Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Warfarin Sodium

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Warfarin sodium
Dosage Form:	Tablet
Route:	Oral
Strengths:	1 mg | 2 mg | 2.5 mg | 3 mg | 4 mg | 5 mg | 6 mg | 7.5 mg | 10 mg
Reference Listed Drug:	NDA 009218
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 10 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Safety recommendations:
   - Exclude CYP2C9 poor metabolizers and/or subjects who are carriers of VKORC1 AA genotype due to increased warfarin sensitivity.
   - Exclude geriatric subjects due to increased risk of bleeding.
   - Exclude subjects who have undergone or plan to undergo elective surgery including dental procedures prior to and for at least one week after the study.
   - Monitor International Normalized Ratio and signs and symptoms of bleeding during the study. Subjects should maintain consistent intake of vitamin K-containing foods prior to and during the study.

- Subjects should avoid consuming dietary supplements or fruits (e.g., grapefruit or grapefruit-containing products) that may increase bleeding risk or affect the exposure of warfarin for a sufficient time prior to and during the study.

Study design recommendations:

- This drug product is classified as a narrow therapeutic index (NTI) drug. Refer to the Explanation section for further information.
- $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparing the extent of absorption due to warfarin's long half-life. Ensure adequate washout periods between treatments in the crossover study.

2. Class of study: Bioequivalence
Type of study: Fed
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
Strength: 10 mg
Subjects: Healthy males and healthy females not of reproductive potential
Safety recommendations: See recommendations under Study #1.
Study design recommendations: See recommendations under Study #1.

Analyte to measure: Warfarin in plasma

Bioequivalence based on (90% CI): Warfarin

Additional strengths: Justification based on (i) acceptable bioequivalence studies on the 10 mg strength, (ii) acceptable comparative in vitro dissolution studies between the additional strengths and the 10 mg strength using 12 units per strength, and (iii) proportional similarity of the formulations across all strengths

Dissolution: Dissolution test(s) should be included for quality control and to support a waiver request of in vivo testing of additional strengths. For the quality control dissolution method, provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

Explanation: FDA has concluded that warfarin is an NTI drug based on the following evidence:

- The range between the effective warfarin concentrations and the concentrations associated with serious toxicity is narrow
- Sub-optimal warfarin concentrations lead to severe therapeutic failure or toxicity
- Warfarin is subject to therapeutic drug monitoring based on pharmacodynamic measures
- Warfarin exhibits low-to-moderate within-subject variability
- Dose adjustments are in small increments (range between 10 % and 25%) in clinical practice

The in vivo bioequivalence studies should be of a fully replicate crossover design to:

- Scale bioequivalence limits to the variability of the RLD
- Compare test product and RLD within-subject variability

For details about the method for statistical analysis using the reference-scaled average bioequivalence approach for NTI drugs, refer to the guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Document History: Recommended December 2012; Revised May 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.