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Draft Guidance on Semaglutide

February 2026

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Active Ingredient:	Semaglutide
Dosage Form:	Tablet
Route:	Oral
Strengths:	1.5 mg, 4 mg, 9 mg, 25 mg
Recommended Studies:	Demonstrate active pharmaceutical ingredient (API) sameness, comparative assessment of impurities, and two options to demonstrate bioequivalence: (1) four in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints with in vitro testing

Recommendations for demonstrating API sameness and comparative impurity assessment:

Semaglutide can be produced using synthetic or semi-synthetic recombinant deoxyribonucleic acid (rDNA) methods. Provide sufficient data and justification to support API sameness (e.g., same primary sequence and physiochemical properties) and compare API-related impurity profile differences between the test product and reference listed drug (RLD).[1]

[1] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions.*

Recommendation for demonstrating bioequivalence:

Cross-referencing strengths between two RLDs: Semaglutide 1.5 mg, 4 mg, 9 mg, and 25 mg tablets (NDA 218316) and semaglutide 1.5 mg, 4 mg, and 9 mg tablets (NDA 213051) are the subject of two separate RLDs. A waiver of in vivo bioequivalence study for the 1.5 mg, 4 mg, and 9 mg strengths may be requested if the following conditions are met:

1. acceptable bioequivalence study results for these strengths in the related ANDA that references NDA 213051,
2. cross-references the related ANDA for these strengths, and
3. meets the criteria of 21 CFR § 320.22

I. Option 1: Four in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Multiple-dose, two-treatment, two-period crossover in vivo
   Strength: 25 mg
   Subjects: Male and female patients who are receiving a stable dose of 25 mg once daily of semaglutide tablet based on the approved indications
   Additional comments:
   - Patients who are receiving a stable dose of semaglutide 25 mg tablets are recommended due to the anticipated significant risk of severe gastrointestinal adverse reactions following a single dose administration of 25 mg tablet in healthy subjects. The labeling allows for switching between dosage forms of oral tablets and injections. However, a decision to switch a patient from injection to oral formulation for the purpose of a conducting a bioequivalence study should be made based on the healthcare provider's assessment of clinical benefits and risks.
   - Exclude patients who may require dosage modification or those with expected changes in concomitant medications that may potentially affect the pharmacokinetics of semaglutide during the study. Implement safety precautions and monitoring during treatment as recommended in the labeling.
   - Refer to the specific administration instruction per the RLD labeling.

2. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 9 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   - Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement appropriate hypoglycemia management protocol. Due to the potential impact of semaglutide-associated gastrointestinal adverse events on subject dropout rates and study power, consider incorporation of safety measures in study design. If such safety measures are implemented during the study, document that they do not impact the study findings.

- Refer to the specific administration instruction per the RLD labeling. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of semaglutide. A replicate crossover study design (i.e., partial or fully replicate) is acceptable regardless of whether the RLD is highly variable or not. For a reference-scaled average bioequivalence approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) of the RLD. For detailed information on this approach, refer to the most recent version of the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[a]

3. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 4 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above for study using 9 mg under Option 1.

4. Type of study: Fasting
Design: Multiple-dose (e.g., administer single 1.5 mg dose for 5 days), two-treatment, two-period crossover in vivo
Strength: 1.5 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above for study using 9 mg under Option I. If it is not feasible to achieve sufficient bioanalytical sensitivity to adequately characterize the pharmacokinetic profile of 1.5 mg strength even after multiple doses in the fasting pharmacokinetic study, the applicant may submit a pre-abbreviated new drug application (ANDA) meeting request to discuss an alternative bioequivalence approach for the 1.5 mg strength. The proposed alternative bioequivalence approach should be scientifically justified and satisfy the requirements of the applicable statutes and regulations.

II. Option 2: Two in vivo bioequivalence studies with pharmacokinetic endpoints with in vitro testing

Semaglutide is co-formulated with salcaprozate sodium which facilitates the absorption of semaglutide after oral administration. Therefore, Option II is acceptable if the test product is qualitatively the same and quantitatively similar to the corresponding strengths of the RLD. A test product of semaglutide tablet is considered quantitatively similar if the change in the amount of salcaprozate sodium is within ±10% of that present in the RLD and the cumulative difference of all excipients, including salcaprozate sodium and expressed as a percentage (w/w) of total test tablet weight, in test product compared to the corresponding strengths of the RLD is within ±10% (w/w). Differences to non-absorption enhancing excipients should not change their functionality in the dosage form and property of the dosage form.[2]

[2] For example, a commonly acceptable difference in the percentage of stearate lubricants weight per total tablet weight between the test and the RLD is recommended not to exceed 0.5%. A deviation from this limit may be acceptable with scientific justification.

1. Type of study: Fasting
   Design: Multiple-dose, two-treatment, two-period crossover in vivo
   Strength: 25 mg
   Subjects: Male and female patients who are receiving a stable dose of 25 mg once daily of semaglutide tablet based on the approved indications
   Additional comments: See comments above for the study using 25 mg strength under Option 1.

2. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 9 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above for study using 9 mg strength under Option 1.

   Waiver request of in vivo testing of 1.5 mg and 4 mg strengths: justification based on (i) an acceptable bioequivalence study on the 9 mg strength, (ii) acceptable comparative in vitro semaglutide dissolution studies between the 1.5 mg, 4 mg strengths and the 9 mg strength using 12 units per strength, and (iii) acceptable comparative in vitro salcaprozate sodium dissolution studies between the 1.5 mg, 4 mg strengths and the 9 mg strength using 12 units per strength

Analyte to measure: Semaglutide in plasma

Bioequivalence based on (90% CI): Semaglutide

Dissolution: Dissolution tests should be included for quality control and to support a waiver request of in vivo testing of additional strengths.

Dissolution test method and sampling times: Provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[3] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

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Unique Agency Identifier: PSG_218316

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

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