were reanalyzed due to significant variation in response of internal standard. The reviewer spot checked the firm's raw data and confirmed that these samples were correctly identified for repeat per the firm's pre-established SOP (b) (4).

- **Processing error**

Four (4) samples were reanalyzed due to processing error (No ISTD area response was obtained) and two (2) samples were reanalyzed due to processing error (less than 5% of mean ISTD area response of CC and QC samples). The reviewer spot checked the 100% raw data and confirmed that the 6 samples were appropriately identified for repeat per the firm's pre-established SOP (b) (4) Section 6.1.4.

Reviewer's Overall Comments on Bioanalytical Results:

The firm provided the complete (100%) numerical raw data, ISR results, and 20% chromatograms in its submission Module 5.3.1.4.

The firm conducted incurred sample reanalysis (ISR) using 254 subject samples for both analytes trans- and cis-phytonadione (93.42% of the total 2719 samples analyzed) as per

its SOP ([(b) (4)], 'Incurred Sample Reproducibility') Section 6.1.2, i.e., "*100 samples (10 % of 1000 samples) + 5 % of (Total samples - 1000 samples.* The ISR results are presented in Fed Bioanalytical Report Tables 08a and 08b. 243 out of 254 samples (95.7%) for trans-phytonadione and 238 out of 254 samples (93.7%) for cis-phytonadione were found to be within ±20 % bias. Of the ISR samples, at least one sample was close to maximum concentration and another sample was close to LQC, to cover the entire concentration range for both analytes. Thus ISR were within acceptance criteria specified in its SOP [(b) (4)].

In summary, the firm's submitted bioanalytical results for the fed study are **adequate**.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Trans-Phytonadione

4.1.2.4.1.1 Arithmetic Mean Pharmacokinetic Parameters

Trans-Phytonadione Baseline Corrected - Reviewer Calculated (N=45)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	1272.022	47.29	452.32	2758.01	1154.068	51.46	447.72	2989.96	1.10
AUCI	ng hr/mL	1325.240	46.57	460.70	2849.77	1202.072	50.39	471.23	3056.20	1.10
CMAX	ng/mL	235.806	40.14	80.67	434.02	231.987	40.05	103.18	489.31	1.02
TMAX	hr	6.000	.	3.00	7.50	6.000	.	2.52	8.00	1.00
KE	hr-1	0.122	35.39	0.04	0.22	0.132	37.63	0.06	0.25	0.93
THALF	hr	6.528	43.62	3.09	16.45	5.963	34.90	2.81	11.09	1.09

Tmax values are presented as median, range

4.1.2.4.1.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Unscaled Average BE for Baseline Corrected Trans-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☐Yes ☒No

Phytonadione Tablets (No of subjects completed, N = 45)
Dose (1 × 5 mg)
Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals

Fed Bioequivalence Study (Project No.766-15)

Parameter	Test	N	RLD	N	Ratio (%)	90% C.I.
AUC_{0-t}	1135.995	45	1030.676	45	110.2	102.29 - 118.77
$AUC_{0-\infty}$	1186.930	45	1076.965	45	110.2	102.49 - 118.51
C_{max}	217.108	45	215.382	45	100.8	92.81 - 109.48

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (5)

Unscaled Average BE for Baseline Uncorrected (For Information) Trans-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☐Yes ☒No

Phytonadione Tablets (No of subjects completed, N = 45) Dose (1 × 5 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fed Bioequivalence Study (Project No.766-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio (%)**	**90% C.I.**
AUC_{0-t}	1140.671	45	1035.827	45	110.1	102.23 - 118.63
$AUC_{0-\infty}$	1194.797	45	1084.805	45	110.1	102.47 - 118.38
C_{max}	217.336	45	215.644	45	100.8	92.80 - 109.46

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (6)

4.1.2.4.1.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Unscaled Average BE for Baseline Corrected Trans-Phytonadione (N=45)

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT (ng.h/mL)	1135.99	1030.68	1.10	102.29	118.77
LAUCI (ng h/mL)	1188.32	1076.96	1.10	102.65	118.60
LCMAX (ng/mL)	217.11	215.38	1.01	92.81	109.48

Unscaled Average BE for Baseline Uncorrected (For Information) Trans-Phytonadione (N=45)

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT (ng.h/mL)	1140.67	1035.83	1.10	102.23	118.63
LAUCI (ng h/mL)	1196.20	1084.81	1.10	102.63	118.47
LCMAX (ng/mL)	217.34	215.64	1.01	92.80	109.46

4.1.2.4.1.4 Additional Information for the Study

Root Mean Square Error	AUCt: 0.2103 AUCi: 0.2033 Cmax: 0.2326
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No For both Test and Reference, Tmax median is 6h. Range: Test 3-7.5 h, Reference: 2.52-8h
Were the subjects dosed in groups?	☐ Yes ☒ No

If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No See comment below
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	45	0.96	0.84	0.99
Reference	45	0.96	0.88	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Reviewer's Comments on Statistical Analysis of Trans-Phytonadione

Per the current draft guidance for Phytonadione tablets[39], *baseline correction should be based on phytonadione levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. If the baseline is stable, you may choose to do baseline correction for 24 hours rather than 48 hours*. The firm used the average levels from -48 to 0 hour as baseline. The reviewer considers that the firm's approach is appropriate because the baseline level of trans-phytonadione shows some fluctuation. The reviewer also spot checked the firm's SAS dataset and confirmed that the firm's calculation of baseline correction is correct.

The reviewer conducted a confirmatory SAS analysis of plasma trans-phytonadione using the CALCKE SAS program with the original dataset submitted by the firm. The results indicate that the geometric mean ratios and 90% CIs of Cmax and AUCt calculated by the reviewer are the same as that by the firm.

There are marginal differences in the results of AUCi between the firm and reviewer's analyses likely due to different selection of data points for the determination of the terminal phase. Both the firm and the reviewer used actual time in the analysis.

[39] OGD Guidance on Phytonadione Tablets, (Recommended Feb 2010, Revised Sep 2012, Jan 2016), available at: https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199670.pdf

For both the firm and the reviewer's calculation, the 90% CIs for least squares geometric mean of LnCmax LnAUCt and LnAUCI of trans-phytonadione in the pivotal fed study are within the BE acceptable range of 80.00-125.00%.

One subject (Subject (b) (6)_Period-I) had a predose concentration of baseline corrected trans-phytonadione (0.119 ng/mL), which is less than 5% of Cmax (374.926 ng/mL). Per the FDA's Guidance for Industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (December 2013)[40], this subject was included in both the firm and reviewer's statistical analysis.

The median Tmax of trans-phytonadione is the same (6 h) for the test and reference products with a slight difference in the individual Tmax range (Test: 3-7.5 h; Reference: 2.52-8 h). The Tmax of trans-phytonadione is considered similar between the Test and RLD.

