Guidelines on Insulin and insulin analogues Master File (IMF) procedure

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1. Background

Diabetes mellitus is a public health challenge due to its high and increasing prevalence and associated morbidity and mortality that have health and economic impact on individuals and societies. It is estimated that about 830 million people are living with diabetes globally, 80% of them in low- and middle-income countries (LMIC). This number has quadrupled since 1980. 14% of adults aged 18 years and older were living with diabetes, an increase from 7% in 1990. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries.. In 2021, diabetes was the direct cause of 1.6 million deaths and 47% of all deaths due to diabetes occurred before the age of 70 years. Another 530 000 kidney disease deaths were caused by diabetes, and high blood glucose causes around 11% of cardiovascular death. Diabetes is a major cause of blindness, kidney failure and lower limb amputation.

About 9 million people that have type 1 diabetes need insulin for survival. Some people with type 2 diabetes also need insulin to manage the condition. It has been estimated that about 15% of people with type 2 diabetes require insulin, but currently only about one-half of them are receiving the insulin they need.

Access to insulin remains inadequate, despite insulin being on the WHO Model List of Essential Medicine. Its unaffordability and unavailability are well documented in LMIC and in some high-income countries as well. The number of suppliers with WHO Listed Authority (WLA) approvals or PQ status is small and the biosimilar market remains very limited. It is critical to ensure the affordability and availability of quality-assured human insulin if the Global Sustainable Development Goal target of a 30% reduction in premature mortality due to non-communicable diseases is to be achieved.

2. Introduction

The objective of the Insulin Master File (IMF) pilot procedure is to increase the number of insulin manufacturers and insulin prequalified products in order to ensure the availability of affordable quality-assured insulins.

This procedure has been designed taking into consideration the API (Active Pharmaceutical Ingredient) master file (APIMF) procedure, a well-established procedure used to preserve the confidentiality of some API information when the same API source is used by several finished product manufacturers (2). The APIMF procedure is applicable only to small molecules and generally not considered applicable to biological products because of risks resulting from their complex molecular characteristics, manufacture and control. However, insulin and certain insulin analogues are relatively simple molecules, well understood in terms of molecular characteristics and clinical effects and therefore an APIMF-like pathway is proposed.

This guideline introduces different risk mitigation measures to reduce risks derived from non-disclosure of confidential information from the Drug Substance (DS) manufacturer and enable the applicant for prequalification or prequalification variation (from now on named in the text as the applicant) to take full responsibility for the manufacturing of finished Drug Product (DP). Among these risk mitigation measures, the present WHO Pilot IMF procedure applies only to drug substance (DS) sites of manufacturer, methods of manufacture and control (CTD module 3.2.S) that are already approved by WLA within the context of a marketing authorization of a DP.

The Insulin Master File (IMF) pilot procedure is a possibility offered to IMF holders and applicants of WHO prequalified insulin DP (herein referred to as the Applicant). It allows valuable confidential

intellectual property or "know-how" of the DS manufacturer to be protected, while at the same time ensuring the applicant can take full responsibility for the quality of finished Drug Product (DP).

In addition to human insulin, this guideline applies also to long-acting insulin analogues, provided that the drug substance (DS) has been approved by WLA within the context of a marketing authorization for a drug product (DP).

Therefore, for the purpose of this guideline, references to drug substance (DS) include both human insulin drug substance and long-acting insulin analogue drug substances, unless otherwise specified.

Since, within the present framework, the DS information (CTD module 3.2.S) is already approved within the context of the marketing authorization of a DP by a WLA, WHO will rely on the assessment and inspections conducted by the WLA to assure the quality of the DS. The module 3.2.S information will therefore not be reassessed by WHO. The module 3.2.S information will be used by WHO to verify that all critical information necessary for the DP manufacturer are present within the Open Part (OP), and to undertake the assessment of any DP applications.

