Navigating Complexity:
Key Considerations in Developing the Oral Semaglutide Product-Specific Guidance

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Outline

I. Background: Oral semaglutide

II. Product-specific guidance (PSG) evolution from 2021: Key changes

III. Analytical challenges and future directions

I. Background: Oral semaglutide

First and the only oral glucagon-like peptide-1 (GLP-1) receptor agonist

Indication	Improve glycemic control in adults with type 2 diabetes
R1 Approval	3 mg, 7 mg, 14 mg strengths approved September 2019
R2 Approval	1.5 mg, 4 mg, 9 mg strengths approved December 2024
Key Formulation Attributes	R1 and R2 require absorption enhancer (salcaprozate sodium [SNAC]) due to low oral bioavailability
PSG Status/ Revisions	Draft PSG published August 2021 for Formulation R1 Revised PSG** published October 2025 for Formulations R1 and R2

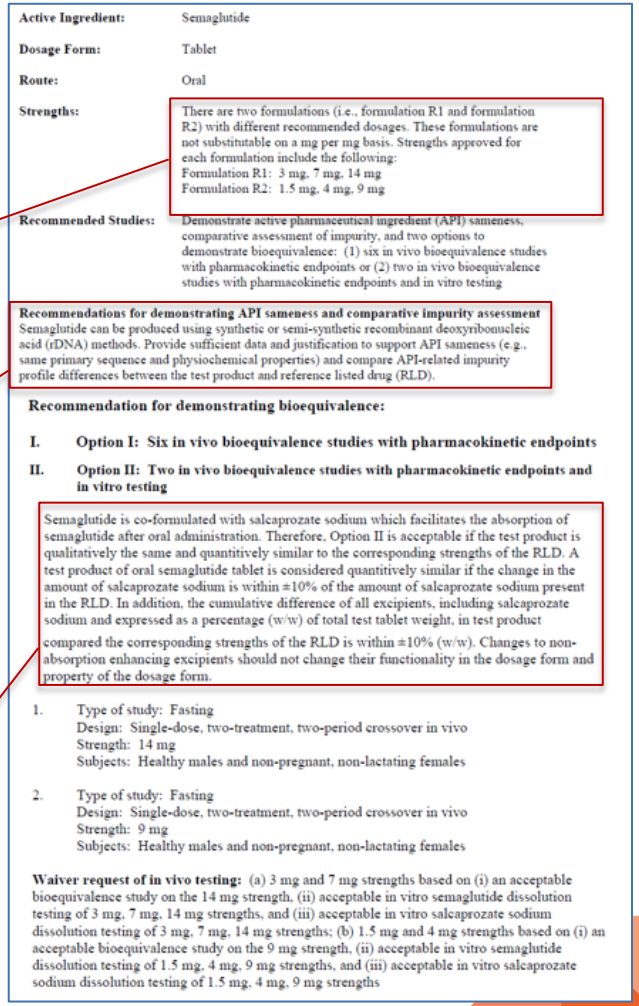
*Code of Federal Regulations: 21 CFR 600.3
**Draft Guidance on Semaglutide Oral Tablet (10/01/2025)

II. PSG Evolution from 2021 to 2025: Key changes

Change # 1
Expanded Study Recommendations for New Strengths

Change # 2
Added Active Pharmaceutical Ingredient (API) Sameness & Impurity Assessment

Change # 3
Clarified Quantitative Criteria for Option II



Active Ingredient: Semaglutide

Dosage Form: Tablet

Route: Oral

Strengths: There are two formulations (i.e., formulation R1 and formulation R2) with different recommended dosages. These formulations are not substitutable on a mg per mg basis. Strengths approved for each formulation include the following:
Formulation R1: 3 mg, 7 mg, 14 mg
Formulation R2: 1.5 mg, 4 mg, 9 mg

Recommended Studies: Demonstrate active pharmaceutical ingredient (API) sameness, comparative assessment of impurity, and two options to demonstrate bioequivalence: (1) six in vivo bioequivalence studies with pharmacokinetic endpoints or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints and 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).

