

# WHO Guidelines on submission of documentation for the pilot procedure for prequalification of biotechnological products for human insulin – full assessment pathway

## Preparation of product dossiers in common technical document format

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## 1. Introduction

The World Health Organization (WHO) Prequalification Unit (PQT) is managed by the WHO department of Regulation and Prequalification (RPQ) to provide United Nations agencies and WHO Member States with guidance on the acceptability, in principle, of medicines, vaccines, in vitro diagnostics, immunization and other medical devices, and vector control products for procurement by such agencies and Member States.

Accordingly, for the purpose of providing guidance to interested United Nations agencies and WHO Member States in their procurement decisions, WHO will undertake a pilot procedure for prequalification of biotherapeutic products for human insulin, to evaluate whether candidate products: (a) meet WHO technical guidance on quality, safety and efficacy or performance, 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) meet relevant operational packaging and presentation specifications; and (c) adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines (1).

Candidate medicines, vaccines, in vitro diagnostics, immunization and other medical devices and vector control products which are found by WHO to meet its recommended standards of quality, safety and efficacy will be included in the WHO list of prequalified products (as manufactured at the specified manufacturing sites) which are considered to be acceptable, in principle, for procurement by United Nations agencies and WHO Member States. However, any United Nations agencies and/or WHO Member States using information from the WHO list of prequalified products should nevertheless perform additional steps of qualification prior to procuring any products included in such list. Such steps include, but are not limited to, ensuring the supplier's financial stability and standing, as well as its ability to supply the required quantities of the product, the security of the supply chain, pre-shipment quality control and other relevant aspects.

Inclusion in WHO's list of prequalified products does not imply: (a) any approval by WHO of the product and/or manufacturing sites in question (which is the sole prerogative of national authorities), or (b) any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the treatment of any specific diseases, or (c) any warrant that the products have obtained regulatory approval for their specified use or any other use in any country of the world, or that their use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws.

Applicants, manufacturers and/or any other party may not use, for any commercial or promotional purposes: (i) the results of the prequalification assessment; (ii) the participation in the WHO prequalification assessment process; (iii) the inclusion of any product in the WHO list of prequalified products; and/or (iv) the WHO's name, acronym or emblem. Additionally, WHO will not accept any liability or responsibility whatsoever for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of or in connection with the procurement, distribution and/or use of any product as to which WHO has published the prequalification assessment results and/or which is or has been included in the WHO list of prequalified products.

## 2. Objective

In recent years, a great number of biotherapeutic products (BTPs) have demonstrated success in treating many life-threatening chronic diseases. In May 2014, the World Health Assembly (WHA) adopted Resolution WHA67.21 (2) on "Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy".

Human insulin was discovered as a treatment for diabetes approximately 100 years ago and has been on WHO's Essential Medicines List since the first list was published in 1977. In spite of this, current insulin prices and availability pose a barrier to treatment in most low- and middle-income countries. In higher income countries, there are several sub-populations that cannot reliably access this life-saving medication because it is unavailable, unaffordable or both (3).

As stated in the WHO Model List of Essential Medicines (4), insulin is used principally to treat diabetes. Insulin BTPs, and the corresponding SBPs, have been selected for this WHO pilot procedure because: (i) insulin is a life-saving medication; (ii) current insulin prices pose a barrier to treatment in most low- and middle-income countries; (iii) there is an established WHO technical guidance for evaluation of biotherapeutic protein products prepared by recombinant DNA technology (7) and on evaluation of similar biotherapeutic products (SBPs) (8, 9).

