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Draft Guidance on Phytonadione

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Phytonadione

Dosage Form: Tablet

Route: Oral

Strength: 5 mg

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 5 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Measure baseline phytonadione levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. If the baseline is stable, applicants may choose to do baseline correction for 24 hours rather than 48 hours. Subjects should fast overnight before dosing and continue to receive standard meals at regular intervals post-dose. The mean of the pre-dose phytonadione levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC.

Alternatively, applicants may use a replicate study design. In addition, applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, provide evidence in the studies of high variability in the bioequivalence parameters of AUC and/or peak concentration (i.e., within-subject variability ≥30%). For detailed information on this approach, refer to the guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[a]

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 5 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comment: See comment above.

Analytes to measure: Phytonadione in plasma [both E isomer (trans) and Z isomer (cis)]

Bioequivalence based on (90% CI): Phytonadione [E isomer (trans)]. Applicants should also submit the Z isomer (cis) data as supportive evidence of comparable therapeutic outcome. For the Z isomer, at a minimum, 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 C_{max}.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test product and reference listed drug (RLD) [1]. Specifications will be determined upon review of the abbreviated new drug application.

If any strength of the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per the most recent version of the FDA guidance for industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.[a]

Additional information:

Drug substance:
To support active ingredient sameness under section 505(j) of the Federal Food, Drug, and Cosmetic Act, phytonadione should be a mixture of E and Z isomers, in any combination, with a total content of no less than (NLT) 97.0% and no more than (NMT) 103.0%, and generally contains a total Z isomer content of NLT 9% and NMT 17%.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.