MPD-G-MA-

Guideline for collaborative registration procedure for pharmaceutical and vaccines 2025

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1.

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Version History

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Table of Content

1. Introduction

The Medical Product Division (MPD) under the Bhutan Food and Drug Authority is responsible for registering medical products, as mandated by the Medicines Act of the Kingdom of Bhutan 2003. According to Chapter VI, Section 16.2 of the Act, "All medicinal products manufactured, sold, distributed, and imported/exported from Bhutan must be registered under the provisions of this Act." In compliance with this requirement, nearly all products approved for market access in Bhutan are registered with the Authority. Marketing Authorization, also known as product registration, is one of the nine core functions of a national regulatory authority (NRA) aimed at ensuring the quality, efficacy/effectiveness, and safety (QES) of medical products. This process is vital in guaranteeing that the public has access to safe and high-quality products.

National regulatory authorities play a critical role in ensuring the timely availability of quality-assured products for their populations. This accessibility is primarily achieved through the issuance of marketing authorizations for medical products. For NRAs with limited resources, reliance is a mechanism that helps facilitate timely access to quality-assured products. Given the challenges posed by limited resources and expertise, coupled with the growing complexity of global supply chains, timely access to essential, high-quality medical products has become more difficult. To address these challenges, facilitated regulatory pathways have been introduced, allowing NRAs to leverage assessments conducted by other regulatory authorities through the principles of reliance and collaboration. Collaborative Registration Procedure (CRP) is one of the facilitated regulatory pathways (FRP) mainly relying on the assessments performed by WHO-PQ and CRP participating reference authorities. Assisted by the WHO facilitated product introduction team, NRAs are enabled to access unredacted documents to facilitate the registration of a medical product.

2. Scope

2.1. This guideline shall apply to following categories of medical products:
- 2.1.1. Pharmaceutical medicines
- 2.1.2. Biologics and Vaccines

3. Objectives

3.1. To provide guidance on compilation and submission of CRP dossiers for the purpose of grant of marketing authorization.
3.2. To guide regulators in the processing of CRP dossiers.

4. Normative references

4.1. Medicines Act of the Kingdom of Bhutan 2003
4.2. Bhutan Medicines Rules and Regulation 2019
4.3. Guideline for registration of medicinal products 2020

5. Definitions

5.1. **Act:** It refers to the Medicines Act of the Kingdom of Bhutan 2003.

5.2. **Authority:** It refers to the Bhutan Food and Drug Authority.

5.3. **Collaborative registration procedure:** It refers to a registration procedure which is facilitated by WHO and registration is accelerated by sharing of detailed assessment and inspection reports generated by the WHO or by a reference authority.

5.4. **CRP dossier**: It refers to the product dossier submitted in the context of collaborative registration procedure.

5.5. **Division:** It refers to the Medical Product Division.

5.6. **Facilitated regulatory pathway:** It refers to a type of regulatory pathway available to NRAs, which are meant to facilitate and accelerate the regulatory decisions and the introduction of quality-assured products, through the use of concepts of reliance and collaboration.

5.7. **Marketing authorization**: It refers to the regulatory approval required to sell a drug or other therapy to the public. It's a formal process where a regulatory agency assesses the quality, safety, and efficacy of a product before it can be manufactured and sold.

5.8. **National registration:** It refers to the grant of marketing authorization by the BFDA.

5.9. **Participating WHO Listed Authorities:** It refers to a reference stringent regulatory authority that agrees to provide outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers, does not object to sharing of these documents with national medicines regulatory authorities and provides, under specified conditions in line with the principles of the Procedure, support to other parties involved in the Procedure.

