MEMORANDUM

From:	Director, RPQ	**To:**	Director, HPS	**Date:**	6 May 2021
Our ref:		**Attention:**			
Your ref:		**Through:**			
Originator:	Unit Head, PQT	**Subject:**	UPDATE ON EXPRESSION OF INTEREST (EOI) FOR PRODCUT EVALUATION TO THE WHO PREQUALIFICATION TEAM - BIOTHERAPEUTIC PRODUCTS (BTPs) – HUMAN INSULIN		

The WHO Prequalification Unit contributes to accelerating access to critical medical products that are quality-assured, affordable and adapted for markets in low- and middle-income countries (LMICs). The Unit does this by evaluating and prequalifying medicinal products developed by manufacturers to ensure their quality, safety and efficacy, thus expanding the pool of available quality-assured products.

Evaluating and prequalifying health products guides international procurement agencies, such as the Global Fund, Gavi, the Vaccine Alliance, and UNICEF, and increasingly countries, to make bulk purchases of medicines, vaccines, diagnostics and other critical health products at lower prices.

Human insulin was discovered as a treatment for diabetes exactly 100 years ago and has been on WHO's Essential Medicines List (EML) since the first list was published in 1977. Despite this, current insulin prices and availability pose a barrier to access to this life-saving medicine (in the case of type 1 diabetes mellitus) in most LMICs. Also, in higher income countries many patients cannot reliably access insulin because it is unavailable, unaffordable or both.

Therefore, in November 2019, the WHO Prequalification Unit published its first invitation to manufacturers for Expression of Interest (EOI) with the aim of facilitating access to biotherapeutic products, including similar biotherapeutic products (SBPs) containing the active ingredient human insulin. The recommended active ingredient, dosage forms and dosage strengths were identified by WHO for effective treatment of patients suffering from type 1 and type 2 diabetes mellitus based on what is specified in the most recent version of the model EML.

In the current EOI, manufacturers are encouraged to submit documentation for human insulins as follows: 1. Human insulin injection (soluble) 40 IU/ mL in 10-mL vial; 100 IU/ mL in 10-mL vial. 2. Human intermediate-acting insulin 40 IU/ mL in 10-mL vial; 100 IU/ mL in 10-mL vial (as compound insulin zinc suspension or isophane insulin).

cc: Dr MIKKELSEN Bente, Director NCD

Dr HUTTNER Benedikt, Team Lead EML

Dr MOJA Lorenzo, Scientist EML

Insulin analogues were not included in the EOI at the time since they are more expensive than human insulin in vial, their use was not considered to have a clinical advantage compared to human insulin and only human insulin in vial is currently included in the EML.

Following the launch of this first-ever insulin prequalification programme, the WHO Prequalification Unit developed and published a number of insulin guidance documents with the aim of guiding the applicants to successful dossier submission. A number of advisory meetings were held by PQT-Medicines (PQT/MED) with mainly Indian manufacturers, including discussions on thermostability, biosimilarity, product characterization, product development and clinical data package. Interactions with other potential applicants of human insulin dossiers are ongoing. However, in many cases major data deficiencies have been identified by PQT/MED, mainly in the areas of biosimilarity, product characterization, product development and clinical data package.

WHO's insulin initiative was presented at several high-level meetings, including the World Diabetes Day (November 2019) and at a global WHO stakeholder workshop entitled "Insulin and associated devices: access for everybody" (September 2020).

Despite the above efforts, manufacturers have yet to submit insulin dossiers to PQT Medicines. The reasons may be multifactorial. Being an old, low-cost but also low-profit product only few manufacturers still produce human insulin. Further, the market is dominated by a few market leaders – big manufacturers with little incentive to submit for prequalification. Moreover, a smaller company with an established local market may not have ambitions beyond the local market due to costs and regulatory resources. Also, manufacturers may not be interested in complying with WHO guidelines (e.g. WHO GMP) or in investing in improving the product or willing to enter into the commitments that inevitably come with prequalification (variations, reinspections, requalification etc.). Applicants may also have to redo the clinical trials that they did for their local market, since these latter trials were not ICH or WHO compliant in the first place. Additionally, the product may have undergone a number of changes in the manufacturing process and the product manufactured at present may not be comparable to the one with which clinical trials were originally done (no pre-post-change comparisons were ever done). Although the clinical trial that would need to be repeated would be small and straight-forward, this requirement may still present an obstacle for a smaller company.

Over the past two years, the WHO Prequalification Unit has had the opportunity to exchange information with companies that produce insulin. From this dialogue, an interest by manufacturers in a prequalification process that could cover more types of insulin has emerged. Creating a sustainable marketplace for insulin is critical. Supporting multi-sourcing tender strategies and accelerating introduction of multiple types of insulin biosimilars can boost competition. This should entail not only the type of insulin itself but also the device. WHO's prequalification of insulin/device is an important leveraging tool to enhance cooperation between regulators and manufacturers to expand the number of producers of quality-assured insulins and associated devices.

In 2019 the Expert Committee on Selection and Use of Essential Medicines recommended to implement "strategies to address current regulatory barriers for biosimilar insulins, including

the expansion of the WHO Prequalification Programme". Expanding the current PQT Medicines EOI to include insulin analogues and single use pre-filled syringes/pens can stimulate dossier submissions for prequalification, fulfilling the request of the EML Expert Committee.

World Health Organization

Approval for eDocument - HQ-2021-DOCS-eMemo-83698

Action	Action Taken By	Received On(UTC)	Action Taken On(UTC)	Comments	Attachments
Submitted	CIVERA, Vanessa	NA	06-May-2021 1:26 PM		
Cleared	MUBANGIZI, Deusdedit	06-May-2021 1:28 PM	06-May-2021 2:10 PM		
Cleared	PINTO DE SÁ GASPAR, Rogerio Paulo	06-May-2021 2:14 PM	10-May-2021 9:40 AM		
Approved	ONDARI, Clive	10-May-2021 9:48 AM	10-May-2021 10:52 AM		