3. Glossary

The definitions given below apply to the terms used in this pilot procedure and should be read in conjunction with other applicable guidelines such as the " WHO Pilot Procedure for Prequalification of Biotherapeutic Products: human insulin" (3) "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of biotherapeutic products for human insulin – full assessment pathway Preparation of product dossiers in common technical document format" (4) and the "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities – abridged assessment pathway" (5) published on the WHO website. Terms may have different meanings in other contexts.

Applicant

The person or entity who submits an Expression of Interest (EOI) to participate in the WHO pilot procedure for prequalification of: (i) human insulin, insulin analogues Biotherapeutics (BTPs), or corresponding Similar Biotherapeutic Products (SBPs), that have been approved by a WLA and marketed in the country of registration, or (ii) human insulin, insulin analogues, BTPs, or corresponding SBPs, that have not been registered by WLAs (in case the product is claimed to be a human insulin or an insulin analogue SBP, the approval should have been based on a reference biotherapeutic product (RBP) approved by a WLA), together with the required documentation on such product(s).

Comparability exercise or Similarity exercise

Head-to-head comparison of a biotherapeutic product with a licensed reference biotherapeutic product (RBP) with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures.

Drug product (DP)

A pharmaceutical product type that contains a drug substance, generally in association with excipients. This refers to a dosage form in the final immediate packaging intended for marketing.

Drug substance (DS)

The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the

production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Head-to-head comparison

Direct comparison of the properties of the SBP with the RBP in the same study.

Impurity

An impurity is any component present in the drug substance or drug product that is not the desired product, a product-related substance, or an excipient (including buffer components). Impurities may be either process- or product-related.

Invitation for expressions of interest (EOIs)

Invitation calling upon interested parties (e.g. manufacturers or other applicants) to submit an expression of interest (EOI) to WHO by a specified deadline for the purpose of participating in the WHO prequalification procedure in respect of the product(s) listed in the invitation. Such an EOI should be accompanied by the required documentation on the product(s) in question.

Manufacturer

Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure. The term "manufacturer" also includes any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsibility for compliance with the applicable product and other established standards.

Originator Product

BTP licensed and approved by a WLA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies.

Prequalification

A standardized procedure of WHO to assess, in principle, whether candidate products: (a) meet WHO technical guidance on quality, safety and efficacy, including compliance with WHO's recommended standards for good clinical practice (GCP), good manufacturing practices (GMP), good laboratory practices (GLP) and good distribution practices (GDP); (b) adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines (1); and (c) meet relevant operational packaging and presentation specifications, for the purpose of providing guidance to interested United Nations agencies and WHO Member States in their procurement decisions. United Nations agencies and WHO Member States using information resulting from the WHO prequalification should perform additional steps of qualification prior to purchasing such products, including ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, pre-shipment quality control and other related aspects, including the registration status of the products to be procured.

Reference biotherapeutic product (RBP)

A reference biotherapeutic product that: (a) has been licensed and approved by a WLA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies; and (b) is used as the comparator for head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy. This definition does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

Risk management plan

A detailed description of the activities that continuously ensure patients' safety and their benefit

from a medicinal ingredient. A risk management plan includes:

- safety specifications, which summarize the known and potential safety issues and missing information about the rDNA-derived biotherapeutic;
- a pharmacovigilance plan to further evaluate important known or potential safety concerns and to provide post-marketing data where relevant information is missing;
- a risk minimization plan, which provides proposals on how to minimize any identified or potential safety risk.

Similarity

Absence of a relevant difference in the parameter of interest. A difference that is expected to induce a difference in clinical effect, such as better impurity profile, could be accepted. No differences exist that are expected to induce impact on clinical activities based on a comparability or similarity exercise.

Similar biotherapeutic product (SBP)

A biotherapeutic product that is similar in terms of quality, safety and efficacy to a reference biotherapeutic product.

WHO Listed Authority (WLA)

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.

4. Scope

This guideline is intended to assist IMF holders and applicants in the compilation of documents and information to be submitted when using the IMF procedure.