Given that BTPs, including their corresponding SBPs, are complex and that the regulatory assessment of those products according to internationally acceptable guidelines and standards can be challenging in some countries, WHO's Prequalification Programme has developed a WHO pilot procedure for prequalification of human insulin, following either one of two pathways:

1) full assessment of human insulin BTPs, or the corresponding SBPs, that have not been registered by SRAs (hereinafter referred to as "Full Assessment" (5); and

2) abridged assessment of human insulin BTPs, or the corresponding SBPs, that have been approved by a stringent regulatory authority (SRA) and marketed in the country of registration (hereinafter referred to as "Abridged Assessment") (6)

The World Health Organization (WHO) recognizes the global use of the Common Technical Document (CTD) guideline (10, 11, 12, 13, 14) and its format developed by the International Council for Harmonisation (ICH). Many manufacturers have a prepared product dossier in CTD format which they have used to register a product in one or more countries. Furthermore, many countries that import prequalified medicinal products require the submission of a product dossier in CTD format for registration of the products.

Therefore, considering the value that BTPs can provide and the fact that some BTPs have already been listed in the WHO Model List of Essential Medicines, WHO's RPQ<sup>1</sup> is exploring options to facilitate access to human insulin, including corresponding insulin similar biotherapeutic products (SBPs), at affordable prices.

### 3. Scope

These guidelines are intended to assist applicants with the submission of documentation for prequalification of human insulin BTPs, or the corresponding SBPs (based on a RBP approved by a SRA), not registered by an SRA.

These guidelines primarily addresses the organization of the information to be presented in PDs for the candidate product as defined above. They are generally not intended to indicate what studies are required. They merely indicate an appropriate format for the data that have been acquired.

These guidelines are also intended to fully adopt the modular format of the CTD, as developed by ICH; and to provide guidance on the location of regional information (Module 1) and other general data requirements.

Applicants should not modify the overall organization of the CTD as outlined in the guidelines.

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<sup>1</sup> RPQ operates in the Division of Access to Medicines and Health Products [MHP].

These measures are intended to promote effective and efficient processes for the development of these PDs and the subsequent assessment procedures.

## 4. General procedure and data requirements

These guidelines present the agreed-upon common format for the preparation of a well-structured CTD for PDs that will be submitted to WHO. A common format for the technical documentation significantly reduces the time and resources needed to compile PDs for the prequalification of the BTPs or the corresponding SBPs, and eases the preparation of electronic submissions.

Assessments and communication with the applicant are facilitated by a standard document containing common elements. In addition, exchange of regulatory information between national regulatory authorities (NRAs) and with WHO are simplified.

These guidelines should be read in conjunction with other applicable WHO and ICH reference documents and from other applicable regulatory Guidelines (and in particular ICH, EMA, US-FDA, PMDA) and Guidelines that provide further guidance and recommendations on the topic-specific content requirements for the BTPs, or the SBPs, notably:

- WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (7)
- Guidelines on evaluation of similar biotherapeutic products (8);
- WHO Questions and Answers: similar biotherapeutic products (9)
- WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23 (1)

## 5. Glossary

The definitions given below apply to the terms used in this pilot procedure and should be read in conjunction with the “*WHO Pilot Procedure for Prequalification of Biotherapeutic Products: human insulin*” (15) and the “*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*” (5) published on the WHO website. Terms may have different meanings in other contexts.

### **Applicant**

The person or entity who, by the deadline mentioned in an invitation for expressions of interest (EOI), submits an EOI to participate in the WHO pilot procedure for prequalification of: (i) human insulin BTPs, or the corresponding SBPs, that have not been registered by SRAs, or (ii) human insulin BTPs, or the corresponding SBPs, that have been approved by a stringent regulatory authority (SRA) and marketed in the country of registration, 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.

### **Comparator for clinical studies**

A comparator for clinical studies for BTPs is an established human insulin product approved by an SRA with a pharmacological profile similar to that of the product to be prequalified.

### **Contract research organization (CRO)**

An organization (commercial, academic or other) to which an applicant may have transferred some of its tasks and obligations in relation to the conduct of clinical studies with the product submitted to WHO for assessment under the above-mentioned procedure.

### **Drug product (DP)**

A pharmaceutical product type that contains a drug substance, generally in association with excipients. The 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.

### **Immunogenicity**

The ability of a substance to trigger an immune response or reaction (e.g. development of specific antibodies, T cell response, allergic or anaphylactic reaction).