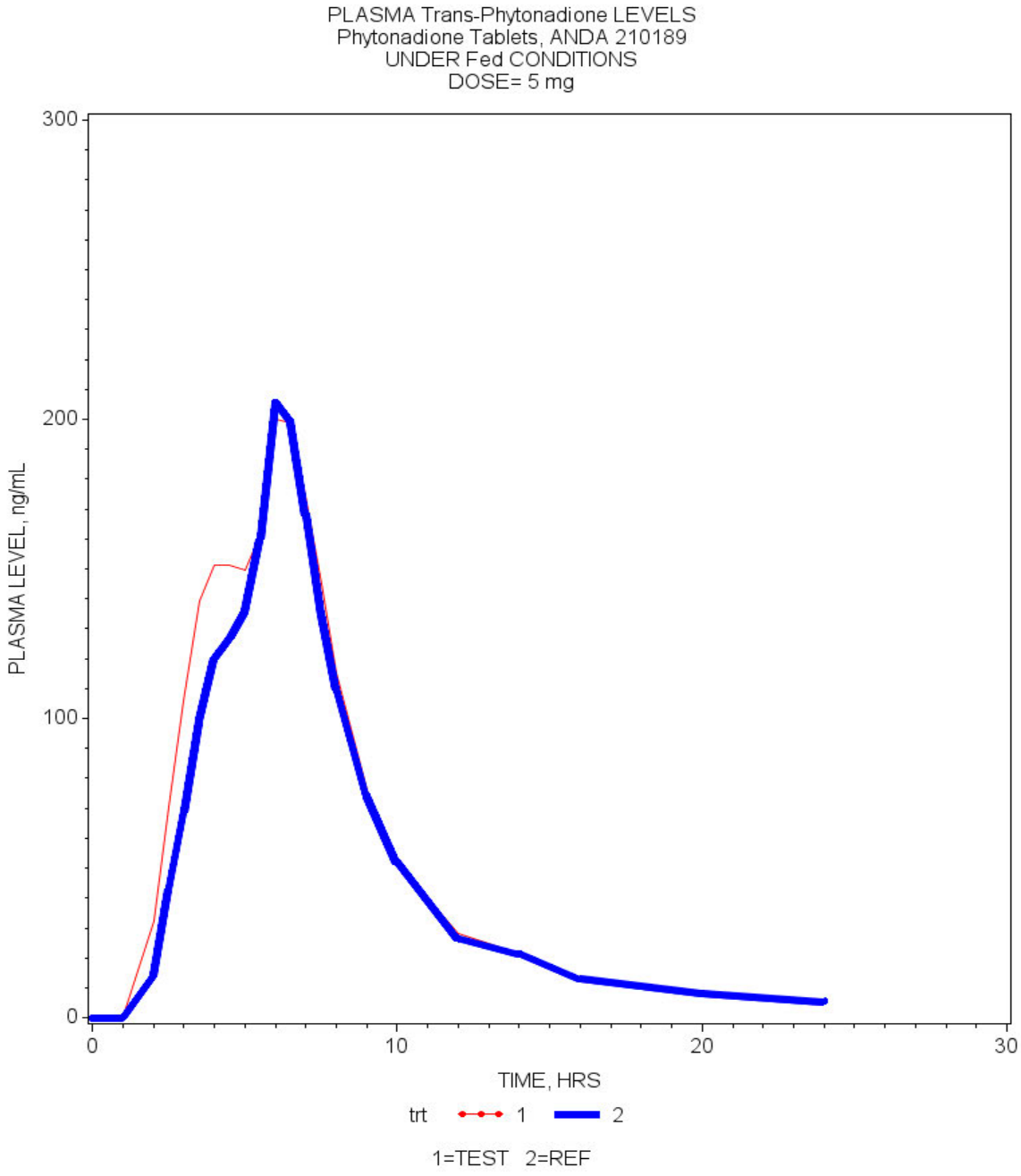
Baseline Corrected Trans-phytonadione Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study – Reviewer Calculated

	Test (n=45)		Reference (n=45)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	670.82	0.00	.	.
1.00	0.62	473.09	0.07	474.97	9.01
2.00	32.40	129.47	14.07	165.75	2.30
2.50	70.31	97.18	43.08	129.04	1.63
3.00	105.92	77.93	68.96	103.53	1.54
3.50	139.13	66.89	99.30	80.82	1.40
4.00	151.10	60.03	120.04	74.64	1.26
4.50	151.26	53.63	126.79	72.63	1.19
5.00	149.51	52.91	135.70	65.47	1.10
5.50	160.95	50.62	159.97	54.94	1.01
6.00	199.99	46.87	205.58	45.99	0.97
6.50	198.59	47.91	199.29	50.45	1.00
7.00	174.30	52.24	168.22	57.60	1.04
7.50	145.13	60.32	134.85	67.69	1.08
8.00	115.13	68.67	109.65	74.59	1.05
9.00	76.23	74.65	74.19	84.23	1.03
10.00	51.97	84.91	52.17	83.15	1.00
12.00	27.96	86.71	26.48	77.92	1.06
14.00	21.57	58.31	21.51	61.93	1.00

40 http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377465.pdf , Recommended on December 2013, Last accessed on 01/18/2017

	Test (n=45)		Reference (n=45)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
16.00	13.02	54.29	12.87	61.51	1.01
20.00	8.63	55.20	8.13	53.76	1.06
24.00	5.70	54.89	5.55	54.80	1.03

Baseline Corrected Trans-phytonadione Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study -– Reviewer Generated



4.1.2.4.2 Cis-Phytonadione

4.1.2.4.2.1 Arithmetic Mean Pharmacokinetic Parameters

Cis-Phytonadione Baseline Corrected - Reviewer Calculated (N=45)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	185.800	47.13	65.15	394.68	153.527	51.61	59.03	403.40	1.21
AUCI	ng hr/mL	196.184	45.72	69.87	412.91	162.576	50.10	66.43	418.44	1.21
CMAX	ng/mL	34.661	38.44	12.10	68.72	31.272	39.19	14.22	69.35	1.11
TMAX	hr	6.000	.	3.00	7.50	6.000	.	2.52	8.00	1.00
KE	hr-1	0.163	43.43	0.05	0.34	0.186	47.29	0.06	0.40	0.87
THALF	hr	5.161	46.85	2.02	13.73	4.683	50.91	1.73	11.00	1.10

Tmax values are presented as median, range

4.1.2.4.2.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Unscaled Average BE for Baseline Corrected Cis-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☐Yes ☒No

Phytonadione Tablets (No of subjects completed, N = 45)
Dose (1 × 5 mg)
Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals

Fed Bioequivalence Study (Project No.766-15)

Parameter	Test	N	RLD	N	Ratio (%)	90% C.I.
AUC_{0-t}	166.169	45	137.072	45	121.2	113.00 - 130.05
$AUC_{0-\infty}$	176.384	45	145.904	45	120.9	112.98 - 129.35
C_{max}	32.190	45	29.199	45	110.2	101.92 - 119.24

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (7)

Unscaled Average BE for Baseline Uncorrected (For Information) Cis-Phytonadione[a]

Reference Scaled Average Bioequivalence Approach Used	☐Yes ☒No

Phytonadione Tablets (No of subjects completed, N = 45)
Dose (1 × 5 mg)
Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals

Fed Bioequivalence Study (Project No.766-15)

Parameter	Test	N	RLD	N	Ratio (%)	90% C.I.
AUC_{0-t}	166.169	45	137.072	45	121.2	113.00 - 130.05

$AUC_{0-\infty}$	176.384	45	145.904	45	120.9	112.98 - 129.35
C_{max}	32.190	45	29.199	45	110.2	101.92 - 119.24

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 3A (8)

4.1.2.4.2.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Unscaled Average BE for Baseline Corrected Cis-Phytonadione (N=45)

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT (ng.h/mL)	166.17	137.07	1.21	113.00	130.05
LAUCI (ng h/mL)	176.65	145.90	1.21	113.22	129.48
LCMAX (ng/mL)	32.19	29.20	1.10	101.92	119.24

Unscaled Average BE for Baseline Uncorrected (For Information) Cis-Phytonadione (N=45)

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT (ng.h/mL)	166.17	137.07	1.21	113.00	130.05
LAUCI (ng h/mL)	176.65	145.90	1.21	113.22	129.48
LCMAX (ng/mL)	32.19	29.20	1.10	101.92	119.24

Reviewer's Note:
For both the reviewer and the firm's calculations, the analysis using baseline corrected data and uncorrected data are identical because all baseline cis-phytonadione levels were BLQ.

4.1.2.4.2.4 Additional Information for the Study

Root Mean Square Error	AUCt: 0.1978 AUCi: 0.1889 Cmax: 0.2210
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No For both Test and Reference, Tmax median is 6h. Range: Test 3-7.5 h, Reference: 2.52-8h
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr?	☐ Yes ☒ No

If yes, please comment (and take necessary action, if needed).	
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	45	0.94	0.81	0.99
Reference	45	0.94	0.86	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Reviewer's Comments on Statistical Analysis of Cis-Phytonadione

The reviewer conducted a confirmatory SAS analysis of plasma cis-phytonadione using the CALCKE SAS program with the original dataset submitted by the firm. The results indicate that the geometric mean ratios and 90% CIs of Cmax and AUCt calculated by the reviewer are the same as that by the firm.

There are marginal differences in the results of AUCi between the firm and reviewer's analyses likely due to different selection of data points for the determination of the terminal phase. Both the firm and the reviewer used actual time in the analysis.

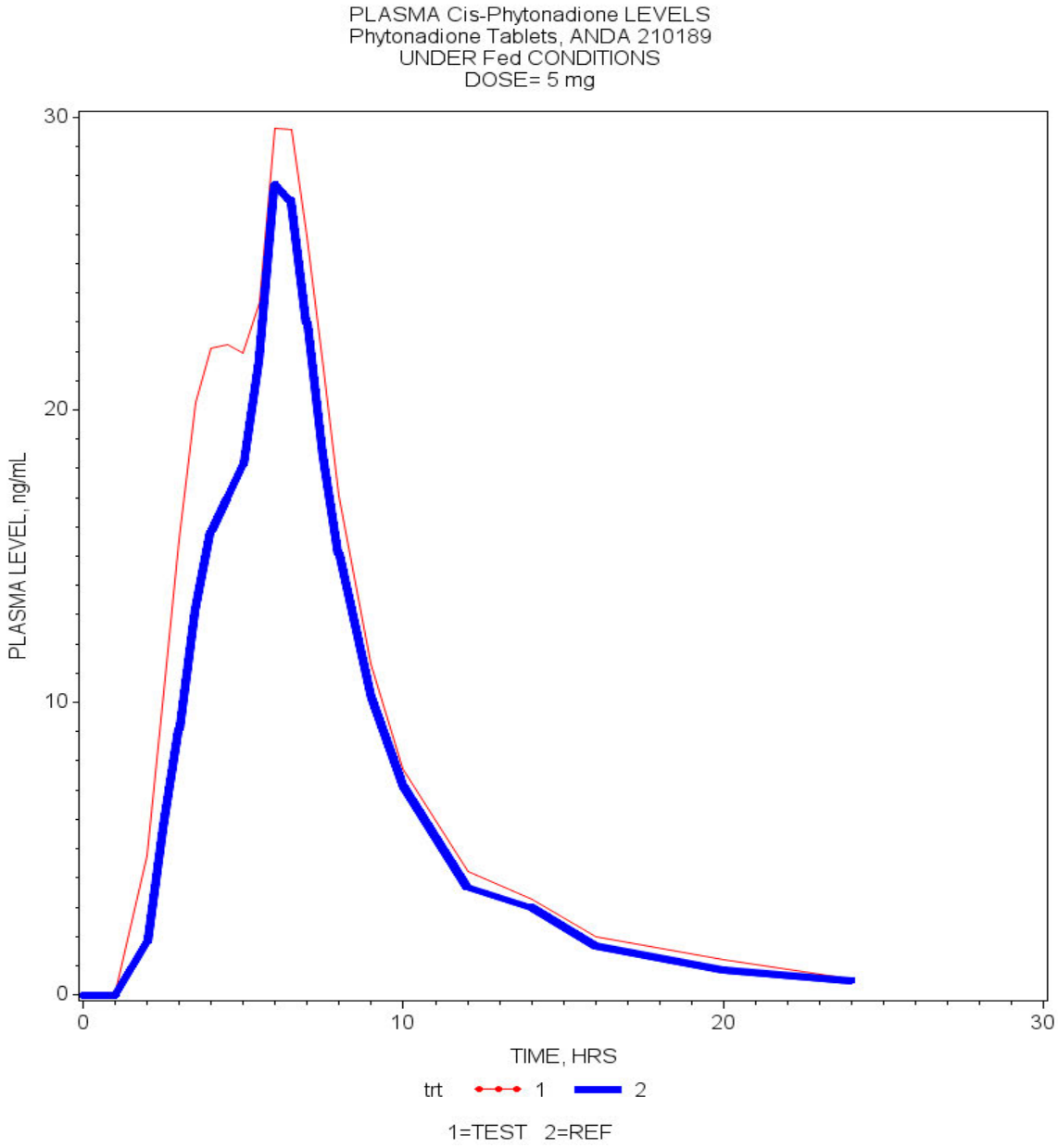
For both the firm and the reviewer's calculation, the 90% CI for least squares geometric mean of Cmax of cis-phytonadione in the pivotal fed study are within 80.00-125.00%. The 90% CIs for least squares geometric mean for AUCt (113.00%-130.05%) and AUCi (113.22%-129.48%) are not within the range of 80.00-125.00%. Therefore, the statistical analysis shows that the test product has higher bioavailability than the reference product for cis-phytonadione. The data for cis-phytonadione are therefore, not considered as supportive of trans-phytonadione analysis. The firm will be requested to explain why the test product shows higher bioavailability for cis-phytonadione than the reference product.

The median Tmax of cis-phytonadione is the same (6 h) for the test and reference products with a slight difference in the individual Tmax range (Test: 3-7.5 h; Reference: 2.52-8 h). The Tmax of cis-phytonadione is considered similar between the Test and RLD.