Within the framework of this WHO Pilot IMF procedure, the CTD module 3.2.S information must already be approved within the context of a marketing authorization of a DP by a WLA.

5. Content and structure of the IMF

The IMF should contain information on DS quality as indicated in the ICH M4Q (6).

Information in the IMF should be physically divided into two separate parts, namely the open part (OP) and the restricted part (RP). In addition to the OP and RP information, the IMF should contain separate tables of content and quality summaries for each of the OP and RP parts. The OP and RP should each have a unique version number given by the IMF holder. Please refer to Annex 1 for further details on the information expected to be present in each of the OP and RP.

The OP contains the information that the IMF holder regards as non-confidential to the applicant, whereas the RP contains the information that the IMF holder regards as confidential. It is emphasized that the OP is still a confidential document that cannot be submitted to third parties without the written consent of the IMF holder. In all cases, the OP should contain sufficient information to enable the applicant to control the quality of the DS and to ensure the suitability of the DS used in the manufacture of the DP.

6. Use of the IMF procedure

Under the scope of the present guideline, the IMF pilot procedure is applicable to Module 3.2.S information pertaining to human insulin and insulin analogues DS already approved by a WLA within the context of a marketing authorization of a DP.

The IMF is only reviewed in connection with a specific product dossier. An IMF is never approved on its own, but can only be accepted in relation to a DP dossier, because the DS information must be assessed in the context of a specific DP. Therefore, the quality of the DS and its suitability for use in the DP needs to be justified in the relevant product dossier.

The IMF holder (manufacturer of the DS or its authorized representative) should provide and maintain a single version of the IMF to WHO, independent of the number of applicants and the number of DP dossiers submitted. Although the IMF procedure is developed to keep the intellectual property relating to the DS confidential, it is also permissible to use the procedure when there is no confidentiality issue between the applicant and the IMF holder, e.g. when the applicant for prequalification manufactures the DS itself.

Preferably, the DS manufacturer should be the holder of the IMF. It is, however, permissible for the IMF to be submitted by another party, who is then considered as the holder. In this case, a formal letter of authorization should be available from the manufacturer of the DS assuring WHO that the IMF holder has full oversight of the DS manufacture and control.

The DS manufacturer should also provide the draft technical agreement to be signed with the DP manufacturer. Within such a technical agreement the DS manufacturer should provide the DP manufacturer with the requirements listed in Annex 1.

7. Steps of the IMF procedure (IMF holder)

The IMF holder (manufacturer of the DS or its authorized representative) should provide the IMF to WHO only once, independent of the number of applicants and the number of DP dossiers submitted.

The IMF holder should submit to WHO:

- a cover letter outlining the purpose of the submission;
- the IMF procedure application form;
- the IMF OP and RP. The OP should contain sufficient information to enable the DP applicant to take full responsibility of the DS to be used in the context of the related DP;
- a declaration that the IMF information submitted is the same as the DS information used in the DP registered with the reference WLA;
- a declaration that the IMF information will be maintained to ensure the IMF information remains the same as the DS information used in the DP registered with the reference WLA;
- a copy of the marketing authorization and Certificate of Pharmaceutical Product (CPP) (if applicable) of the associated DP, or equivalent, issued by the reference WLA demonstrating that the DS is used in a product that is registered or licensed in accordance with the reference WLA's requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
- the complete DS data on quality (CTD - Module 3);
- quality summaries for the RP and the OP;
- the letter of access (see Annex 2);

- the corresponding assessment reports from WLA, or a letter authorising WHO to obtain these documents from the WLA through information sharing mechanism.

WHO will contact the IMF holder directly if additional information is needed. Once the verification has been completed (i.e. the IMF is considered to be acceptable), the IMF details are considered to form part of the DP dossier.

8. Steps of the IMF procedure (DP manufacturer)

When the IMF procedure is used, the applicant for prequalification should provide a "letter of access", in which WHO is given the permission to assess the data in the IMF in relation to the DP application (see Annex 2).

