Additional Guidance on Submission Requirements for Semaglutide (glucagon-like peptide-1 (GLP-1) receptor agonist) for subcutaneous injection

1. INTRODUCTION

To support national and global efforts to increase access to, and the affordability of, medicinal products used in the area of diabetes, WHO invites manufacturers of selected medicines to submit Expressions of Interest (EOI) for product evaluation.

The 3rd invitation for medicines used in the management of diabetes includes those containing the active ingredient semaglutide.

The invited semaglutide products are semaglutide injection solution: 0.68 mg per mL; 1.34 mg per mL; and 2.68 mg per mL in vials or 3 mL cartridges.

This document provides additional guidance to manufacturers regarding the assessment expectations and routes for assessment of semaglutide-containing products.

2. SCOPE AND SUBMISSION PATHWAY

Eligible products are limited to semaglutide indicated for diabetes management. Eligible products include semaglutide formulations for the treatment of diabetes produced either by recombinant biological processes or by chemical synthesis.

- All formulations that have been approved by a stringent regulatory authority (SRA)/WHO listed authority (WLA) and are marketed in the country of registration. These will be assessed via an Abridged Assessment pathway.

- Formulations containing semaglutide produced as Similar Biotherapeutics Products (SBPs) that have not been registered by SRAs/WLAs. These will be assessed through the Full Assessment pathway.

- Formulations containing semaglutide produced as a synthetic peptide that have not been registered by SRAs/WLAs. These will be assessed via the Full Assessment pathway.

3. ASSESSMENT APPROACH

A distinction is made between products using semaglutide active pharmaceutical ingredient produced biologically or synthetically.

Biological products (recombinant origin)

Products developed as Biotherapeutic Products (BTPs) or SBPs, on the basis of a RBP approved by a SRA, should follow the applicable WHO biosimilar guidelines (e.g., WHO

Guidelines on evaluation of biosimilars. Replacement of Annex 2 of WHO Technical Report Series, No. 977 and WHO Procedure for Prequalification of BTPs or their corresponding SBPs).

Further reference should be made to the following guidance:

- The general procedure framework: WHO Procedure for Prequalification of Biotherapeutic Products or their corresponding Similar Biotherapeutic Products[1].
- Document requirements for full assessment: WHO Guidelines on submission of documentation for the procedure for prequalification of similar biotherapeutic products.
- Document requirements for abridged assessment: WHO Guidelines on submission of documentation for the procedure for prequalification of biotherapeutic products or their corresponding similar biotherapeutic products approved by stringent regulatory authorities.

Synthetic products
Products developed as synthetic peptides fall outside the definition of biological medicinal products and, therefore, cannot follow the biotherapeutic/biosimilar framework.

Neither can synthetic peptides referencing a biological product be considered classical generics due to differences in manufacturing origin, impurity profiles, and potential impact on quality attributes.

Instead, they should be developed and assessed using a hybrid approach, combining principles of generic medicines development and evaluation (e.g., annex 4, TRS 970) with additional comparability requirements against a suitable WLA approved biological medicinal product as a reference product.

Additionally, the guidance listed below, beginning with Section 4, should be consulted when preparing a prequalification dossier for synthetic products submitted through the full assessment pathway. Synthetic products approved by a WLA/SRA should be submitted according to the guidelines for prequalification of products approved by SRAs. Additional considerations for such products are described in section 10 of this additional guidance document.

4. Dossier Structure and Assessment Approach

Module 3 should be primarily structured according to WHO guidance for generic medicines. However, additional information is required to demonstrate comparability with the reference biological product.

The following sections require additional assessment and may involve joint assessment by small molecule and biotherapeutic assessors:

3.2.S.2 – Manufacture
3.2.S.3 – Characterisation
3.2.S.4 – Control of drug substance
3.2.S.5 – Reference standards
3.2.S.7 – Stability
Relevant sections of 3.2.P
3.2.R – Comparability exercise (cross-cutting)

Comparability Requirements

A head-to-head comparability exercise with a suitable WLA sourced reference biological product is required.

The comparability exercise should follow a stepwise approach, including but not limited to:

- Structural (physicochemical) comparison
- Impurity profile comparison
- Functional/biological activity assessment

Impurity profiles are considered comparable:

a. if no new impurities are observed that do not occur in the reference product, and the levels of known impurities are equal to, or less than, the reference product; or

b. if no new impurity occurs at a level greater than 0.5% and any new impurities occurring at levels 0.1% to 0.5% are justified with respect to efficacy and safety (including immunogenicity).