5.10. **Vaccine:** A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, one of its surface proteins or genetically-engineered material. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

6. Acronyms

6.1. **BMRR:** Bhutan Medicines Rules and Regulation

6.2. **MAH:** Market Authorization Holder

6.3. **BFDA**: Bhutan Food and Drug Authority

6.4. **CRP:** Collaborative registration procedure

6.5. **FRP:** Facilitated regulatory pathway

6.6. **FPP:** Finished pharmaceutical product

6.7. **IVD:** Invitro Diagnostics

6.8. **MA** : Market Authorization

6.9. **NRA:** National regulatory authority

6.10. **PAV:** Post approval variation
6.11. **PQ:** Prequalification
6.12. **PQT**: Prequalification team
6.13. **TAT**: Turn around time
6.14. **WHO:** World Health Organization.
6.15. **WLA:** WHO listed authority

7. General Principle

7.1. Regulatory reliance is the main basis for Collaborative Registration Procedure.
7.2. The following are the key principles of CRP:
7.2.1. Voluntary - A manufacturer of a product(s) voluntarily expresses interest in applying this procedure to facilitate in-country registration of its product(s) in the country.
7.2.2. Confidentiality - The authority signs a participation agreement and confidentiality undertaking with the WHO, whereby it adheres to the provisions of the procedure. Only countries with a signed agreement with WHO can participate in the procedure.
7.2.3. Product sameness - A manufacturer must submit the same product as the one prequalified or stringently approved in countries where application of the CRP is sought. Product sameness is a mandatory prerequisite for applying a collaborative procedure.
7.3. The applicable fees for registration will be levied for the products intending to be registered through the collaborative registration procedure.
7.4. Samples for CRP will be exempted however, the clear legible pictures of the product sample in its commercial packaging should be provided along with the dossier.
7.5. A communication of two rounds shall be provided to complete missing parts of documentation, provide additional data and/or clear any discrepancies raised by the authority.
7.6. CRP for pharmaceuticals & vaccine and biologics are carried out based on WHO prequalification or registration by a reference authority.
7.7. Within the context of this procedure, the same pharmaceutical product or vaccine is characterised by:
7.7.1. PQ-CRP
7.7.1.1. the same product dossier;
7.7.1.2. the same manufacturing chain, processes, control of materials and finished product, and in the case of vaccines also by the same batch release scheme;
7.7.1.3. the same active ingredient and finished product specifications;
7.7.1.4. the same essential elements of product information for pharmaceutical products, in the case of vaccines by the same product information, packaging presentation and labelling.

7.7.2. WLA-CRP

7.7.2.1. the same qualitative and quantitative formulation;
7.7.2.2. the same manufacturing site(s) for API and FPP including specific block(s)/unit(s), chain, processes, control of materials and final product, and in the case of vaccines also by the same batch release scheme;
7.7.2.3. the same specifications for excipient, API and FPP;
7.7.2.4. the same essential elements of product information.

7.8. The applicant must ensure that any post approval variations to the medical product approved under CRP are accordingly informed to WHO, WLA and the authority.

8. PQ-CRP for pharmaceutical medicines & Vaccines

8.1. Procedure

8.1.1. The manufacturer submits the duly filled and signed ***consent form (Appendix 2)*** and ***Appendix 3, Part A*** to the WHO (prequalreg@who.int) and the CRP focal point respectively. The filled and signed ***appendix 3, Part A*** should be submitted to the WHO as well.
Any differences between the prequalified dossier/data and dossier for national submission should be stated as requested by ***Appendix 3, Part A***.

8.1.2. On receipt of the application, the authority may accept or refuse to apply the procedure to the FPP. Signed ***Appendix 3, Part B*** is submitted to the WHO via email (prequalreg@who.int) and/or confidential restricted-access website. The outcome is to be communicated to the applicant also.

8.1.3. On acceptance, the WHO shares with the authority information relating to its evaluation of the FPP for prequalification and any variations (if applicable) via confidential restricted-access SharePoint website.
On refusal, the justification for its refusal should be provided to the WHO and reflected in ***Appendix 3, Part B*** before submission.

8.1.4. The authority conducts assessment of the FPP using the information provided by WHO with a TAT of 60 calendar days considering the stop clock principle.

