Caribbean Public Health Agency / Caribbean Regulatory System (CARPHA/CRS)

Guidance Document:
Requirements for the Preparation of a Dossier for Medicines Recommendation for Marketing Authorization/Import Permit in CARICOM States

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Foreword

The following are the CARPHA/CRS requirements for the preparation of a dossier for the assessment of medicines for safety, quality and efficacy. This guidance document is intended to provide the sponsor with needed information on how to engage with the policies and procedures of the CARPHA/CRS.

Guidance documents do not have the force of law and are flexible in nature. Alternate approaches to the guidance may be acceptable but must be justified. Any alternative approach must be discussed with the CARPHA/CRS staff in advance.

The CARPHA/CRS reserves the right to request information other than defined in this document, if appropriate, in order to assess safety, efficacy, or quality of a medicine. The CARPHA/CRS is committed to making sure that such requests are justifiable.

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Section 1: Introduction, Background, Objectives, and Scope

The CARPHA/CRS is a regional regulatory system being implemented via the Caribbean Community and Common Market's (CARICOM's) regional public health agency, the Caribbean Public Health Agency. It is an outgrowth of a number of factors, including the Caribbean Pharmaceutical Policy; the intergovernmental agreement establishing CARPHA as a legal entity; and ministerial endorsements given by CARICOM's Council for Human and Social Development (COHSOD) in 2014, 2015, and 2016.

The objective of this document is to provide the sponsor with the necessary guidance to submit dossiers to the CARPHA/CRS. The scope applies to priority generic medicines that have been registered by one of the ten[1] Pan American Health Organization (PAHO) designated reference authorities.

The guidance was developed using standards from multiple recognized sources, including the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the World Health Organization (WHO) Prequalification Program, and the Pan American Network for Drug Regulatory Harmonization/Pan American Health Organization (PANDRH/PAHO).

[1] PAHO designated reference authorities include: Argentina, Brazil, Canada, Chile, Colombia, Cuba, European Union, Mexico, United States, and WHO Prequalification

Section 2: Eligibility Criteria

Major eligibility criteria for submission to the CARPHA/CRS include:

1. That the submission represents a priority generic (multisource) medicine for the region (http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf);

2. The product has been given marketing authorization by any of the following reference national medicines regulatory authorities: Argentina, Brazil, Canada, Chile, Colombia, Cuba, European Union, Mexico, United, Kingdom, United States, or;

3. The product has been favorably assessed by WHO and therefore included in the WHO prequalification list (WHO PQ).

Section 3: Technical Requirements

All documents submitted by the sponsor as part of the technical requirements should be submitted in English. If original documents are available in other language(s), the sponsor is required to provide a certified translation in English.

The following documentation should be submitted:

1. A cover letter, which should include:
   a. A statement indicating that the information submitted is true and correct;
   b. A statement confirming that the finished pharmaceutical product (FPP), including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information- will, at the time of submission and after recommendation, in all respects be the same as the product registered with the reference authority (RA);
   c. A statement indicating that the product is on the market in the RA country or region;

2. A. A copy of the marketing authorization, or the equivalent, issued by the RA to demonstrate that the product is registered or licensed in accordance with the RA requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
   B. List all the countries where the product has been granted marketing authorization. This should include country and number and date of latest marketing authorization, as well as date of marketing authorization expiration, if applicable.
   C. List any countries where the product has been refused marketing authorization or has been withdrawn from the market, as well as the reasons.

3. The latest RA approved product information (summary of product characteristics (SmPC) or an equivalent, if applicable), the patient information leaflet (PIL), and the labeling. Provide a web link to the RA approved product information if available.

4. A list of the RA approved manufacturer(s) of the FPP, including manufacturers of intermediates, primary packaging sites and release-testing sites, with the physical address of the manufacturing site(s). List for each site the last three inspections and include the corresponding inspection reports.

5. A list of the RA approved manufactures of the active pharmaceutical ingredient(s) (API(s)) used in the manufacture of the finished product, with the physical address of the manufacturing site. List for each site the last three inspections and include the corresponding inspection reports.

6. If available, a public assessment report, such as the Scientific Discussion of the European Public Assessment Report, issued by the RA.

7. A certificate of analysis on a current batch of the FPP.

8. Mock ups and pictures of the product in market packaging(s) including the primary and secondary packaging, labeling, insert(s) and both sides of tablet, if applicable, is required. A sample of the product in market packaging may be requested. All should be provided in color (not black and white).

9. A copy of the currently approved FPP specifications (release and shelf-life), dated and signed or certified by authorized personnel with the analytical test procedure. Please indicate the specification numbers of the specifications that were submitted to the RA. If these are superseded please also provide the most up to date versions of the specifications.

10. Proof of therapeutic equivalence submitted to the RA (i.e. bioequivalence/bioavailability studies, when applicable, or comparative in vitro dissolution tests, when applicable, according to conditions described in the latest edition of the WHO multisource pharmaceutical products guidelines on registration requirements to establish interchangeability).

11. A summary of the stability studies for long term and accelerated storage conditions performed according to internationally recommended standards. The summary should include result tables and conclusions for three different batches, include the batch size and API source. In the case where stability data is something other than zone IVB, this can be submitted initially, but the sponsor must initiate stability studies at zone IVB per the WHO prequalification policy on this subject and submit this data in 12 months. Zone IVB conditions are:
    Long term: 30±2°C - 75%± 5%RH
    Accelerated: 40°C±2°C - 75%±5% RH

12. Most recent periodic safety update report (PSUR)/ periodic benefit risk evaluation report (PBRER).

13. A completely filled in Quality Information Summary (QIS). The QIS-SRA template, available on the WHO Prequalification Programme website (http://apps.who.int/prequal/), should be fully completed and submitted with the application. It provides a condensed summary of key information on the FPP as approved by the RA at the time of application of the FPP.

