

Draft Guidance on Phytonadione

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient: Phytonadione

Dosage Form; Route: Tablets; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 5 mg
Subjects: Normal healthy males and nonpregnant females, general population.
Additional Comments: Please measure baseline 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. 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.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 5 mg
Subjects: Normal healthy males and nonpregnant females, general population.
Additional Comments: Please see comments above regarding baseline correction. In addition, please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Phytonadione in plasma (both E isomer (trans-configuration) and Z isomer (cis-configuration))

Bioequivalence based on (90% CI): Phytonadione (E isomer (trans-configuration))

Please submit the Z isomer (cis-configuration) data as 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 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 on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).