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Draft Guidance on Phytonadione

November 2024

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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:	Injectable
Route:	Injection
Strength:	10 mg/mL; 1 mg/0.5 mL
Recommended Studies:	Two options: (1) in vitro characterization studies, or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints

I. Option I: In vitro characterization studies

To qualify for demonstrating bioequivalence under Option I, a generic phytonadione injectable injection product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test products are within ±5% of those used in the RLD product.
[3] Per 21 CFR 314.94(a)(9)(iii), an applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Applicants should provide physicochemical characterization data of the test product to demonstrate it is a thermodynamically stable micellar solution.[4] This can include but is not limited to information that supports the thermodynamically driven self-assembly of a homogeneous, optically translucent, micellar solution with micelle size less than 80 nm.

II. Option II: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with subcutaneous administration
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg/mL
   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.

2. Type of study: Bioequivalence study with subcutaneous administration
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg/0.5 mL
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: 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: Not applicable

[4] Also, commonly known as a microemulsion. For more information, refer to McClements, David Julian. "Nanoemulsions versus microemulsions: terminology, differences, and similarities." Soft Matter 8.6 (2012): 1719-1729.

Additional information:

Drug substance:
To support active ingredient sameness under section 505(j) of the Federal Food, Drug, and Cosmetic Act, in addition to meeting the USP drug substance monograph, an ANDA applicant should provide evidence that the phytonadione drug substance in their proposed product is 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 contains a total Z isomer content of NLT 9% and NMT 17%.

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