8.1.5. The authority, within further 30 days, informs the applicant of its regulatory decision, and completes ***Appendix 3, Part C*** and provides it to WHO via email (prequalreg@who.int) or confidential restricted-access SharePoint website. The appendix may be shared to the applicant as well.

8.2. Post approval variations

8.2.1. PAV applications for changes that do not affect the QSE and sameness of the product with the prequalified product will be accepted. Relevant guidelines for PAVs will be applicable for the process to receive PAV applications.

Post approval variations approved by WHO will be considered via CRP mechanisms wherein the PAV dossier submitted should essentially be the same as the PAV dossier submitted to the WHO. It must also be accompanied by an assessment report if applicable or evidence of acceptance of PAV by WHO PQT.

8.2.2. Any approved PAVs for the FPP must be informed to the WHO using ***Appendix 4*** via email (prequalreg@who.int) or confidential restricted-access SharePoint website within 30 calendar days.

8.2.3. In cases where a national variation procedure results in the FPP being no longer the same as the WHO-PQ'ed product, or in the event that a variation of a WHO-PQ'ed product is not followed by the same variation of the nationally registered product, the authority will inform the WHO/PQT by submitting ***Appendix 4***, specifying the deviations.

8.2.4. On receiving information from WHO-PQT regarding approval of PAV, the authority will respond on the acceptance of PAV or refusal to accept PAV by informing the WHO-PQT using ***Appendix 4*** within 30 calendar days. No response from the authority will be considered as accepted by WHO from the date of sharing information.

8.2.5. If a prequalified product is withdrawn by the WHO PQ holder, or is suspended or delisted by WHO/PQT, WHO/PQT will inform each participating authority that has approved, or is in the process of reviewing the product pursuant to this Procedure, of the withdrawal, suspension or delisting and the reasons for taking this action, through the restricted access website and subject to the obligations of confidentiality contained in Appendix 1, Part A. Similarly, when an NRA deregisters or suspends the registration of a prequalified pharmaceutical product or vaccine for any reason, it will inform WHO/PQT of this decision and of its reasons through the restricted-access website. Other participating NRAs which have registered the WHO-prequalified product in question pursuant to this Procedure will be made aware of such national deregistration or suspension through the restricted-access website. In addition, if the fact that a WHO-prequalified product has been registered in a country pursuant to this Procedure has been made public, any subsequent deregistration or suspension should also be made public by posting on the WHO/PQT website.

8.3. Document requirements

8.3.1. The dossier submitted should be in English or Dzongkha.

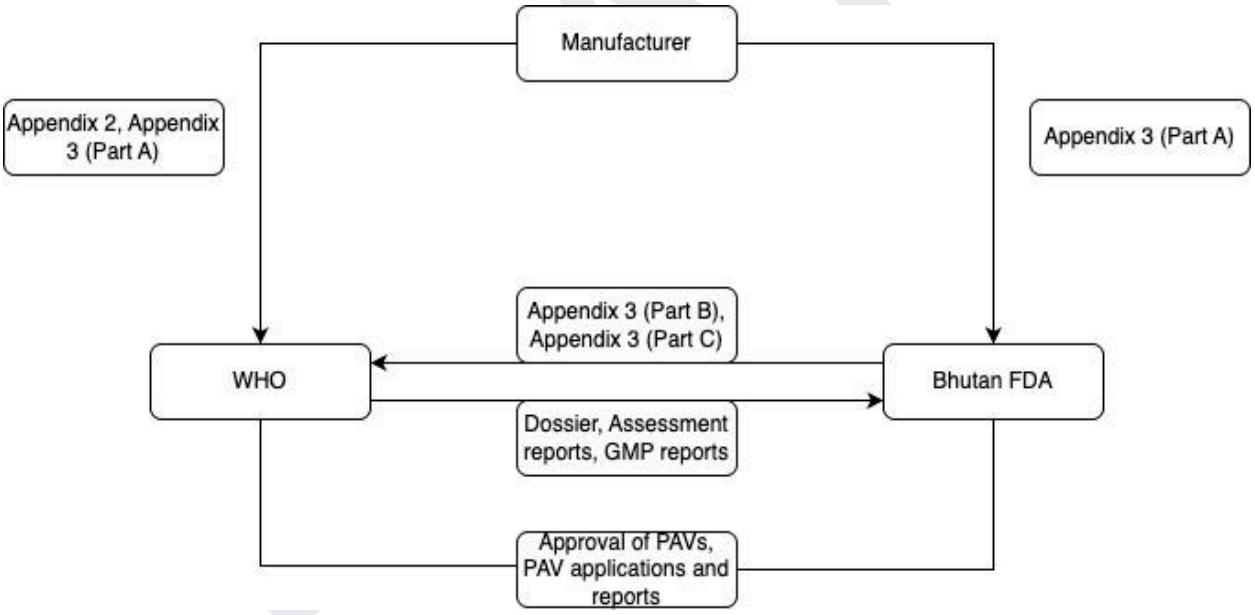
8.3.2. For any certificate or reports or authorizations in a language other than English or Dzingkha, the document must be translated with a valid notarization.