### **Impurity**

Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient including buffer components. It 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 an SRA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies.

### **Prequalification**

Standardized prequalification procedure of WHO to assess, in principle, whether candidate BTP or SBP products, as applicable: (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 an SRA 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.

### **Stringent regulatory authority<sup>2</sup> (SRA)**

A regulatory authority which is:

- a. a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or
- b. an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or
- c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

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<sup>2</sup> For the purpose of WHO pilot procedure, this interim definition taken from the "[WHO Technical Report Series TRS 1003, Fifty-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations](#)" is used. Note: This interim definition is currently being revised.

## 6. Organization of a product dossier for an SBP in CTD format

The CTD is organized into five modules. Module 1 is region-specific. Modules 2, 3, 4 and 5 are intended to be common for all regions. Conformance with these guidelines facilitates the provision of Modules 2, 3, 4 and 5 in a format acceptable to WHO and to regulatory authorities.

This section provides an overview of module contents for the BTP or SBP in greater detail.

### Module 1: Administrative information and prescribing information

- This module should contain documents specific to WHO and each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by WHO and the relevant regulatory authorities.
- If applicable, a summary of the similarity information should be provided according to WHO's applicable guidelines on SBP (8, 9).
- Risk management plan and methods used to report adverse events, safety specification, pharmacovigilance plan, post-marketing safety reports according to the WHO Guidelines on evaluation of similar biotherapeutic products (8) should also be provided.
- WHO prequalification-specific addendum to the risk management plan (RMP) as detailed on the PQT web page.

### Module 2: CTD summaries

- This Module should begin with a general introduction to the BTP and SBP, including its pharmacological class, mode of action and proposed clinical use. In general, the Introduction should not exceed one page.
- A summary of the quality, non-clinical and clinical information should be provided according to WHO's applicable guidelines (7, 8, 9).
- The organization of these summaries is described in Guidelines for ICH M4, M4Q, M4S and M4E (10, 11, 12, 13, 14).

### Module 3: Quality

- Information on manufacturing and quality should be presented in the structured format described in ICH M4Q (10). In addition applicants should note that the comparability exercise for a SBP versus a RBP is an additional element to the normal requirements of a quality dossier in the case where biosimilarity is claimed of the proposed product to an RBP. Such exercise should be discussed separately in section 3.2.R when presenting the data in module 3.

### Module 4: Nonclinical study reports

- Information on nonclinical study reports should be presented in the structured format described in ICH M4S (13).

### Module 5: Clinical study reports

- The human study reports and related information should be presented in the order described in ICH M4E (14).

The overall organization of the CTD is presented in Figure 1.<sup>3</sup>

If the candidate product is claimed to be an SBP, and the Module 3 data demonstrate sufficient

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<sup>3</sup> Figure 1 is reproduced with the kind permission of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA)

comparability of the candidate SBP to the RBP, then reduced Module 4 and 5 data packages may be submitted.