Baseline Corrected Cis-phytonadione Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study – Reviewer Calculated

	Test (n=45)		Reference (n=45)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	0.06	670.82	0.00	.	.
2.00	4.76	123.50	1.84	171.62	2.59
2.50	10.32	92.34	5.73	126.28	1.80
3.00	15.54	75.56	9.11	101.10	1.70
3.50	20.26	65.24	13.16	78.87	1.54
4.00	22.12	58.67	15.85	71.57	1.40
4.50	22.25	51.80	17.01	73.96	1.31
5.00	21.96	51.66	18.14	63.37	1.21
5.50	23.68	48.21	21.72	52.84	1.09
6.00	29.62	45.17	27.71	43.61	1.07
6.50	29.57	44.97	27.16	47.73	1.09
7.00	25.94	49.30	22.97	54.72	1.13
7.50	21.40	57.29	18.45	63.69	1.16
8.00	17.05	65.90	15.08	69.99	1.13
9.00	11.30	72.31	10.17	78.13	1.11
10.00	7.72	80.85	7.13	75.88	1.08
12.00	4.23	82.58	3.68	72.00	1.15
14.00	3.28	57.34	3.00	57.88	1.09
16.00	1.98	58.18	1.69	74.55	1.17
20.00	1.20	81.76	0.87	106.78	1.38
24.00	0.54	148.11	0.50	144.33	1.08

Baseline Corrected Cis-phytonadione Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study -– Reviewer Generated



Was the fed bioequivalence study acceptable? Inadequate

4.1.3 Single-dose Pilot Fasting Bioequivalence Study

The firm submitted summary tables of a pilot fasting (Study Number: 763-15) on batch #5-F012A in Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, pages #78-100.

The reviewer confirmed that the formulation of lot# 5-F012A used for pilot fasting study (Module 2.7.1, page #87 Table 6) are qualitatively and quantitatively different from the formulation of Lot# EE60280 used for pivotal fating and fed studies (Module 2.3 Quality Overall Summary). Per current DB practice, the pilot BE study using different formulation from the ANDA exhibit batch are provided for information only.

The summary tables for the pilot fasting study (Study Number: 763-15) are presented below.

TABLE 2(A): SUMMARY OF BIOAVAILABILITY STUDIES (E isomer-**TRANS-PHYTONADIONE BASELINE CORRECTED)-FASTING**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study # 763-15	To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's Test Product relative to that of Reference Product in normal, healthy, adult subjects under fasting conditions and to assess the bioequivalence. To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, replicate, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fasting conditions.	Phytonadione Tablets 5 mg 1× 5 mg, Oral, [Batch No.: 5-F012A]	12 dosed, 11 completed study (11 males) Healthy male subjects Age: 29.7 (19-38) years	16973.072±9709.368 (57.205)	6.750 (5.000-10.000)	139981.440±81828.544(58.457)	146838.003±86682.084 (59.032)	3.740±1.225 (32.768)	0.207±0.071 (34.140)	NA
			MEPHYTON® (Phytonadione) Tablets 5 mg 1× 5 mg, Oral, [Lot No.: 14A094P]		18077.897±13100.069 (72.465)	6.500 (5.500-12.000)	133854.956±100377.811 (74.990)	152751.595±101103.729 (66.188)	4.097±1.533 (37.410)	0.193±0.082 (42.199)	

Note: The mean age is calculated based on completed subjects Tmax is presented as Median (Range).

Table 2 (B): Summary of Bioavailability Studies (E isomer-Trans-Phytonadione Baseline Uncorrected)-Fasting

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/ mL)	AUCi (ng*hr/ mL)	tHalf (hr)	Kel (1/hr)	
Study # 763-15	To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's Test Product relative to that of Reference Product in normal, healthy, adult subjects under fasting conditions and to assess the bioequivalence. To monitor the safety of the subjects.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, replicate, crossover, single dose, oral bioequivalence study in normal, healthy, adult subjects under fasting conditions.	Phytonadione Tablets 5 mg 1× 5 mg, Oral, [Batch No.: 5-F012A]	12 dosed, 11 completed study (11 males) Healthy male subjects Age: 29.7 (19-38) years	18219.465±9955.164 (54.64)	6.750 (5.000-10.000)	168592.393±87676.166 (52.005)	187050.557±99674.625 (53.288)	5.629±1.301 (23.113)	0.129±0.028 (21.856)	NA
			MEPHYTON® (Phytonadione) Tablets 5 mg 1× 5 mg, Oral, [Lot No.: 14A094P]		19427.927±13265.695 (68.282)	6.500 (5.500-12.000)	163499.306±106158.214 (64.929)	184047.964±113963.124 (61.92)	6.719±3.598 (53.55)	0.124±0.044 (35.778)	

Note: The mean age is calculated based on completed subjects Tmax is presented as Median (Range).

Table 1A Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies (E isomer-Trans-Phytonadione Baseline Corrected)-Fasting

Reference Scaled Average Bioequivalence Approach Used ☑ Yes □ No						
If No, then complete Table 3A only						
If Yes, then complete Tables 3A and 3B						
Phytonadione Tablets 5 mg (No of subjects completed= 11) 1× 5 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (763-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUCt	123990.92	11	102832.26	11	120.58%	(84.23%; 172.61%)
AUCi	129863.79	11	129005.56	11	100.67%	(81.44%; 124.44%)
Cmax	15192.23	11	14259.94	11	106.54%	(78.98%; 143.71%)

Table 3B Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	NA	NA	NA	0.5437	0.7374	-0.0733<0	Reference scaled	bioequivalent
LAUCi	NA	NA	NA	0.2182	0.4671	-0.0640<0	Reference scaled	bioequivalent
LCMAX	NA	NA	NA	0.4246	0.6516	-0.1399<0	Reference scaled	bioequivalent

Table 3A Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (E isomer-Trans-Phytonadione Baseline Uncorrected)-Fasting

Reference Scaled Average Bioequivalence Approach Used ☑ Yes □ No						
If No, then complete Table 3A only						
If Yes, then complete Tables 3A and 3B						
Phytonadione Tablets 5 mg (No of subjects completed= 11) 1× 5 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (763-15)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUCt	153653.92	11	138833.98	11	110.67%	(87.15%; 140.55%)
AUCi	169994.47	11	157069.05	11	108.23%	(84.15%; 139.20%)
Cmax	16481.49	11	15891.40	11	103.71%	(79.97%; 134.51%)

Table 3B Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	NA	NA	NA	0.2260	0.4753	-0.0380<0	Reference scaled	bioequivalent
LAUCi	NA	NA	NA	0.2306	0.4802	-0.0470<0	Reference scaled	bioequivalent
LCMAX	NA	NA	NA	0.3299	0.5744	-0.1188<0	Reference scaled	bioequivalent