8.3.3. Essentially, the CRP dossier (including changes made post authorization) submitted to the WHO-PQT for the purpose of prequalification should be submitted to the authority for the grant of marketing authorization. All portions in module 2-5 of the dossier should be the same as the WHO prequalified product dossier.

8.3.4. The following documents will be required for module 1 of the dossier.

8.3.4.1. Application form
8.3.4.2. Letter of authorization
8.3.4.3. SMF
8.3.4.4. Regulatory documents - cGMP
8.3.4.5. Declaration letter - Declare that the product submitted for MA is the same as the prequalified product
8.3.4.6. Price structure
8.3.4.7. Product specimen of packaging - Identical to the specimen submitted to the WHO

8.4. Process flow



9. WLA-Collaborative registration procedure

9.1. Procedure

9.1.1. The applicant submits dossier and relevant reports as per clause 9.3 of this guideline after completion of necessary formalities required to apply the collaborative registration procedure.

Formalities are as follows:

- The applicant with WLA marketing authorization agrees with WHO that the procedure will be applied to the specific product and that WHO will have access to the data shared with the authority using ***Appendix 8 (Confidential disclosure agreement)***.
- The applicant with WLA marketing authorization grants the WLA permission to share information concerning the product with the authority and WHO (***Appendix 3A***) and requests WLA permission to share the WLA's assessment and inspection reports with NRAs and WHO (***Appendix 3B***).
- The applicant with WLA marketing authorization submits an expression of interest to the authority (***Appendix 7***) followed by an application for registration of the product, in line with the procedure and respecting specific national requirements (***Appendices 4-WLA validated QIS, 6-Bridging report where applicable***).

9.1.2. On receipt, the authority will validate the completeness of the dossier as required and decide whether or not to apply the procedure in each specific case and inform the applicant of its decision within 30 calendar days. The reasons for non-acceptance will be relayed to the WHO and the applicant.
The authority may reach out to the reference authority for further validation of the assessment and/or inspection reports shared.

9.1.3. On acceptance, the authority will conduct assessment of the dossier and depth of assessment may vary depending on the type of product and the WLA approving mechanism for the marketing authorization.
The following components may be required to be reviewed separately(Not limited to):

- Stability study data
- Labelling and product information

The CRP focal may present on the outcomes of the assessment to relevant registration committees upon a non-disclosure undertaking by the members.

9.1.4. Whenever required, reference authorities may be approached to provide additional explanation or justification with regards to the marketing authorization of the product.

9.1.5. The authority will issue a decision within a maximum of **60 calendar days** from the date of submission considering stop-clock principle. However, such applications will be prioritised considering its need in the market.

9.1.6. Grant of marketing authorization by the authority according to this procedure is notified by the manufacturer to the WHO as per ***Appendix 9***.

The appendix provides information about the registered product, deviations from the decision of the reference WLA, dates of submission and others.