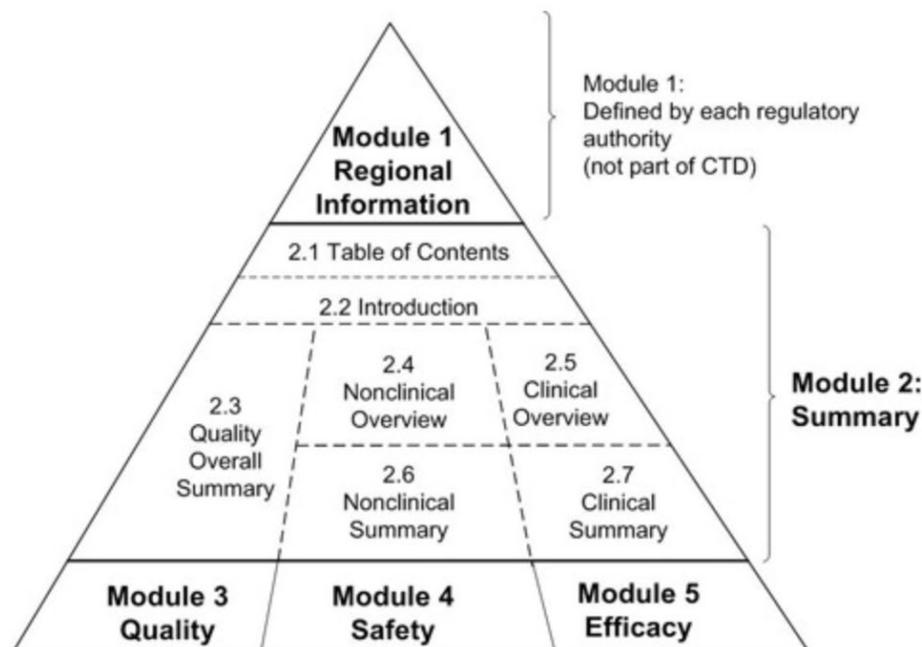


Figure 1. The overall organization of the CTD

## 7. Modules (including Module 1) of a product dossier for an SBP

The data for a BTP or an SBP should follow the structure of the CTD format for the applicable sections:-

### Module 1.

Additional guidance for some of the applicable sections to be included in Module 1 is provided below:

#### 1.0 Cover letter

The cover letter submitted with the PD should include a clear statement by the responsible person submitting the PD, indicating that the information submitted is complete and correct.

#### 1.2.2 Manufacturing and marketing authorization(s)/international registration status

List the countries in which:

- The BTP or SBP has been granted a marketing authorization (If applicable);
- the BTP or SBP has been withdrawn from the market; and
- an application for the marketing of the BTP or SBP has been rejected, deferred or withdrawn.

#### 1.4 Regional summaries

The regional summaries should be prepared in accordance with the available WHO templates, which are found on the WHO Prequalification web site.

#### 1.5 Electronic review documents

Electronic submission of documentation (CD or DVD) should be submitted in Microsoft Word or text-selectable PDF format (other documentation).

## 1.6 Samples (e.g. DP, device(s))

Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalized. For guidance regarding labelling, refer to the information on WHO public assessment reports (WHOPARs) available on the WHO Prequalification web site under <https://extranet.who.int/prequal/key-resources/prequalification-reports/whopars>

### Module 3. Quality

The applicable WHO guidelines (7, 8, 9) provide detailed guidance on the preparation of the BTP and SBP information by the applicant.

### Module 4. Non-clinical study reports

The non-clinical part of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, the WHO Guidelines on evaluation of similar biotherapeutic products and the WHO Questions and Answers: similar biotherapeutic products (7,8,9) addresses the pharmaco-toxicological assessment of the BTP or SBP. The establishment of safety and efficacy of an BTP or SBP may require the generation of some non-clinical data.

If the candidate product is claimed to be an SBP, the demonstration of a high degree of molecular similarity between the SBP and RBP should significantly reduce the need for nonclinical studies since the RBP would normally already have a significant clinical history. Nonclinical studies should be conducted with the final formulation of the SBP intended for clinical use.

The applicable WHO guidelines (7,8,9) provide detailed guidance on this issue and on the preparation of the BTP or SBP information by the applicant.

### Module 5. Product dossier for BTP or SBP

*If the candidate product is claimed to be an SBP:*

Demonstration of similar pharmacokinetic (PK) and pharmacodynamic (PD) profiles is considered the mainstay of proof of similar efficacy of the biosimilar and the reference insulin. Cross-over, preferably double-blind hyperinsulinaemic euglycaemic clamp studies using single subcutaneous doses of the test and reference agents are considered most suitable.

Specific efficacy studies are not anticipated to be required as the endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins.

The amount of safety data will be dependant on whether biosimilarity between the SBP and RBP can be convincingly concluded from the physicochemical/functional characterisation and comparison using sensitive, orthogonal and state-of-the-art analytical methods, and from the comparison of the PK and PD profiles. In addition, it will depend on whether the impurity profile and the nature of excipients give rise to any concerns.