Table 4 Bioanalytical Method Validation-Fasting

Information Requested	Data	
Bioanalytical method validation report location	N/AP	
Analyte	Trans-Phytonadione and Cis-Phytonadione	
Internal Standard (IS)	Trans-Phytonadione-d7 for Trans-Phytonadione Cis-Phytonadione-d7 for Cis-Phytonadione	
Method description	(b) (4)	
	Trans-Phytonadione	Cis-Phytonadione
Limit of quantitation (pg/mL)	200.021 pg / mL	200.141 pg / mL
Average Recovery of drug (%) (LQC, MQC and HQC)	Not performed	Not performed
Average Recovery of IS (%)	Not performed	Not performed
Standard curve concentrations (pg/mL)	200.021 to 75006.575 pg / mL	200.141 to 10056.925 pg/mL
QC concentrations (pg/mL) (LOQ QC, LQC, LMQC, MQC & HQC)	203.110 pg/mL, 597.384 pg/mL, 7508.593 pg/mL, 30647.320 pg/mL and 45069.588 pg/mL	201.546 pg/mL, 592.783 pg/mL, 1054.023 pg/mL, 4216.093 pg/mL and 7665.624 pg/mL
QC Intraday precision range	1.0 % to 2.2 %	1.3 % to 2.7 %
QC Intraday accuracy range (%)	88.3 % to 100.3 %	91.9 % to 106.3 %
QC Interday precision range (%)	6.7 % to 9.4 %	2.7 % to 10.5 %
QC Interday accuracy range (%)	92.2 % to 98.3 %	100.2 % to 107.7 %

Bench-top stability (hrs)	11.0 hours (in ice-cold water bath)
Stock stability (days)	Not performed
Processed stability (hrs)	101.0 hours (within 2 to 8°C)
Freeze-thaw stability (cycles)	3 cycles (at -65 ± 10 °C)
Long-term storage stability (days)	Not performed
Dilution integrity	Not performed
Selectivity	Not performed

Table 7 Demographic Profile of Subjects Completing the Bioequivalence Study-Fasting

Study No. 763-15			
Parameters		**Treatment Groups**	
		Test Product N = 11	**Reference Product N = 11**
Age (years)	Mean ± SD	29.7 ± 5.10	29.7 ± 5.10
	Range	19-38	19-38
Age Groups	< 18	0 (0%)	0 (0%)
	18-40	11 (100%)	11 (100%)
	41-64	0 (0%)	0 (0%)
	65-75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	11 (100%)	11 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	11 (100%)	11 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	21.975 ± 2.3925	21.975 ± 2.3925
	Range	18.71-24.73	18.71-24.73
Other Factors		NA	

Table 8 Incidence of Adverse Events in Individual Study-Fasting

Body System / Adverse Event	**Reported Incidence by Treatment Groups**
	Fasting Bioequivalence Study Study No. 763-15

	Test Product	Reference Product
There were no adverse events during the conduct of the study.		

Table 9a Reanalysis of Study Samples (E isomer-Trans-Phytonadione)-Fasting

Study No. 763-15 (Trans-Phytonadione)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic [1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Significant variation in response of internal standard	5.0	2.0	0.8 %	0.3 %	5.0	2.0	0.8 %	0.3 %
Entire run was reanalyzed due to insufficient sample volume after reinjection.	52.0	52.0	8.7 %	8.7 %	52.0	52.0	8.7 %	8.7 %
Total	57.0	57.0	9.5 %	9.5 %	57.0	57.0	9.5 %	9.5 %

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
Total assay for Test Product (T):598 and Total assay for Reference Product (R):598

Table 9b Reanalysis of Study Samples (Z isomer-Cis-Phytonadione)-Fasting

Study No. 763-15 (Cis-Phytonadione)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Significant variation in response of internal standard	3.0	0.0	0.5 %	0.0 %	3.0	0.0	0.5 %	0.0 %
Concentration above highest standard	7.0	1.0	1.2%	0.2%	7.0	1.0	1.2%	0.2%
Entire run was reanalyzed due to insufficient sample volume after reinjection.	52.0	52.0	8.7 %	8.7 %	52.0	52.0	8.7 %	8.7 %
Total	62.0	53.0	9.9 %	8.9 %	62.0	53.0	9.9 %	8.9 %

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
Total assay for Test Product (T):598 and Total assay for Reference Product (R):598

Table 10 Study Information-Fasting

Study Number	763-15
Study Title	An open label, balanced, randomized, two-treatment, two-sequence, four period, replicate, crossover, single dose, oral bioequivalence study of Phytonadione tablets 5 mg of Cadila Healthcare Ltd., India comparing with MEPHYTON® (Phytonadione) tablets 5 mg of Aton Pharma, Lawrenceville, NJ 08648, USA in normal, healthy, adult subjects under fasting condition
Study Type	☑ *In-vivo* BE ☐ *In-vitro* BE ☐ Permeability ☐ Other
Submission Location: Study Report: Validation Report: Bio-analytical Report:	 Not applicable Not applicable Not applicable
Clinical Site **(Name, Address, Phone #, Fax #)**	Lambda Therapeutic Research Ltd. Plot No. 38, Near Silver Oak Club, S.G. Highway, Gota, Ahmedabad-380 061, Gujarat, India. Tel. No. + 91-79-40202020 Fax No. + 91-79-40202021
Principal Clinical Investigator **(Name, Email)**	Dr. Ketul Modi, M.B.B.S. ketulmodi@lambda-cro.com
Analytical Site **(Name, Address, Phone #, Fax #)**	(b) (4)
Principal Analytical Director	
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20° C to -80° C)**	(a) 38 days (28 January 2016 to 06 March 2016) (b) At -65 ± 10 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Not performed
LTSS Data Location	Not performed

Table 11 Product Information

Product	**Test**	**Reference**
Treatment ID	T	R
Product Name	Phytonadione Tablets USP, 5 mg	MEPHYTON® (Phytonadione) Tablets 5 mg
Manufacturer	Cadila Healthcare Limited,	***Manufactured By:***

	Ahmedabad, India	Valeant Pharmaceuticals, Inc. Steinbach, MB R5G 1Z7 Canada ***Distributed By:*** Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807
Batch/Lot No.	5-F012A	14A094P
Manufacture Date	May 2015	N/A
Expiration Date	N/A	July 2016
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4) Tablets	N/A
Production Batch Size	NA	N/A
Potency	100.4%	99.9%
Content Uniformity (mean, %CV)	NA	NA
Dose Administered	1 x (5 mg)	1 x (5 mg)
Route of Administration	Oral	Oral

Table 12 Dropout Information -Fasting

Study No. 763-15					
Subject No.	**Reason for dropout**		**Period**	**Replaced?**	**Replaced with**
(b) (6)	The subject was found positive during breath test for alcohol consumption on the day of check-in for Period-III. Hence, he was withdrawn from the study on the grounds of protocol non-compliance.		III	No	-
	Time and date of last IMP administered	**Last IMP administered**			
	09:10 hours 02 February 2016	Test Product-T			

Table 13 Protocol Deviations-Fasting

Study No. 763-15		
Type	**Subject #s (Test T)**	**Subject #s (Ref. R)**
Plasma separation As per the protocol, transfer of plasma samples into freezer was to be taken place as soon as possible, so that total time elapsed from blood collection to placement of plasma samples in the freezer should not be exceed 90 minutes. However, for the subjects deviation was observed in this regard as for samples of -48.000 hours time point, total time exceeded 02 to 20 minutes from 90 minutes in Period-II.		(b) (6)

