Contains Nonbinding Recommendations

Draft Guidance on Phytonadione

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Phytonadione

Form/Route: Injectable/Injection

Recommended studies: 2 studies

1. Type of study: Subcutaneous administration
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 10 mg/mL
   Subjects: 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.

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2. Type of study: Subcutaneous administration
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1 mg/0.5mL
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comment above.

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 Cmax.

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

Waiver request of *in-vivo* testing: Not Applicable

Dissolution test method and sampling times: Not applicable