

## 3rd<sup>1</sup> Invitation to Manufacturers of medicinal products for management of diabetes to Submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team

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 containing the active ingredients human insulin, insulin analogues and semaglutide to submit Expressions of Interest (EOI) for product evaluation.

### 1. Procedure for this Invitation to EOI

Assessment of product(s) submitted under this Invitation for EOI will include, but not be limited to:

- Assessment of product dossiers, which must meet WHO technical guidance on quality, safety and efficacy or performance.
- Inspection of manufacturing sites, which must adhere to current good manufacturing practices (cGMP) and good distribution practices (GDP).
- Inspection of clinical sites (if applicable), which must adhere to current good clinical practice (cGCP) and current good laboratory practices (cGLPs).
- Assessment during dossier assessment and/or inspection of ability to meet relevant operational packaging and presentation specifications; and adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines<sup>2</sup>.

If evaluation demonstrates, as determined by WHO, that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, the product (as manufactured at the specified manufacturing site(s)) will be included in the WHO list of prequalified products that are considered to be acceptable, in principle, for procurement by interested United Nations agencies and WHO Member States.

### 2. Products included in the 3rd Invitation

The aim of this 3<sup>rd</sup> EOI is to facilitate access to selected medicines used in the management of diabetes containing the active ingredient human insulin, insulin analogues and semaglutide. The recommended active ingredients, dosage forms and strengths listed in this document have been identified by WHO for effective treatment of type 1 and/or type 2 diabetes.

These formulations are included in the WHO Model List of Essential Medicines<sup>3</sup>. Products included in the WHO Model List of Essential Medicines are those which satisfy the priority health care needs of a population. They are selected based on disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness. Products included in WHO treatment guidelines are selected based on an assessment of the quality of evidence for benefits, harms, costs, and appropriateness for use in a variety of situations, considering needs of special populations, and the values and preferences of the groups (professional and patient) using them.

Interested manufacturers are encouraged to submit documentation for the medicinal products used within the indication of treatment of diabetes as specified below:

1. Human insulin injection solution (short-acting) 40 IU/mL in 10mL vial; 100 IU/mL in 10 mL vial and 3 mL cartridge\*.
2. Human intermediate-acting insulin injection suspension 40 IU/mL in 10mL vial; 100 IU/mL in 10mL vial and 3 mL cartridge\*.
3. Long-acting insulin analogues injection solution 100 IU/mL in 10 mL vial and 3 mL cartridge\*
4. **Rapid-acting insulin analogues injection solution 100 IU/ mL in 10 mL vial and 3 mL cartridge\***

<sup>1</sup> Additions are in red

<sup>2</sup> [Guidelines for the international packaging and shipping of vaccines, 7th ed](#)

<sup>3</sup> [WHO Model Lists of Essential Medicines](#)

5. Semaglutide\*\*, injection solution, 0.68 mg per mL; 1.34 mg per mL; and 2.68 mg per mL in vial or 3 mL cartridge\*

\* If the product has been approved by a WHO-Listed Authority for medicines (WLA – see art. 5 for further information) together with a prefilled pen/syringe, that presentation, as approved by the WLA, will be eligible for prequalification. WHO PQ is working in extending its expertise to be able to also conduct full assessment of prefilled pens/syringes very soon.

\*\*For Semaglutide, injection solution, with a prefilled pen/syringe 0.68 mg per mL (each dose contains 0.5 mg of semaglutide in 0.74 ml solution); 1.34 mg per mL (each dose contains 0.25 mg of semaglutide in 0.19 ml solution, 0.5 mg of semaglutide in 0.37 ml solution or 1 mg of semaglutide in 0.74 ml solution); and 2.68 mg per mL (each dose contains 1 mg of semaglutide in 0.37 ml solution or 2 mg of semaglutide in 0.74 ml solution).