9.2. Post approval variations

9.2.1. Variations that were submitted or notified to the reference authority should be submitted to the Authority by the applicant to assure consistency of the regulatory status of the approved products between the reference WLA and authority over the product life-cycle.

9.2.2. The cover letter or application letter submitted with each variation should indicate if a variation was submitted or notified to and approved by the reference authority, or if a variation is a national variation only. For the latter, the existing guideline for post approval variation of medical products shall apply.
For the former, as long as the variation is of relevance, the authority will recognize the decision made by the reference authority and as much as possible, make the product consistent with the product approved by the WLA.

9.2.3. Line extensions of already registered medicines (e.g. new formulations, additional strengths, new routes of administration, changes in active substance(s)), which were submitted to the reference authority as a new application, will not be considered as a variation.

9.2.4. All variations currently under assessment by the reference authority should be reflected and identified in ***QIS-WLA or Appendix 4***.

9.2.5. The applicant should notify the authority as regards to the reference authority's decision outcome(s) and conditions within **30 days**.

9.2.6. In cases of variations not concluded by the reference authority before the grant of national marketing authorization, the authority, on a case-by-case basis, will either:

- register the product based on the current conditions of market authorization by the WLA and await submission of variations or;
- defer the decision on grant of marketing authorization until the acceptance of variations by the WLA.

9.2.7. The authority on receipt of any PAV applications that has already been approved by the reference authority, will rely on the decision and conduct sameness verification or expedited assessment as long as the PAV is of relevance to the authority. This assessment and its outcome will be relayed to the WHO and applicant within **30 calendar days** from the date of receipt of application.

In disagreement to a PAV decision made by the reference authority, the applicant should be notified within 30 days on receipt of application otherwise, the PAV shall be considered as accepted by the applicant.

9.2.8. The PAV application dossier submitted to the authority should be the same as the variation dossier that has been assessed and approved by the reference authority. If an assessment report is issued, a copy should be provided on completion or satisfactory documented evidence that reflects the acceptance of variation by the reference authority. An updated reference, WLA validated QIS should be submitted as well if the variation changes the information provided in the initial QIS.

9.2.9. The applicant should inform the authority on any regulatory action taken towards the product (Eg. Safety restrictions/withhold, suspensions, cancellations).

9.3. Documents required

9.3.1. The dossier submitted should be in English or Dzongkha.

9.3.2. For any certificate or reports or authorizations in a language other than English or Dzongkha, the document must be translated with a valid notarization.

9.3.3. As relevant, a bridging report may be requested to the applicant to support the application by providing evidence of a positive benefit-risk profile as per indication and should provide with the justification of the:

- comparability of the studied population to the target population (e.g. ethnicity, gender representation, age groups) as regards demonstration of safety and efficacy;
- relevance of reference authority-approved conditions of use as regards epidemiology and disease pattern in the target countries as well as other implications for efficacy and safety, e.g. feasibility of monitoring and precautionary measures (e.g. resistance testing or therapeutic drug monitoring);
- interactions with food and with other medications relevant in the target countries that are not discussed in the reference SRA's assessment report;
- therapeutic role of a product and its recommended use according to relevant national and international treatment guidelines;
- other related quality issues, including but not limited to, storage conditions and conditions of administration and use.