Study No. 763-15		
Type	**Subject #s (Test T)**	**Subject #s (Ref. R)**
Bio-analysis As per protocol, section 8.10.2, plasma concentrations of Trans (E) Phytonadione & Cis (Z) Phytonadione were to be quantified using validated LC-MS/MS method. However, plasma concentrations of Trans (E) Phytonadione & Cis (Z) Phytonadione were quantified using pre-validated LC-MS/MS method. This has no impact on the final outcome of study results, as being a pilot study it was decided to perform study sample analysis based on pre method validation data after sponsor's approval. Moreover, linearity, precision, accuracy as well as stability data were generated in purview of study to support study sample analysis	All	All
Bio-analysis As per protocol, section 8.10.2, Bio-analytical study plan needed to be prepared before study sample analysis. However, study sample analysis was carried out without preparing Bio-analytical study plan. Being a pilot study and was to be carried out based on pre-method validation data using draft method SOP, it was decided not to prepare study plan for the project after getting sponsor's approval. This has no impact on generated data as study sample analysis was carried out as per requirement of protocol and based on pre defined criteria	All	All

Table 14a Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses- E isomer-Trans Phytonadione-Fasting

Bioequivalence Study No. 763-15 Analyte Name: Trans Phytonadione								
Parameter	**Parameter**							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD 8
Concentration (pg/mL)	200.021	400.042	3773.982	11265.617	37552.057	56299.935	67505.918	75006.575
Inter day Precision (% CV)	2.6	4.9	3.2	4.4	2.2	2.7	4.5	4.7
Inter day Accuracy (% Actual)	0.9928 to 0.9985							
Linearity	200.021 pg/mL to 75006.575 pg/mL							
Linearity Range (pg /mL)	200.021 pg/mL							

Bioequivalence Study No. 763-15 Analyte Name: Trans Phytonadione				
Parameter	**Quality Control Samples**			
Quality Control Sample Ids	HQC	MQC	LMQC	LQC
Concentration (pg / mL)	45069.588	30647.320	7508.593	597.384
Inter day Precision (% CV)	6.7	5.1	7.5	11.2
Inter day Accuracy (% Actual)	98.3	98.0	99.0	92.2

Bioequivalence Study No. 763-15 Analyte Name: Trans-Phytonadione			
Parameter	**Formulation Quality Control Samples**		
Quality Control Sample Ids	HQC	MQC	LQC
Inter day Precision (% CV)	8.4	9.8	9.6

Table 14b Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses- Z isomer-Cis-Phytonadione-Fasting

Bioequivalence Study No. 763-15 Analyte Name: Cis-Phytonadione								
Parameter	**Standard Curve Samples**							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (pg/mL)	200.141	400.283	503.500	1510.501	5035.002	7548.728	9051.233	10056.925
Inter day Precision (% CV)	3.5	4.7	3.3	5.6	3.6	3.5	6.5	5.9
Inter day Accuracy (% Actual)	95.2	104.0	109.2	97.9	97.7	101.4	98.5	97.0
Linearity	0.9867 to 0.9983							
Linearity Range (pg /mL)	200.141 pg/mL to 10056.925 pg/mL							
Sensitivity/ LOQ (pg/mL)	200.141 pg/mL							

Bioequivalence Study No. 763-15 Analyte Name: Cis-Phytonadione				
Parameter	**Quality Control Samples**			
Quality Control Sample Ids	HQC	MQC	LMQC	LQC
Concentration (pg / mL)	7665.624	4216.093	1054.023	592.783
Inter day Precision (% CV)	6.3	5.7	6.6	12.0
Inter day Accuracy (% Actual)	96.2	101.3	98.4	99.7

Bioequivalence Study No. 763-15 Analyte Name: Cis-Phytonadione			
Parameter	**Formulation Quality Control Samples**		
Quality Control Sample Ids	HQC	MQC	LQC
Inter day Precision (% CV)	5.0	8.5	11.7

Reviewer's Comments on Pilot Fasting Study:

- The firm conducted a pilot fasting BE study fasting (Study Number: 763-15) using batch # 5-F012A, which had different formulation from the ANDA exhibit batch (Lot# EE60280) used in the pivotal fasting and fed studies.

- The pilot fasting study was designed as randomized, two-treatment, two-sequence, four period, replicate, crossover, single dose study in a total of 11 healthy male subjects.

- There was no AE reported in the pilot fasting BE study.

- The firm conducted statistical analysis for trans-phytonadione using both reference scaled average BE (SABE) approach and unscaled average BE approach. The estimated within subject variability (s_{WR}) > 0.294 for all 3 parameters AUCt, AUCi and Cmax. The results of the SABE analysis shows that the 95% upper confidence bounds for $(\mu T - \mu R)^2 - \theta s^2_{WR}$ for AUCt, AUCi and Cmax of baseline corrected trans-phytonadione are all < 0.

4.2 Formulation Data

4.2.1 Test Formulation [a,b]

Sr. No.	Name of Ingredient	5 mg		Function
		mg/unit	%w/w[$]	
[redacted]				
[redacted]	Phytonadione, USP*	5.000	[redacted]	API
	Lactose Monohydrate, NF [redacted]	[redacted]		
	Microcrystalline Cellulose [redacted]			
	Hydroxypropyl Cellulose, [redacted]			
	[redacted]			
	[redacted]			
	Croscarmellose Sodium, NF [redacted])			
	Colloidal Silicon Dioxide, NF [redacted]			
	Magnesium Stearate, NF [redacted]			
	Total weight of Uncoated Tablet			

4.2.2 Inactive Ingredients (IIG Table)

(b) (4)

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A

If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:

Based on the maximum daily dose (MDD) of 100 mg, the amounts of inactive ingredients in the test formulation are below those used in the approved drug products based on FDA's Inactive Ingredient Guide (IIG) for Approved Drug Products.

The RLD is available in 2.5 mg, 7.5 mg and 10 mg waiver strengths. The applicant did not request a waiver for these strengths.

The formulation of the test product is **acceptable**.

4.3 Dissolution Testing

Dissolution Review Path[41]	GDRP ANDA 210189-ORIG-1, Documents, *Phytonadione Tabs Biopharm Review_1st IR final.docx*, 08/04/2017

Reviewer's Note: The test product has one strength (5 mg) only and there is no waiver request. This section is for information only.