This invitation is limited to:

- Human insulin Biotherapeutic Products (BTPs), insulin analogues, semaglutide, in formulation used for diabetes management or the corresponding Similar biotherapeutic Products (SBPs), that have been approved by a stringent regulatory authority (SRA)/WHO listed authority (WLA) and are marketed in the country of registration, will be assessed via an Abridged Assessment pathway. The Abridged Assessment will include verification of the data submitted by the applicant to demonstrate that the product submitted for WHO prequalification is the same as the product approved by the SRA or WLA. In addition, the applicant should provide evidence that the product proposed for prequalification under this procedure adheres to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines and meets relevant operational packaging and presentation specifications.
- Human insulin BTPs, or the corresponding SBPs, that have not been registered by SRAs/WLAs will be assessed through the Full Assessment pathway. Where a product is claimed to be a BTP, the Full Assessment will include evaluation of the complete set of data on quality, safety and efficacy.
- Insulin analogues SBPs, that have not been registered by SRAs/WLAs will be assessed via a Full Assessment pathway, in accordance with, among other documents, the WHO Procedure for Prequalification of BTPs or their corresponding SBPs<sup>4</sup> and the WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab<sup>5</sup>.
- Semaglutide formulations for diabetes that contain semaglutide SBPs and have not been registered by SRAs/WLAs will be assessed through the Full Assessment pathway, in accordance with, among other documents, the WHO Procedure for Prequalification of BTPs or their corresponding SBPs and the WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab .
- Semaglutide formulations for diabetes containing semaglutide produced as a synthetic peptide will be assessed via the abridged pathway (if registered by an SRA/WLA) or the full assessment pathway (see below)

Where a product is claimed to be an SBP, the Full Assessment will include an evaluation of the data submitted by the applicant to demonstrate similarity to a suitable Reference Biotherapeutic Product (RBP) in terms of quality characteristics, biological activity, safety and efficacy. Demonstration of similarity between an SBP and RBP should be based on scientific evidence and a comprehensive comparability exercise. The applicant must provide WHO with the evidence necessary to support all aspects for a successful SBP qualification. A comparability exercise (i.e., a head-to-head comparison of the SBP with a RBP that, in turn, has been registered/licensed by an SRA/WLA based on a full dossier including comprehensive non-clinical and clinical data) will be required. This exercise should begin with comparison of quality characteristics and serve as the basis for any reduction in the non-clinical and clinical data package required for registration and prequalification.

For semaglutide formulations developed as synthetic peptides and submitted for prequalification via the abridge assessment pathway, the dossier submission will be according to the guidelines for human insulin products approved by SRAs/WLAs.

<sup>4</sup> [01\\_Prequalification\\_procedure\\_General.pdf](#)

<sup>5</sup> [01\\_Pilot\\_PQ\\_antancer\\_procedure\\_feb2020.pdf](#)

For semaglutide formulations developed as synthetic peptides and submitted for prequalification via the full assessment pathway, the dossier submission will be based on the generic guideline (Annex 4, TRS 970 and Annex 15, TRS 961). Additional product specific guidelines will be issued in due course.

### Article 3. How to submit an EOI

In order to submit an expression of interest for product evaluation, the manufacturer must send the required documentation, arranged according to the information provided on the WHO Prequalification Team website <http://www.who.int/medicines/regulation/prequalification/en/> or by writing to [prequalbiosimilar@who.int](mailto:prequalbiosimilar@who.int).

### Article 4. Quality assessment procedure following submission of an EOI by a manufacturer

The quality assessment is undertaken to determine whether the product being evaluated meets the requirements recommended by WHO and is manufactured in compliance with current good manufacturing practices (cGMP).

The procedure established by WHO for quality assessment incorporates:

- general understanding of the production and quality control activities of the manufacturer
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results
- assessment of the manufacturing site's adherence to cGMP and GDP, and its consistency in production and quality control of starting materials, with specific emphasis on active ingredients, and finished product
- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with current good clinical practice (cGCP) and current good laboratory practices (cGLP), as appropriate
- random sampling and testing of the products supplied.