Recommendation for demonstrating bioequivalence:

I. **Option I: Six in vivo bioequivalence studies with pharmacokinetic endpoints**

II. **Option II: Two in vivo bioequivalence studies with pharmacokinetic endpoints and 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 quantitively similar to the corresponding strengths of the RLD. A test product of oral semaglutide tablet is considered quantitively similar if the change in the amount of salcaprozate sodium is within ±10% of the amount of salcaprozate sodium present in the RLD. In addition, 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 the corresponding strengths of the RLD is within ±10% (w/w). Changes to non-absorption enhancing excipients should not change their functionality in the dosage form and property of the dosage form.

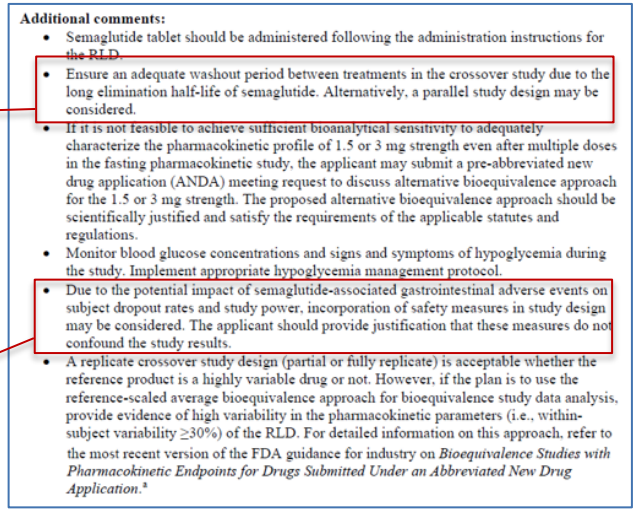
1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 14 mg
   Subjects: Healthy males and non-pregnant, non-lactating females

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

Waiver request of in vivo testing: (a) 3 mg and 7 mg strengths based on (i) an acceptable bioequivalence study on the 14 mg strength, (ii) acceptable in vitro semaglutide dissolution testing of 3 mg, 7 mg, 14 mg strengths, and (iii) acceptable in vitro salcaprozate sodium dissolution testing of 3 mg, 7 mg, 14 mg strengths; (b) 1.5 mg and 4 mg strengths based on (i) an acceptable bioequivalence study on the 9 mg strength, (ii) acceptable in vitro semaglutide dissolution testing of 1.5 mg, 4 mg, 9 mg strengths, and (iii) acceptable in vitro salcaprozate sodium dissolution testing of 1.5 mg, 4 mg, 9 mg strengths

Change # 4
Washout Period Recommendations Addressing Long Half-Life Challenges

Change # 5
Gastrointestinal (GI) Adverse Events and Safety Measures



Additional comments:

- Semaglutide tablet should be administered following the administration instructions for the RLD.
- Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of semaglutide. Alternatively, a parallel study design may be considered.
- If it is not feasible to achieve sufficient bioanalytical sensitivity to adequately characterize the pharmacokinetic profile of 1.5 or 3 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 alternative bioequivalence approach for the 1.5 or 3 mg strength. The proposed alternative bioequivalence approach should be scientifically justified and satisfy the requirements of the applicable statutes and regulations.
- 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, incorporation of safety measures in study design may be considered. The applicant should provide justification that these measures do not confound the study results.
- 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 approach for bioequivalence study data analysis, 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 FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[8]

Change # 1
Expanded Study Recommendations for New Strengths

2025 Change: Option I

Six bioequivalence studies recommended for Option I (both R1 and R2 formulations) vs. three studies in 2021

- 2021: 3 fasting BE studies for Option I (Formulation R1 only)
- 2025: 6 fasting BE studies (Both formulations)
  - Formulation R1: 14 mg, 7 mg (single dose), 3 mg (multiple dose)
  - Formulation R2: 9 mg, 4 mg (single dose), 1.5 mg (multiple dose)

Rationale

- R1 Approved in Sep 2019, R2 Approved in Dec 2024
- "These formulations are not substitutable on a mg per mg basis”*
- Oral bioavailability differences: R1 (0.4-1%) vs R2 (1-2%)

*Drugs@FDA. RYBELSUS® (semaglutide) tablets, for oral use (12/2024)

Change # 2
Added API Sameness & Impurity Assessment

2025 Change

Added new language: "Semaglutide can be produced using synthetic or semi-synthetic recombinant deoxyribonucleic acid (rDNA) methods.”

