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Draft Guidance on Semaglutide

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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.

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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

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.

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.

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.

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