Previous evaluation conducted by relevant national regulatory authorities (NRAs) may, at WHO's discretion, be considered during the evaluation conducted by WHO, provided that the NRA has expertise in the product area. If appropriate, WHO may collaborate with relevant NRAs regarding the product evaluation. Accordingly, any manufacturer who submits a product for evaluation is therefore encouraged to: (i) request its NRAs to collaborate with WHO in the evaluation process including, in particular, the quality assessment process; and (ii) authorize its NRAs to discuss relevant product files with WHO representatives during assessments and inspections, if required (subject to appropriate confidentiality provisions, if necessary).

Once WHO is satisfied of the quality assessment of the manufacturer of the relevant active ingredient and finished product, and of the clinical testing units, and the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the WHO List of Prequalified Products.

### Article 5. References and further information

For further information on the WHO Prequalification Team please visit PQT website at: [Medicines | WHO - Prequalification of Medical Products \(IVDs, Medicines, Vaccines and Immunization Devices, Vector Control\)](#)

If you have any questions relating to the procedure for responding to an EOI, please write to PQT at its email address: [prequalbiosimilar@who.int](mailto:prequalbiosimilar@who.int) and [fppassessment@who.int](mailto:fppassessment@who.int)  
Your question(s) will be directed to the prequalification team member who can best advise you.

For further information on the WHO Model List of Essential Medicines, and WHO Expert Committee on the selection and use of Essential Medicine, please visit the Programme's website at: <http://www.who.int/medicines/publications/essentialmedicines/en/>  
<https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines>

World Health Assembly (WHA) adopted Resolution WHA 67.21 on “Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy”

[Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy](#)

WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23,

<https://www.who.int/publications/i/item/guidelines-on-the-international-packaging-and-shipping-of-vaccines>

WHO Guidelines on evaluation of biosimilars, Replacement of Annex 2 of WHO Technical Report Series, No. 977

[https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-\(ecbs\)/annex-3---who-guidelines-on-evaluation-of-biosimilars\\_22-apr-2022.pdf](https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/annex-3---who-guidelines-on-evaluation-of-biosimilars_22-apr-2022.pdf)

WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977, 2009,

[Guidelines on evaluation of similar Biotherapeutic Products \(SBPs\), Annex 2, TRS No 977](#)

WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, Annex 4, Technical Report Series No. 987, 2014,

<https://www.who.int/publications/m/item/recombinant-dna-annex-4-trs-no-987>

Guidelines for the preparation of a contract research organization master file, Annex 7, Technical Report Series No. 957, 2010, [https://www.who.int/docs/default-source/medicines/norms-and-](https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs957-annex7-)

[standards/guidelines/regulatory-standards/trs957-annex7-guidelinespreparationcontractresearchorgmasterfile.pdf?sfvrsn=958aef39\\_2](https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs957-annex7-guidelinespreparationcontractresearchorgmasterfile.pdf?sfvrsn=958aef39_2)

WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, Technical Report Series No. 1011, 2018.

<https://www.who.int/publications/m/item/approved-biotherapeutics-a3-trs-no-1011>

Guidelines on submission of documentation for a multisource (generics) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: Quality part, Annex 4, Technical Report Series No. 970, 2021 [https://cdn.who.int/media/docs/default-source/medicines/norms-and-](https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/prequalification/trs970-annex4--multisource-prequal-quality-partpdf.pdf?sfvrsn=70912c7a_2)

[standards/guidelines/prequalification/trs970-annex4--multisource-prequal-quality-partpdf.pdf?sfvrsn=70912c7a\\_2](https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/prequalification/trs970-annex4--multisource-prequal-quality-partpdf.pdf?sfvrsn=70912c7a_2)

Guidelines on submission of documentation for a multisource (generic) finished product. Preparation of product dossiers in common technical document format, Annex 15, Technical Report Series No. 961, 2011

<https://iris.who.int/server/api/core/bitstreams/d0447d6c-418e-435d-96d0-5a081498f153/content>

WLA refers to a national regulatory authority (NRA) or a regional regulatory system (RRS) that has successfully completed assessment via the WHO Global Benchmarking Tool (GBT) and undergone the performance evaluation phase for publicly designating regulatory authorities as a WHO Listed Authority. The listing of WLAs refers to specific product streams (medicines or vaccines) and regulatory functions. For purposes of prequalification, the reference WLA's listing status should include all regulatory functions.