Acceptance criteria should be predefined, scientifically justified, and based on a sufficient number of batches of both the test and reference products. Batches preferably from the commercial process should be used for the analyses.

The reference product used in comparability studies should be sourced from an SRA/WLA-approved market.

The applicant will need to fully characterise all differences between peptides produced by chemical synthesis and peptides produced by recombinant technology and demonstrate that both products are comparable.

Any specific difference related to the manufacturing process, in terms of product- and process-related impurities should be investigated and clearly identified. The applicant should consider what analytical tests might be used to confirm comparability and to define and justify these, prior to conducting these studies, the acceptance range to conclude comparability. Any observed differences between the proposed the reference medicinal products should be evaluated and justified with regard to their potential impact on safety and efficacy. Additional tests and studies (including non-clinical studies and/or clinical trials) may be required to address residual uncertainty.

Particular emphasis should be placed on demonstrating that the synthetic manufacturing process does not result in differences in the quality profile of the product that are clinically meaningful. Comparability should not be limited to confirmation of the primary amino acid sequence, but should include an extensive evaluation of physicochemical properties, higher-order structure (where relevant), degradation pathways, biological activity, and impurity profiles.

Analytical methods used in the comparability exercise should be appropriately qualified or validated and demonstrated to be sufficiently sensitive and discriminatory to detect potential

differences between the products. Where orthogonal analytical methods are available, their use is encouraged to increase confidence in the comparability conclusions.

Applicants should refer to relevant international guidelines, including:

- Guideline on the Development and Manufacture of Synthetic Peptides (EMA/CHMP/CVMP/QWP/367182/2025); and
- ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (FDA guideline May 2021 Generics).

5. Analytical and Quality Considerations

A comprehensive analytical package is required, including:

- High-resolution physicochemical characterisation
- Evaluation of process- and product-related impurities
- Assessment of differences between synthetic and recombinant peptides
- Suitability of analytical methods to detect potential differences

Comparative forced degradation studies are recommended to evaluate degradation pathways and confirm that analytical methods are stability-indicating.

The clearance and control of the following impurities should be demonstrated in accordance with applicable guidelines.

- residual solvents
- reagents
- elemental impurities
- mutagenic impurities, including nitrosamines if applicable
- undesirable product variants

Particular attention should be paid to the identification, characterization and qualification of process-related and product-related impurities that may arise from chemical synthesis. The Applicant should demonstrate that impurities unique to the synthetic manufacturing process are adequately controlled and do not adversely impact safety, efficacy or immunogenicity.

Where differences in impurity profiles are identified compared with the reference product, these differences should be scientifically justified. The Applicant should discuss the potential toxicological and immunogenicity implications of such differences and provide additional supporting studies where necessary.

The comparability exercise should include orthogonal evaluation of purity, degradation products, aggregates, charge variants and other relevant product variants, as appropriate for the molecule under development.

6. Immunogenicity and Safety Considerations

The Applicant should demonstrate that the totality of analytical and quality data supports the conclusion that there are no new or increased immunogenicity risks associated with the synthetic product compared with the reference biological product.

Particular attention should be given to impurities, degradation products, aggregates, oxidized forms, deamidated forms and other product variants that may alter the immunogenicity profile of the product.

Where the analytical characterization and impurity qualification package is sufficiently robust and no residual uncertainty remains, additional clinical immunogenicity studies may not be required.

Any novel or unexpected impurities should be identified, characterised, and controlled to the extent possible.

7. Functional Assays

Functional assays (e.g., receptor binding or cell-based assays) should be developed and used as part of the comparability exercise.

Correlation to the in vivo mechanism of action should be demonstrated.

Where robust structural and comparative analytical data are provided, routine potency testing may be adapted or replaced by alternative approaches. Any such approach should be fully justified.

8. Stability

Stability data should be generated for the synthetic peptide product. Extrapolation from the reference biological product is not acceptable.

Stability studies should support:

- proposed shelf-life
- storage conditions
- in-use stability
- degradation pathways

9. Bioequivalence / PK Requirements

For synthetic semaglutide products developed under a hybrid approach, the objective is not only to demonstrate classical bioequivalence (BE) as for generic medicinal products, but to establish comparability with a suitable reference biological product approved by an SRA/WLA based on the totality of evidence.