Rationale

1	Multiple controlled correspondences questioned whether rDNA-derived semaglutide qualified for 505(j) ANDA pathway given existing peptide guidance*
2	May 2021 peptide guidance addressed injectable peptides
3	Oral route of administration is generally associated with lower immunogenicity. Furthermore, low oral bioavailability of semaglutide attenuates the risk of immune responses relative to injectable formulations, thereby permitting greater flexibility in the manufacturing approaches for oral products.
4	2025 PSG clarifies that both synthetic and rDNA manufacturing methods are acceptable for ANDA pathway

FDA Guidance: "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin," May 2021

Change # 3

Clarified Quantitative Criteria for Option II

(fasting BE studies on 9 mg and 14 mg. Waiver request for lower strengths)

- 2021 PSG Option II recommended products be qualitatively the same and **quantitively similar** to the RLD without defining "similar," creating uncertainty in formulation assessment

Background:

- Qualitatively the same = same inactive ingredients
- Quantitively the same = within +/- 5% of RLD concentration*
- Quantitively similar: no formal definition exists

*ANDA Submissions - Refuse-to-Receive Standards Guidance, December 2016

2025 Change

Added specific criteria for similarity assessment for oral semaglutide tablet: **A test product is considered quantitively similar if**:

- The amount of SNAC (which facilitates oral absorption) is within ±10% of the amount of SNAC in the RLD
- Cumulative difference of all excipients (including SNAC), expressed as % (w/w) of total test tablet weight, is within ±10% (w/w) compared to the RLD

Rationale

- 2025 PSG provides clear evaluation criteria, creating enhanced guidance that supports standardized assessment approaches

Change # 4

Washout Period Recommendation Addressing Long Half-Life Challenges

2025 Change

Added new language: "Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of semaglutide. Alternatively, a parallel study design may be considered."

Rationale

- Semaglutide exhibits ~1 week elimination half-life with drug present for about 5 weeks after last dose
- FDA's BE guidance* recommends a washout that is 5x the drug's half-life

*FDA Guidance: "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA," August 2021

Change # 5
GI Adverse Events and Safety Measures

2025 Change

Added new language: “Due to the potential impact of semaglutide-associated gastrointestinal adverse events on subject dropout rates and study power, incorporation of safety measures in study design may be considered."

Rationale*

- GI adverse events (nausea, vomiting) are well documented with semaglutide use
- High dropout rates in bioequivalence studies can compromise study validity and statistical power

*Shu Y, He X, Wu P, Liu Y, Ding Y, Zhang Q. Gastrointestinal adverse events associated with semaglutide: A pharmacovigilance study based on FDA adverse event reporting system. Front Public Health. 2022;10:996179.

Study Design Considerations for GI Adverse Events

1	Titration schemes may reduce adverse events but increase study duration and participant exposure.
2	Safety measures, including antiemetics, may be considered to manage vomiting and reduce dropout rates.
3	Antiemetics may affect gastric motility and drug absorption and may complicate bioanalytical methods.
4	Each approach must be justified to demonstrate it does not confound study results.

III. Analytical challenges and future directions

Alternative Absorption Enhancement Strategies

- Develop bioequivalence recommendations for non-SNAC formulations
- Create waiver pathways for products using different enhancement strategies

Advanced Analytical Methods

- Improved lower limit of quantification (LLOQ) methods may enable single-dose studies for 1.5 mg and 3 mg strengths
- Improved analytical techniques to better handle SNAC matrix effects
- Enable more precise characterization of peptide-related impurities for better API sameness assessment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