4.3.1 Dissolution Data

Phytonadione Tablets, USP 5 mg [Reference Product (Lot No.: 14A094P)] vs. Test Product (Batch No.: EE60235)]

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid + 0.5% Triton X – 100
	Volume:	900 mL
	Temperature:	37ºC ±0.5ºC
Firm's Proposed Specifications	Not less than (b) (4)% (Q) of the labeled amount of Phytonadione is dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Limited Plot No 1A/ 1&2, Pharma-Sez, Sarkhej-Bavla Highway, NH 8A, Village Matoda, Tal-Sanand, Ahmedabad, Gujarat 382213, India	

Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report	June 23, 2016	MEPHYTON® (Phytonadione) Tablets, 5 mg **Lot No.:** 14A094P **Expiry Date**: July 2016 **Manufactured By**: Valeant Pharmaceuticals International, Inc. **Distributed By:** Valenat Pharmaceuticals North America LLC.	5 mg, Tablets	12	**Mean**	**46.8**	**63.7**	**73.8**	**78.7**	**82.7**	**86.1**	**88.3**	**Please refer Module 2.7.1.2 of this application**
					Range	(b) (4)							
					%CV	21.8	10.3	5.2	3.1	2.7	2.3	2.5	
Study Report	June 15, 2016	Phytonadione Tablets, USP 5 mg **Batch No**. EE60235 **Mfg Date**: May 2016 **Mfg. By:** Cadila Healthcare Ltd., Matoda,India	5 mg, Tablets	12	**Mean**	**71.7**	**83.5**	**87.7**	**91.1**	**93.6**	**96.4**	**97.4**	
					Range	(b) (4)							
					%CV	5.4	3.7	4.5	3.7	3.5	3.4	3.1	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 5

[41] GDRP ANDA 210189-ORIG-1, Documents, *Phytonadione Tabs Biopharm Review_1st IR final/docx*, 08/04/2017

Phytonadione Tablets, USP 5 mg [Reference Product (Lot No.: 14A094P)] vs. Test Product (Batch No.: EE60236)]

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid + 0.5% Triton X – 100
	Volume:	900 mL
	Temperature:	37°C ±0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Phytonadione is dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Limited Plot No 1A/ 1&2, Pharma-Sez, Sarkhej-Bavla Highway, NH 8A, Village Matoda, Tal-Sanand, Ahmedabad, Gujarat 382213, India	

Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report	June 23, 2016	MEPHYTON® (Phytonadione) Tablets, 5 mg **Lot No.:** 14A094P **Expiry Date**: July 2016 **Manufactured By**: Valeant Pharmaceuticals International, Inc. **Distributed By:** Valenat Pharmaceuticals North America LLC.	5 mg, Tablets	12	**Mean**	**46.8**	**63.7**	**73.8**	**78.7**	**82.7**	**86.1**	**88.3**	**Please refer Module 2.7.1.2 of this application**
					Range	(b) (4)							
					%CV	21.8	10.3	5.2	3.1	2.7	2.3	2.5	
Study Report	June 16, 2016	Phytonadione Tablets, USP 5 mg **Batch No**. EE60236 **Mfg Date**: May 2016 **Mfg. By:** Cadila Healthcare Ltd., Matoda,India	5 mg, Tablets	12	**Mean**	**73.0**	**84.6**	**88.4**	**90.8**	**93.2**	**95.4**	**96.6**	
					Range	(b) (4)							
					%CV	6.0	4.6	4.0	3.9	3.5	2.9	2.3	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 5

Phytonadione Tablets, USP 5 mg [Reference Product (Lot No.: 14A094P)] vs. Test Product (Batch No.: EE60237)]

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid + 0.5% Triton X – 100
	Volume:	900 mL
	Temperature:	37°C ±0.5°C
Firm's Proposed Specifications	Not less than (b) (4)% (Q) of the labeled amount of Phytonadione is dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Limited Plot No 1A/ 1&2, Pharma-Sez, Sarkhej-Bavla Highway, NH 8A, Village Matoda, Tal-Sanand, Ahmedabad, Gujarat 382213, India	

Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report	June 23, 2016	MEPHYTON® (Phytonadione) Tablets, 5 mg **Lot No.:** 14A094P **Expiry Date**: July 2016 **Manufactured By**: Valeant Pharmaceuticals International, Inc. **Distributed By:** Valenat Pharmaceuticals North America LLC.	5 mg, Tablets	12	**Mean**	**46.8**	**63.7**	**73.8**	**78.7**	**82.7**	**86.1**	**88.3**	**Please refer Module 2.7.1.2 of this application**
					Range	(b) (4)							
					%CV	21.8	10.3	5.2	3.1	2.7	2.3	2.5	
Study Report	June 18, 2016	Phytonadione Tablets, USP 5 mg **Batch No**. EE60237 **Mfg Date**: May 2016 **Mfg. By:** Cadila Healthcare Ltd., Matoda,India	5 mg, Tablets	12	**Mean**	**73.2**	**83.1**	**87.4**	**89.8**	**92.9**	**95.6**	**97.2**	
					Range	(b) (4)							
					%CV	7.1	4.8	4.0	3.6	3.5	3.4	2.8	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 5

Phytonadione Tablets, USP 5 mg (Split Tablets) – Hand (Non-mechanically)[Reference Product (Lot No.: 14A094P)] vs. Test Product (Batch No.: EE60280)]

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid + 0.5 % Triton X – 100
	Volume:	900 mL
	Temperature:	37ºC ±0.5ºC
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Phytonadione is dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Limited, Sarkhej-Bavla NH 8A, Moraiya, Tal: Sanand, District: Ahmedabad 382 210 Gujarat, India	

Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	30	45	60	Study Report Location
Study Report	December 06, 2016	MEPHYTON® (Phytonadione) Tablets, 5 mg **Lot No.:** 14A094P **Expiry Date**: July 2016 **Manufactured By**: Valeant Pharmaceuticals International, Inc. **Distributed By:** Valenat Pharmaceuticals North America LLC.	5 mg, Tablets	12	**Mean**	**72.4**	**79.4**	**85.3**	**87.0**	**88.6**	**Splitability report in Module 3.2.P.2 of this application**
					Range	(b) (4)					
					%CV	3.1	3.1	2.8	3.5	4.0	
Study Report	October 11, 2016	Phytonadione Tablets, USP 5 mg **Batch No**. *EE60280 **Mfg Date**: May 2016 **Mfg. By:** Cadila Healthcare Ltd., Matoda,India	5 mg, Tablets	12	**Mean**	**83.2**	**87.1**	**91.9**	**93.5**	**94.1**	
					Range	(b) (4)					
					%CV	6.4	4.7	3.3	2.5	2.3	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 5

Phytonadione Tablets, USP 5 mg (Split Tablets) – Mechanically [Reference Product (Lot No.: 14A094P)] vs. Test Product (Batch No.: EE60280)]

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid + 0.5 % Triton X – 100
	Volume:	900 mL
	Temperature:	37ºC ±0.5ºC
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Phytonadione is dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Limited, Sarkhej-Bavla NH 8A, Moraiya, Tal: Sanand, District: Ahmedabad 382 210 Gujarat, India	