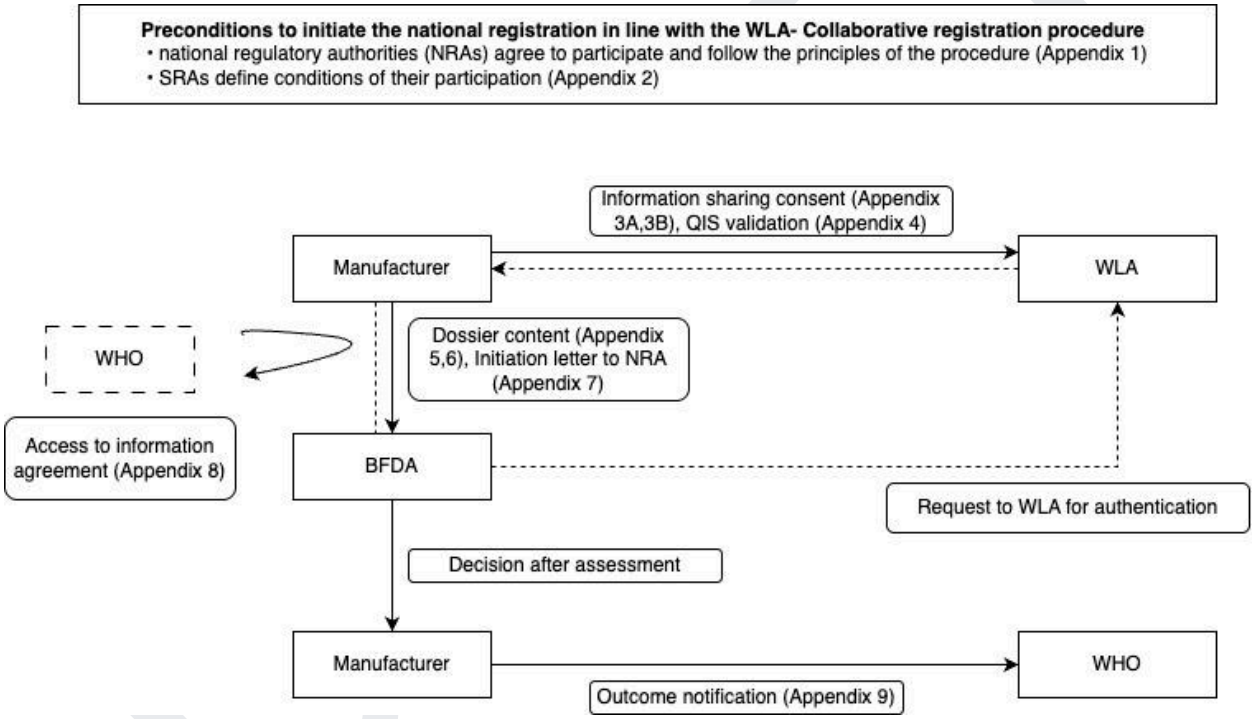
9.3.4. The dossier content should be as follows:

	Module	Documentation to be provided and further details
Module 1 -Administrative Information and Prescribing Information		
1	Application form and Price Structure	As per national requirement
2	Attachments to application form: a. Appendix 3A b. Appendix 3B	
3	Table of contents (TOC)	Comprehensive TOC including Module 1 information
4	Appendix 4 - Letter format	The letter should commit to the submission of additional administrative and stability study data as requested by the authority. *Any differences in the dossier submitted to the reference SRA should be explained, including differences in product information.
5	Quality information Summary (QIS-WLA)	As per format
6	SmPC or package insert	Should be in English or equivalent English translations must be provided.
7	Patient information leaflet or package leaflet	a. Should be in English or equivalent English translations must be provided. b. Provide Mock-ups or samples
8	Labelling - Specimen of package	c. Should be in English or equivalent English translations must be provided. d. Provide Mock-ups or samples
7	MA from reference authority a. MA certificate or evidence b. Assessment report	Full assessment report
9	GMP certification a. Copy of the GMP certificate of the active pharmaceutical ingredient (API) supplier b. Copy of the GMP certificate of the finished	For 9a - If not available, a statement signed by the qualified person from the finished product manufacturing site to be provided. *Manufacturing sites of the FP to be inspected by WHO or any WLA (2 years from the submission of MA application)

	product manufacturer(s) c. GMP inspection report of the manufacturing site(s) of FP from any reference SRA	*Public reports are also accepted.
10	Other documentations: a. *For generic dossiers* - full GCP inspection report of the bioequivalence study from any reference SRA, if applicable. b. *For innovative medicines* - Bridging report (where applicable) (Appendix 6). c. Information on local representatives or distributors.	*Public reports are also accepted.
Module 2 - CTD summaries		
11	All components *In the case of generic medicines for which a Clinical summary is not available, the Clinical overview (Module 2.5) should be included.	Should be complete as submitted to the reference authority.
Module 3 - Quality documentation		
12	All components *Stability study data as per ICH zone IVb must be submitted otherwise, a commitment letter (Module1) and the protocol may be submitted.	Should be complete as submitted to the reference authority.
Module 4 - Non-clinical documentation		
13	As requested	Data to be provided only if required by the Authority especially for innovative medicines.