To qualify for a waiver from the requirement to conduct BE/PK studies, the composition of the proposed product formulation should be qualitatively (Q1) and quantitatively (Q2) similar to that of the reference product. Beyond this, the need for BE/PK studies should be determined according to a risk-based, stepwise approach, taking into account the totality of evidence generated during the quality and analytical comparability exercise.

The primary objective of development is to demonstrate that the synthetic peptide product is highly similar to the reference biological product. Consequently, the extent of non-clinical and clinical data should be proportionate to the level of residual uncertainty remaining after comprehensive characterization of the quality attributes, impurity profile, biological activity and comparability package.

For clinical requirements, the following two scenarios are anticipated:

1. In the case a high degree of structural, physicochemical and functional comparability, including extensive characterization and qualification of impurities and product variants is demonstrated, BE/PK studies could be waived.

2. In the case that the comparability exercise identifies uncertainties (related to structural and physicochemical differences, impurity profiles, aggregation and degradation products) BE/PK studies are generally required. Additional studies to address the immunogenicity of the product may be necessary.

The Applicant should therefore justify the proposed clinical development programme based on the residual uncertainty identified following the quality comparability exercise and its potential clinical relevance.

Available clinical data might be submitted as supportive evidence.

Pharmacokinetic Studies

BE/PK studies should be designed to maximise sensitivity to detect potential differences between the products.
Preferred study designs include:

- Randomised, single-dose, crossover design; or
- Parallel-group, single-dose design, where a crossover design is not feasible and appropriate justification is provided.

Primary PK parameters should include:

- Area under the curve (AUC_{0-t})
- Maximum concentration (Cmax)

Acceptance criteria:
Acceptance ranges for PK parameters should be predefined and justified.
Generally, a conventional equivalence range of 80.00–125.00% for the 90% confidence intervals will be applicable.

Studies may be conducted in healthy volunteers.

10. Principles of WHO guidelines on the international packaging and shipping of vaccines

The product should be maintained at required temperature while shipped from the manufacturing site to any market worldwide.

For this purpose, an Operational Qualification (OQ) study should be conducted providing evidence, according to WHO guideline, that the shipment containers are able to maintain the required temperature while exposed to a continuous external temperature of 43°C for 48 hours.

Furthermore, a Performance Qualification (PQ) study should be conducted to provide evidence that the shipment set up (qualified carriers, qualified transport containers, continuous temperature monitoring with calibrated temperature probes, evaluation of temperature data etc.) can be successfully performed for all shipments and will meet the required criteria (supported by stability data). Since a PQ study cannot be performed for every single country where the product is going to be shipped, the PQ study should be based on a criticality assessment for shipment lanes.

Finally, storage conditions (as in Product Information) and any special precautions for storage (including storage conditions after reconstitution/first opening, where applicable) should be described.

Short term storage excursions outside the label storage condition that may occur during shipping should be detailed and supported by appropriate data.

Allowable temperature excursion and temperature excursion duration outside the label storage condition that may occur during shipping should be clearly detailed

Differences from the approach above should be justified, and the equivalence of the approach should be discussed and supported by data, including a summary of the packaging procedures for international shipments (including box sizes and types, packing volumes, etc.), the validation protocols and reports of the shipping boxes used for supply of the product based on its prequalification status.

11. PRESUBMISSION MEETING

A pre-submission meeting with WHO PQT is mandatory prior to dossier submission.

The objective of the meeting is to discuss the proposed development and assessment strategy, particularly where the Applicant intends to combine principles applicable to generic medicines and biotherapeutic products.

Applicants are expected to present and discuss:

- the overall development strategy and proposed assessment pathway;
- the reference product selection and justification;
- the proposed comparability strategy, including structural, physicochemical, impurity and functional comparisons;
- the extent of quality, non-clinical and clinical data proposed to support the application;
- the justification for any proposed waiver of BE/PK, immunogenicity or other clinical studies based on the totality of evidence;

- the proposed acceptance criteria and statistical approaches for comparability assessments;
- the strategy for characterization, qualification and control of process-related and product-related impurities;
- the approach to address differences arising from synthetic versus recombinant manufacturing processes;
- any residual uncertainties identified following the quality comparability exercise and the proposed strategy to address them;
- the proposed shipping, stability and temperature excursion strategy, where relevant.

Applicants should be prepared to justify how the totality of evidence supports comparability with the selected reference product and how any remaining uncertainty is addressed through additional data.