This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic semaglutide.

**Active Ingredient:** Semaglutide  
**Dosage Form; Route:** Tablet; oral  
**Recommended Studies:** Two options

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**Option I:** Three bioequivalence studies with pharmacokinetic endpoints:

1. **Type of study:** Fasting  
   **Design:** Single-dose, two-treatment, two-period crossover in vivo  
   **Strength:** 14 mg  
   **Subjects:** Males and non-pregnant, non-lactating females, general population

2. **Type of study:** Fasting  
   **Design:** Single-dose, two-treatment, two-period crossover in vivo  
   **Strength:** 7 mg  
   **Subjects:** Males and non-pregnant, non-lactating females, general population
3. **Type of study:** Fasting  
**Design:** Multiple-doses (e.g., administer single 3 mg dose for 5 days), two-treatment, crossover in vivo  
**Strength:** 3 mg  
**Subjects:** Males and non-pregnant, non-lactating females, general population  
**Additional comment:** If it is not feasible to adequately characterize the pharmacokinetic profile of 3 mg strength even after multiple doses in the fasting pharmacokinetic study, the applicant may submit a pre-ANDA meeting request to discuss alternative bioequivalence approach for the 3 mg strength. The proposed alternative bioequivalence approach should be scientifically justified and satisfy the requirements of the applicable statutes and regulations.

**Waiver request of in vivo testing:** Not applicable.

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**Option II:** One bioequivalence study with pharmacokinetic endpoints together with appropriate in vitro testing. To qualify for this option, a proposed test product should be qualitatively the same and quantitively similar to the reference listed drug (RLD) product.

1. **Type of study:** Fasting  
**Design:** Single-dose, two-treatment, two-period crossover in vivo  
**Strength:** 14 mg  
**Subjects:** Males and non-pregnant, non-lactating females, general population

**Waiver request of in vivo testing:** Pharmacokinetic bioequivalence testing for 3 mg and 7 mg doses may be waived based on (i) acceptable bioequivalence study on the 14 mg strength, (ii) acceptable in vitro semaglutide dissolution testing of all strengths, (iii) acceptable in vitro salcaprozate sodium (SNAC) dissolution testing of all strengths of the product, and (iv) proportional similarity of the formulations across all strengths of the product.

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**Additional comments:**

- Semaglutide tablet should be administered following the administration instructions for the RLD.

- For all in vivo bioequivalence studies, subjects should be appropriately monitored for hypoglycemia during the study, which may include a period of on-site monitoring. When the study subjects are not confined at the clinical site, they should be provided with a glucometer and instructed on its use.

- A replicate crossover study design (partial or fully replicate) is acceptable whether the reference product is a highly variable drug or not. However, if the plan is to use the reference-scaled average bioequivalence (RSABE) approach for bioequivalence study data analysis, provide evidence of high variability in the pharmacokinetic parameters.
(i.e., within-subject variability ≥ 30%) of the reference product. For detailed information on this approach, refer to the guidance for progesterone oral capsules.

**Analyte to measure:** Semaglutide in plasma

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

**Dissolution test method and sampling times:** The applicant should develop and validate a method to determine in vitro dissolution of semaglutide. 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 application.

**Unique Agency Identifier:** PSG_213051