The applicable WHO guidelines (7,8,9) provide guidance on this issue and on the preparation of the SBP information by the applicant.

*If the candidate product is not claimed to be an SBP:*

Comparative PK and PD profiles of the product to be prequalified and the comparator human insulin should be demonstrated. Cross-over, preferably double-blind hyperinsulinaemic euglycaemic clamp studies using single subcutaneous doses of the test and comparator agents are considered most suitable.

Comparative safety data, usually of 6 months duration, will also be required. The Applicant is encouraged to consult with WHO Group Leader Medicine Assessment prior to initiation of a study.

For SBPs or BTPs with different preparations containing the same active ingredient

In case different preparations (e.g. short-acting and intermediate-acting human insulin products, containing the same active ingredient) are developed on a case by case basis the same level of clinical data may not be required for all of the preparations.

Applicants are also referred to WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (7) and other applicable regulatory guidelines for the development of biological products for the treatment of diabetes mellitus.

## 8. Guidance on format and presentation of a product dossier in CTD

### 8.1 Guidance on format

The submission must be in English and must include officially certified English translations of product information and other documents, if applicable. The English language version of the product information, in the case of English translations, should also be submitted as Word files.

Throughout the CTD, the information should be displayed in an unambiguous and transparent manner. Text and tables should be prepared using margins that allow the document to be printed on both A4-sized paper (European Union and Japan) and 8.5 × 11-inch paper (US). The left-hand margin should be sufficiently large that information is not obscured whatever the method of binding.

Fonts for text and tables should be of a style and size large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

Acronyms and abbreviations should be defined the first time they are used in each module.

References should be cited in accordance with the current edition of the *Uniform requirements for manuscripts submitted to biomedical journals*, International Committee of Medical Journal Editors (ICMJE). Copies of relevant pages of references should be provided, with a copy of the full article in the case of a publication.

### 8.2 Guidance on presentation

The paper copies of the application should be bound for easy access to information.

Each binder should be labelled with the proprietary name (if applicable) and the non-proprietary name of the BTP or SBP and the company name of the applicant. For ease of reference, the following information could also be included on the label of each binder (space permitting): the volume number for that binder (out of the total number of volumes *for that module*), the section(s) contained within each volume and the date of the application (month and year), e.g.:

DP “Name ABC”

Nonproprietary name

Applicant “XYZ”

Module 3 — Quality

Volume 1 of 3

Module 3.1 — 3.2.S.3

Month/year

## 9. Variations

All variation applications, as described in the WHO “Guidelines on procedures and data requirements for changes to approved biotherapeutic products” (16) plus the general principles outlined in the existing WHO Guidance on variations for pharmaceuticals (17) and vaccines (18) should be submitted using the CTD format.

In the case of the filing of a variation, applicants should normally provide only the relevant modules or sections affected by the change. For example, if the variation was for a change in the shelf-life of the DP, only those sections affected by the change would need to be submitted.

## References

1. WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23
2. WHA 67.21 Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy, 2014
3. Basu, Yudkin J, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ, Sussman JB, Beran D. Lancet Diabetes Endocrinol. 2019 Jan;7(1):25-33
4. WHO Model List of Essential Medicines, 21<sup>th</sup> List 2019
5. 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
6. WHO WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities – abridged assessment pathway
7. 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
8. WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977, 2009
9. WHO Questions and Answers: similar biotherapeutic products
10. Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use: M4 (R4): Organisation Including the Granularity document that provides guidance on document location and paginations.
11. M4 Implementation Working Group Questions & Answers (R3)
12. The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q (R1).
13. The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety – M4S (R2).
14. Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH: Efficacy – M4E (R2).
15. WHO Pilot Procedure for Prequalification of Biotherapeutic Products: human insulin
16. WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, Technical Report Series No. 1011, 2018
17. WHO guidelines on variations to a prequalified product
18. Guidance on reporting variations to a prequalified vaccine