Module 5 - Clinical documentation		
14	a. Generic medicine - Bioequivalence studies and reports. b. Innovative medicine - As requested	For 14a - Complete documentation on bioequivalence studies should be provided in the dossier in-line with WHO Guidelines on registration requirements to establish interchangeability and national registration guidelines. For 14b - Data to be provided only if required by the Authority especially for innovative medicines.

9.4. Flow chart



10. Relevant forms

10.1. PQ-CRP for pharmaceutical medicines & Vaccines

10.1.1. **TRS 966 Appendix 2** - It is to the consent of WHO prequalification holder for WHO to share information with the NRA confidentially under the procedure- chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://extranet.who.int/prequal/sites/default/files/document_files/Appendix2_TRS996_2016_Annex8.pdf

10.1.2. **Appendix 3, Part A** - It is the expression of interest to NRA in the assessment and accelerated national registration, acceptance by NRA and notification of procedure outcomes - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://extranet.who.int/prequal/sites/default/files/document_files/Appendix3_PartA_WHO_TRS_996_2016_Annex8.pdf

10.1.3. **Appendix 3, Part B** -Decision on the acceptance by the NRA to apply the procedure to a specified WHO-prequalified product and request for access to product-specific information and documentation - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://extranet.who.int/prequal/sites/default/files/document_files/Appx%203%20part%20B.pdf

10.1.4. **Appendix 3, Part C** - Notification of outcomes of national registration procedure by the NRA - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://extranet.who.int/prequal/sites/default/files/document_files/Appendix3_PartC_WHO_TRS_996_2016_Annex8.pdf

10.1.5. **Appendix 4** - Report on post-registration actions in respect of a product registered under the procedure - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://extranet.who.int/prequal/sites/default/files/document_files/Appendix4_WHO_TRS_996_2016_Annex8.pdf

10.2. **WLA-CRP for pharmaceutical medicines & Vaccines** - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1010-annex11.pdf?sfvrsn=b7c8b9c1_2&download=true

10.2.1. **Annex 11, Appendix 8** - Confidential disclosure agreement made between WHO and the manufacturer.

10.2.2. **Annex 11, Appendix 3B** -Manufacturer's request for stringent regulatory authority's (SRA's) permission for sharing SRA-owned nonpublic information with participating national regulatory authority(ies) and the World Health Organization.

10.2.3. **Annex 11, Appendix 3A** - Manufacturer's consent for information sharing with participating national regulatory authority(ies) and the World Health Organization.

10.2.4. **Annex 11, Appendix 7** - Expression of interest to national regulatory authority.

10.2.5. **Annex 11, Appendix 4** - Quality information summary of the finished pharmaceutical product or vaccine approved by the reference SRA (QIS-SRA (crp))

10.2.6. **Annex 11, Appendix 5** - Proposed documentation for collaborative procedure for reference SRA-approved pharmaceutical products and vaccines

10.2.7. **Annex 11, Appendix 6** - Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries

10.2.8. **Annex 11, Appendix 9** - Notification of an outcome of the national registration provided by the participating manufacturer to the World Health Organization

11. References

11.1. WHO TRS 966 - Annex 8: WHO collaborative procedure between the WHO prequalification team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines

11.2. WHO TRS 1010 - Annex 11: Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

"We commit to provide consistent regulatory operations with risk based planning and continual improvement in compliance with the recognized standards to meet our consumers' satisfaction and confidence".

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