14. The checklist of the technical documents included in the technical proposal, completed and signed by the appropriate representative.

Section 4: Quality Requirements

1. Production

1.1 Products submitted to the CARPHA/CRS shall conform to the following:

General and product specific guidelines related to production, quality, safety, efficacy and potency adopted by the RA or WHO Expert Committees.

- **Medicines**: WHO Expert Committee on Specifications for Pharmaceutical Preparations guidelines available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_992/en/

1.2 Notifiable change(s) in the product

The sponsor shall inform the CARPHA/CRS of any changes related to the product submitted for registration to CARPHA/CRS. The sponsors shall provide the approval letter of the corresponding RA or WHO regarding the change(s).

2. Marketing Authorization

2.1 Products submitted to the CARPHA/CRS shall be manufactured under a current marketing authorization issued by the RA. Any suspension or termination of the marketing authorization, for any reason, shall be reported immediately to the CARPHA/CRS.

2.2 The sponsor must be willing to provide the following documents if requested by the CARPHA/CRS:

- Quality control methodology approved by the RA (see Section 3 Technical Requirements)
- Other technical documents and data requested for clarification or to resolve any potential claims (e.g. Sources of the Active Pharmaceutical Ingredient(s) utilized in the finished product and the corresponding quality assurance

documents, manufacturing process description, clinical trial data showing the product efficacy, etc.).

3. Labeling

3.1 Product labels shall conform to RA or WHO prequalification requirements.

3.2 Labels shall be in the language of the country(ies) of destination, which will be specified in the dossier. Languages can be discussed with CARPHA/CRS staff.

3.3 Product labels must be consistent with the label evaluated by the responsible RA or the WHO Prequalification Programme, as applicable.

3.4 Under no circumstances shall labels include any of the following: "donation" or "free medicine."

3.5 Re-labeling or over-labeling is not acceptable, unless agreed to in writing by the CARPHA/CRS.

4. Adverse events

4.1 The sponsor shall notify the CARPHA/CRS of any adverse events related to the product as reported to the RA or in any other country where the product is being marketed.

5. Testing

5.1 Unless otherwise indicated by CARPHA/CRS, all submitted dossiers can be subject to random quality control testing by the CARPHA/CRS and/or an independent third party reference laboratory selected by the CARPHA/CRS to ensure conformity with specifications. The decision not to test shall not constitute a waiver of any of its rights, or release the sponsor of any of its obligations. Non-conforming products may be rejected at CARPHA/CRS's discretion. The CARPHA/CRS may request the sponsor to furnish additional samples and/or reference standards to the reference laboratory for testing. The decision of the reference laboratory shall be considered final.

6. Right to share information with CARPHA/CRS member states

6.1 CARPHA/CRS at its sole discretion may share with National Regulatory Authorities from CARICOM, documents from the technical proposal or other documents and data requested for clarification or to resolve any potential claims or inquiries.

Section 5: Instructions for Submission of Technical Documents

- The documents set forth in Section 3, Technical Requirements (1 to 14), can be submitted as individual files via email and each file can be sent as a PDF (selectable text) to crsregistration@CARPHA.org. Files can also be made available electronically, for example, through FTP platforms. If questions, please consult the CARPHA/CRS staff.
- All documents submitted must correspond to the documents included in the checklist below and must follow the corresponding nomenclature.
- When sending the email:
    - Include in the reference/subject, the *name of the sponsor and product;*
    - Include in the body of the message the files to be attached;
    - Files attached must follow the nomenclature as defined in Annex 1 Checklist plus include the manufacturer name and product name;
- An option for expedited submission is to submit the dossier in Common Technical Document (CTD), WHO PQ, or the format submitted to a CARICOM Member State. In this case, the CARPHA/CRS will still look for the requirements listed in this document. If they are not found, the sponsor will be asked to provide them.

Section 6: Annexes to be Submitted by Sponsors

Annex 1: Checklist

This annex is both a form that should be submitted to the CARPHA/CRS as a technical requirement and a guide for naming files. Regarding the latter point, nomenclature assigned for technical requirements should follow the indications in the table below. Please use the following format for the main file name: [sponsor name][product name (international non-proprietary name (INN))].

Technical Requirements	
File name [PDF and selectable text required]	Submitted ☑ or N/A
1. Cover letter	
2. Marketing authorization status	
3. Product information (SmPC, PIL, Labeling)	
4. Manufacturer(s) FPP	
5. Manufacturer(s) API	
6. Public Assessment Report(s)	
7. Certificate of analysis for FPP	
8. Mock ups and pictures of product	
9. Currently approved FPP specifications	
10. Proof of therapeutic equivalence	
11. Stabilities studies	
12. PSUR/PBRER	
13. Quality Information Summary (QIS)	
14. Annex 1: Checklist	

*Legend: Document has been submitted: **☑;** Document does not apply to this product: **N/A**

We hereby certify all technical requirements included in this list were reviewed, approved and authorized for submission by the sponsor representative.

Name and Signature of sponsor representative:_____

Date [dd/mm/yyyy]: _____