

Draft Guidance on Phytonadione

November 2024

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Active Ingredient:	Phytonadione
Dosage Form:	Injectable
Route:	Injection
Strength:	1 mg/0.5 mL
Recommended Studies:	Two options: (1) in vitro characterization studies, or (2) one in vivo bioequivalence study 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

Applicants should provide physicochemical characterization data of the test (T) product to demonstrate it is a thermodynamically stable micellar solution.⁴ This can include but is not

¹ Q1 (Qualitative sameness) means that the T 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 T products are within $\pm 5\%$ 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.

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.

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: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with subcutaneous administration
Design: Single-dose, two-way crossover in-vivo
Strength(s): 1 mg/0.5 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, 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.

Analyte(s) 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

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%.

Device:

The RLD is presented in a vial co-packaged with a vial injector and a staked needle with needle guard. The vial and vial injector with needle are the device constituent parts.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the T device including:

- Single-use, variable-dose injector format
- Volume markings
- Needle gauge and length
- Needle guard system

User interface assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^a

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Unique Agency Identifier: PSG_083722

^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.