The applicant seeking prequalification of the DP is responsible for ensuring that they have access to the relevant information concerning the current manufacture of the DS. The specifications used by the applicant to control the quality of the received DS should be unambiguously laid down in the product dossier. The applicant should include the OP part of the IMF and specify the version numbers of the OP and RP sections supporting their application.

The versions of the OP and RP referred to should be identical to those WHO hold as part of the IMF procedure.

The applicant should include all relevant details from the OP in the Quality summary of the product dossier. Aspects of the IMF that are specifically relevant to the DP under consideration should be highlighted in this summary. In cases where the DP applicant uses a different analytical method for control of the DS to the one described in the IMF, the method should be fully validated and demonstrated as equivalent to the method described in the IMF.

WHO will assess the DP dossier according to the principles laid down in "WHO Pilot Procedure for Prequalification of Biotherapeutic Products: human insulin".

9. Changes and updates to the IMF

Changes to the DS details approved by the WLA in the context of a registered DP should be reflected in the IMF held by WHO. All changes submitted to WHO should first be approved by the reference WLA. It is the IMF holder's responsibility to notify WHO and DP manufacturers affected by the variation.

Since the changes to the IMF apply to all other DP dossiers referencing that specific IMF, it is the responsibility of the IMF holder to notify the applicants of changes to the OP and/or RP, so that applicants can update their prequalified product details and file the appropriate variation(s) with WHO as necessary.

Changes or updates to the IMF should be notified by the IMF holder to WHO. The submitted package should include following information.

- a cover letter;
- an Application form;
- a table summarizing the changes carried out since the IMF was first compiled;
- an overview comparing the old and new content of the IMF;
- the WLA approval of the variation together with the WLA assessment reports;
- the names and PQT product codes for relevant products;

- the new OP and/or RP with each new version number;
- an updated Quality summary, if relevant;
- a discussion of the potential impact on the quality of the DS as a result of the change(s);.
- a comparability exercise pre- and post-change if required by relevant guidelines.

Other DP variation applications as described in the WHO “Guidelines on procedures and data requirements for changes to approved biotherapeutic products” should, as a matter of course, be submitted to WHO, taking into account also the general principles outlined in the existing WHO guidance on variations for pharmaceuticals (7) and vaccines (8) should be submitted using the CTD format.

10.Reference

1. WHO TRS 948 - Annex 4: Guidelines on active pharmaceutical ingredient master file procedure

3. WHO Pilot Procedure for Prequalification of Biotherapeutic Products: Human Insulin

4. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of biotherapeutic products for human insulin- full assessment pathway

5. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities- abridged assessment pathway

6. https://www.ich.org/page/ctd

7. WHO guidelines on variations to a prequalified product

8. WHO Guidelines on procedures and data requirements for changes to approved vaccines, Annex TRS No 993

9. WHO diabetes factsheet - https://www.who.int/news-room/fact-sheets/detail/diabetes

ANNEX 1 - Technical content of the IMF

The present technical content of the IMF should be read in conjunction with, and its applicability is limited to, the IMF procedure and is applicable only within that procedure. The present technical content intends to specify in detail the information to be included in content of the IMF.

The structure of the version numbers of the IMF should be unique and the following structure is suggested: Name IMF holder / human insulin / OP or RP/ version number / date in dd-mm-yyyy.

Content of the Open part of the IMF

For the OP, at least those aspects listed below must be covered by appropriate documentation in the IMF

General information

- nomenclature
- structure
- general properties.

Manufacture

- Manufacturers (details of sites used for the manufacture and testing of the DS) and responsibilities
- Description of the manufacturing process and controls

  A flow chart and brief outline of the manufacturing process is regarded as sufficient, if detailed information is presented in the RP. Manufacturing process and controls that are key to control the quality of the DP (e.g microbiological controls) should be detailed in the OP.
- control of critical steps and intermediates

  in so far as the information is also relevant for the applicant to prequalification.
- Manufacturing process development

  A summary of major manufacturing changes made throughout development, even in a tabular format, is regarded as sufficient.

