

## Draft Guidance on Digoxin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Tablets; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting  
Design: Single-dose, 2-treatment, 2-sequence, 4-way, fully replicated crossover in vivo  
Strength: 0.25 mg  
Subjects: Normal healthy males and females, general population  
Additional comments: If reliable blood drug levels cannot be obtained using a 1 x 0.25 mg dose, you may use a single dose of 2 x 0.25 mg tablets. Please carefully monitor the study subjects for adverse events. A washout period between doses of at least two weeks is suggested. Please continue sample collection for at least three or more terminal half-lives of the drug.

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  2. Type of study: Fed  
Design: Single-dose, 2-treatment, 2-sequence, 4-way, fully replicated crossover in vivo  
Strength: 0.25 mg  
Subjects: Normal healthy males and females, general population  
Additional comments: Please see comments above
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**Analytes to measure:** Digoxin in plasma

**Bioequivalence based on (90% CI):** Digoxin

**Waiver request of in vivo testing:**

In vivo BE studies for the 0.0625 mg, 0.125 mg and 0.1875 mg strengths may be waived based on (i) acceptable bioequivalence studies on the 0.25 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, 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).

**Explanation:** FDA has concluded that digoxin is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between digoxin therapeutic and toxic plasma concentrations is narrow;
- Sub-therapeutic doses or concentrations may lead to therapeutic failure;
- Digoxin is subject to therapeutic monitoring based on pharmacokinetic measures;
- Digoxin has small to medium within-subject variability;
- Doses are adjusted in small increments (less than 20%) in clinical practice.

The study should be a fully replicated crossover design in order to:

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference products' within-subject variability.

For details about the “Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach” for NTI drugs, see the guidance on warfarin sodium.