Study Ref No.	**Testing Date**	**Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
Study Report	September 29, 2016	MEPHYTON® (Phytonadione) Tablets, 5 mg **Lot No.:** 14A094P **Expiry Date**: July 2016 **Manufactured By**: Valeant Pharmaceuticals International, Inc. **Distributed By:** Valenat Pharmaceuticals North America LLC.	5 mg, Tablets	12	**Mean**	**62.0**	**70.9**	**78.7**	**82.4**	**84.0**	**Splitability report in Module 3.2.P.2 of this application**
					Range	(b) (4)					
					%CV	11.5	10.2	10.0	9.5	9.5	
Study Report	October 11, 2016	Phytonadione Tablets, USP 5 mg **Batch No**. *EE60280 **Mfg Date**: May 2016 **Mfg. By:** Cadila Healthcare Ltd., Matoda,India	5 mg, Tablets	12	**Mean**	**81.7**	**85.8**	**91.3**	**94.3**	**96.1**	
					Range	(b) (4)					
					%CV	6.6	5.9	4.5	3.6	3.7	

[a]: Module 2.7.1, Summary of In Biopharmaceutic Studies and Associated Analytical Method, Table 5

4.4 Attachments

4.4.1 Additional Studies (If applicable)

Refer details of pilot BE study to **Section 4.1.3**

4.4.2 SAS Output

Study Type/No.	Analyte	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting #765-15	Baseline corrected trans-phytonadione	RefScale trans fasting-trans-baseline(	210189 fasting trans basecorrect RefScale	210189-STAT OUTPUT.doc	210189-ANALYSIS.doc
	Baseline corrected trans-phytonadione (excluding (b) (6)	210189 fasting trans basecorrect RefScale	210189 fasting trans basecorrect RefScale	210189-STAT OUTPUT.doc	210189-ANALYSIS.doc
	Baseline corrected trans-phytonadione (excluding (b) (6) and using original value of (b) (6) P-IV_24h)	RefScale trans fasting-trans-baseline(	210189 fasting trans basecorrect RefScale	210189-STAT OUTPUT.doc	210189-ANALYSIS.doc
	Baseline uncorrected trans-phytonadione (excluding (b) (6)	RefScale fasting-trans-baseline-	RefScale fasting-trans-baseline-	210189-STAT OUTPUT.doc	210189-ANALYSIS.doc
	Baseline corrected cis-phytonadione	RefScale fasting-cis-baselineco	210189 fasting cis basecorrect RefScale	210189-STAT OUTPUT.doc	210189-ANALYSIS.doc
	Baseline corrected cis-phytonadione (excluding (b) (6)	RefScale fasting-cis-baselineco	210189 fasting cis basecorrect RefScale	210189-STAT OUTPUT.doc	210189-ANALYSIS.doc

	Baseline corrected cis-phytonadione (excluding (b) (6) and using original value of (b) (6) P-IV_24h)	 RefScale fasting-cis-baselinecor	 210189 fasting cis basecorrect RefScale	 210189-STAT OUTPUT.doc	 210189-ANALYSIS.doc
	Baseline uncorrected cis-phytonadione (excluding (b) (6)	 RefScale fasting-cis-baselineunc	 210189 fasting cis baseuncorrect RefSca	 210189-STAT OUTPUT.doc	 210189-ANALYSIS.doc
Fed #766-15	Baseline corrected trans-phytonadione	 fed-trans-baseline-corrected.xlsx	 210189 fed trans basecorrect_TWOWA	 210189_Fed_stat_Trans-PhytonadioneACTU	 210189_Fed_table_Trans-PhytonadioneACT
	Baseline uncorrected trans-phytonadione	 fed-trans-baseline-uncorrected.xlsx	 210189 fed trans baseuncorrect_TWOW	 210189_Fed_stat_Baselin Uncorrected Trans	 210189_Fed_table_Baselin Uncorrected Trar
	Baseline corrected cis-phytonadione	 fed-cis-baseline-corrected.xlsx	 210189 fed cis basecorrect_TWOWA	 210189_Fed_stat_Cis-PhytonadioneACTUAL	 210189_Fed_table_Cis-PhytonadioneACTUA
	Baseline uncorrected cis-phytonadione	 fed-cis-baseline-uncorrected.xlsx	 210189 fed cis baseuncorrect_TWOW	 210189_Fed_stat_Baseline Uncorrected Cis-	 210189_Fed_table_Baseline Uncorrected Cis

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 210189

APPLICANT: Zydus Worldwide DMCC

DRUG PRODUCT: Phytonadione Tablets, USP, 5 mg

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and has identified the following deficiencies:

Deficiency Related to Pre-Study Method Validation

1. The recovery of trans-phytonadione QC samples and cis-phytonadione QC samples in the method validation (Report #MV(I)-221-16 Submit Date: January 3, 2017) for the fasting BE study (Study #765-15) were substantially lower than that in the method validation (Report # MV(I)-226-16 Submit Date: January 3, 2017) for the fed BE study (Study #766-15). For example, in the fasting method validation (Report #MV(I)-221-16), the average recovery of Trans-Phytonadione ranged 39.2%-43.9% in normal human plasma and ranged 39.0%-41.6% in UV light exposed human plasma; whereas in the fed method validation (Report #MV(I)-226-16), the average recovery of Trans-Phytonadione ranged 66.8%-74.5% in normal human plasma and ranged 58.2%-70.7% in UV light exposed human plasma. Please explain the difference in recovery of QC samples between the fasting and fed method validation reports and the relevant impact it might have on fasting and fed study results.

Deficiencies Related to Fasting (#765-15) and Fed (#766-15) Bioequivalence (BE) Studies

2. Please provide the potencies of each phytonadione isomer (trans- and cis-) in the test (lot # EE60280) and reference products (lot #14A094P) used in the fasting (#765-15) and fed (#766-15) BE studies.

3. For the fasting study (Study #765-15), our statistical analysis using the reference scaled average BE approach shows that the 95% upper confidence bounds for $(\mu T - \mu R)2 - \theta s2_{WR}$ for AUCinf of baseline corrected cis-phytonadione is greater than 0. Therefore, the statistical analysis shows that the test product has higher bioavailability than the reference product for cis-phytonadione. The data for cis-phytonadione are therefore, not considered supportive of the trans-phytonadione analysis. Please explain how these findings affect your conclusion for bioequivalence of the test product to the reference product under fasting conditions.

4. For fed study (Study #766-15), the statistical analysis using unscaled average BE approach shows that the 90% CIs for least squares geometric means of AUCt and AUCinf of baseline corrected cis-phytonadione are not within the range of (b) (4) Therefore, the statistical analysis shows that the test product has higher bioavailability than the reference product for cis-phytonadione. The data for

cis-phytonadione are therefore, not considered supportive of the trans-phytonadione analysis. Please explain how these findings affect your conclusion for bioequivalence of the test product to the reference product under fed conditions.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 *COMPLETED ASSIGNMENT FOR 210189 ID: 32388*

Reviewer: Cui, Dapeng **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Phytonadione Tablets, USP, 5 mg

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
32388	9/29/2017	BIO	ANDA Original [1]	1	1
32388	9/29/2017	Parallel	Fasting Study (Full template) [1]	1	1
32388	9/29/2017	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25
32388	9/29/2017	Parallel	Fed Study (Full Template) [1]	1	1
32388	9/29/2017	Parallel	Fed Study (Full Template - Additional Analyte) [0.25]	0.25	0.25
32388	9/29/2017	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation [0.25]	0.25	0.25
				Total:	3.75