Control of material

- Description of the raw material and starting material used in the manufacture of the DS

  Detailed description of the control of material derived from human, animal and recombinant origin should be appropriately described in the OP. If applicable, certificate of absence of transmissible spongiform encephalopathy (TSE) should be present in the OP. CoA of the MCB, WCB should be attached to the OP.

Process validation

A brief outline of the manufacturing process validation studies is regarded as sufficient. Information on the validation of reprocessing, if any, should also be included in the OP. A summary of the leachable and extractable study performed on the DS primary contained closure system should be summarized. Impact of holding on product quality of intermediates (with the inclusion of potential bioburden proliferation) should also be addressed within the OP.

Characterization

- Elucidation of structure and other characteristics.

  Summary of elucidation of structure and other characteristics.

- Detailed description of the nature of impurities (product and process related) that are expected to occur during the manufacture of the DS.

Control of the DS

- Specification
- Analytical procedures

  A summary of the analytical procedure should be part of the OP. Reference to compendial method should be provided. In/house method should be detailed as much as possible.

- Validation of the analytical procedure

  A summary of the analytical procedure validation should be part of the OP.

- Batch analysis

  The batch analysis should include batch number, manufacturing site, manufacturing date, expiry date.

- Justification of the specification

  in so far as the information is also relevant for the applicant to prequalification.

Reference standards or materials

A summary of the reference standard information that is relevant for the applicant to prequalification should be part of the OP. Detailed information (with the inclusion of the CoA) on the current Internal Reference Standard (IRS) used for analytical method development/calibration, in-process testing, release and stability testing should be part of the OP and/or of the technical agreement.

Container closure system

Description of the identity, compliance status, specification (and any additional testing) of the packing material should be part of the OP. Details of the extractable and leachable studies and a summary of the toxicological risk assessment for leachable should also be included in the OP.

Stability

A summary of the stability and post approval stability commitment should be provided in the OP.

Content of the restricted part (RP) of the IMF

The RP should contain all the information present in the CTD, such as a detailed description of the individual steps of the manufacturing process (operating conditions, data on validation and evaluation of critical steps) and in-process controls for the DS, detailed description of the starting

and raw material, characterization, process development, in-house analytical method development and validation etc.

Information relevant to the applicant such as that on impurities should be discussed in the RP, but it may be also submitted in the OP if considered necessary to enable the applicant to take full responsibility for its product.

Technical agreement

The DS manufacturer should also provide the draft technical agreement to be signed with the DP manufacturer. Within such a technical agreement the DS manufacturer should provide the DP manufacturer with, among other requirement:

- Summary of batch records including summary of the critical quality attributes, deviations and CAPAs
- Details of specific training on the correct handling of insulin DS for DP manufacturing provided to the DP manufacturer resulting in certification of successful training released by the DS manufacturer.
- The DS manufacturer should be responsible for providing the certificate of analysis of the DS.

ANNEX 2 - Model Letter of Access: Insulin Master File (IMF)

Active pharmaceutical ingredient: human insulin and insulin analogues

IMF **holder's name and address:**

Active pharmaceutical ingredient manufacturing site(s):

IMF **version number:**

Open part:

Restricted part:

(IMF holder name) hereby authorizes the relevant WHO staff members and external experts to refer to and review the above-mentioned IMF (and subsequent versions) in support application(s) submitted by (finished Drug Product (DP) manufacturer's name) for the following products:

(DP product name), (strength) and (dosage form) (WHO reference code if known)

The aforementioned IMF holder refers to a human insulin/insulin analogue CTD module 3.2.S that has been already approved within the context of a marketing authorization of a DP by a WLA. The holder is committed to notify (FPP manufacturers name) and WHO of any change in the Open or Restricted parts of this IMF.

Signed

Signature for the IMF holder

(Date, name and address)