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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1	GD-ReqDS001	26/09/2016
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Foreword

The following are the requirements for the preparation of a dossier submission to the CARPHA/CRS. 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 should 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 understand the safety, efficacy, or quality of a medicine. The CARPHA/CRS is committed to making sure that such requests are justifiable.

Abbreviations/ Definitions

API	Active Pharmaceutical Ingredient
Application/ Dossier	The documentation provided by the sponsor to the CRS attesting to the product's safety, quality, and efficacy. The CRS uses these terms interchangeably
ATC	Anatomical Therapeutic Chemical
CARICOM	Caribbean Community
CARPHA	Caribbean Public Health Agency
COHSOD	Council for Human and Social Development (this is a CARICOM body comprised of all Ministers of Health in CARICOM states)
CRS	Caribbean Regulatory System
CTD	Common Technical Document (this is a product of the ICH (see below))
EML (WHO)	Essential Medicines List from the World Health Organization (published every 2 years)
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Import Permit	Some countries in the Caribbean do not have the legal requirements for marketing authorization (see below) but do require that a product have an "import permit" to legally enter the market
INN	International Nonproprietary Name

Marketing Authorization/ Registration/ Approval	The legal act of permitting a health product to be sold in a given market, based on a review of safety, efficacy, and quality. The CRS uses the terms "Marketing Authorization", "Registration", and "Approval" interchangeably
PAHO	Pan American Health Organization (the Americas arm of the World Health Organization)
PANDRH	Pan American Network for Drug Regulatory Harmonization
PIL	Patient Information Leaflet
PSUR/PBRER	Periodic Safety Update Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER).
RA	Reference Authority
R	Release
SL	Shelf life
SmPC	Summary Product Characteristics
Applicant/ Sponsor	The entity that is submitting the product to the regulatory authority for marketing authorization/import permit. The CRS uses the terms interchangeably
WHO	World Health Organization
WHOPQ	WHO Prequalification

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Section 1: Introduction, Background, Objectives, and Scope

The CARPHA/CRS is a regional regulatory mechanism through which market access to safe and effective essential medicines of high quality is accelerated. It is implemented by the Caribbean Community and Common Market's (CARICOM's) regional public health agency, the Caribbean Public Health Agency (CARPHA), in technical collaboration with the Pan American Health Organization/World Health Organization (PAHO/WHO). The CRS resulted from several factors, including the Caribbean Pharmaceutical Policy, the intergovernmental agreement establishing CARPHA as a legal entity, and ministerial endorsements from CARICOM's Council for Human and Social Development (COHSOD) in 2014, 2015, 2016, and 2017.

When the CARPHA/CRS reviews a sponsor's submission favorably, a recommendation and assessment report is disseminated to all CARICOM governments via government appointed focal points, and the recommended products are published on a publically accessible webpage. Governments are then asked to make a marketing authorization/import permit decision based on the CARPHA/CRS recommendation within 60 calendar days. The sponsor works with the CRS and the government of interest to satisfy three basic local requirements: 1) payment of a nominal local user fee, 2) completion of any additional local administrative forms for record-keeping (the CRS provides the regulatory information through the assessment report), and 3) identification of an importer.

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 essential medicines that have already been granted marketing authorization/registration by one of the eleven[1] Pan American Health Organization (PAHO) designated reference authorities (RAs).

The guidance was developed using standards from multiple recognized sources, including the International Council for

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

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the World Health Organization (WHO) Prequalification Program, and the Pan American Network for Drug Regulatory Harmonization/PAHO (PANDRH/PAHO).

Section 2: Eligibility Criteria

Eligibility criteria for submission to the CARPHA/CRS are:

1. That the submission represents an essential medicine, as listed on the most recent WHO Essential Medicines List (EML) (March 2017): http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1);

   Note: proposals for medicines not listed on the WHO EML can be considered, provided there is a justified public health need. Applicants should contact the CRS for more information in these cases: CRSregistration@carpha.org

2. That the product is registered and has been granted a marketing authorization by one of the following reference authorities (RAs): Argentina, Brazil, Canada, Chile, Colombia, Cuba, European Union, Mexico, United Kingdom, United States, or;

3. That 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 written in other language(s), the sponsor is required to provide a certified translation in English.

The following documentation should be submitted:

1. Provide a cover letter addressed to CARPHA/CRS, 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. Provide an overview of the Marketing Authorization status:
   A. Provide a copy of the most recent marketing authorization, or the equivalent, issued by the RA to demonstrate that the product is registered or licensed in accordance with the RA requirements.
   B. List all the countries where the product has been granted marketing authorization. This should include the country name, marketing authorization number and date of issuance and expiration of the marketing authorization. C. List all the countries where the product has been refused marketing authorization or has been withdrawn from the market and provide the reasons for refusal/withdrawal. If not applicable, please include a clear statement that no refusal and/or withdrawal was received for the product.

3. Provide the latest version of the product information (summary of product characteristics (SmPC) or an equivalent, if applicable) and the patient information leaflet (PIL) approved by the RA. If

available, provide the link to the website of the RA where the approved SmPC and/or PIL is published.

4. Provide the following information related to the manufacturing site(s) of the active pharmaceutical ingredient(s) (API(s)):
   A. List of all sites involved in the manufacturing process of the API(s), including name, address and responsibilities of each site.
   B. For each site listed under section 4A, the most recent Good Manufacturing Practices (GMP) certificate issued by the RA must be submitted. If available, include inspection reports.

5. Provide the following information related to the manufacturing site(s) of the finish pharmaceutical product (FPP):
   A. List of all sites involved in the manufacturing process of FPP, including name, address and responsibilities of each site.
   B. For each site listed under section 5A, the most recent GMP certificate issued by the RA must be submitted. If available, include inspection reports.

6. Provide a certificate of analysis on a current batch of the FPP.

7. Provide the current FPP specifications (release and shelf-life) approved by the RA, dated and signed or certified by authorized personnel with the analytical test procedure.

8. Provide a summary of long term and accelerated stability studies performed at zone IVB conditions and according to internationally recommended standards. The summary should include result tables and conclusions for three different batches, the batch size and API source. In the case where stability data is different than zone IVB, the data may be submitted with the understanding that the sponsor must initiate stability studies at zone IVB per the WHO prequalification policy and submit this data twelve (12) months from the date of the initial submission.
   Zone IVB conditions are:
   Long term: 30±2°C - 75%± 5%RH
   Accelerated: 40ºC±2°C - 75%±5% RH

9. Provide pictures of the product as it will be sold in the CARICOM market, including both sides of the tablet or pictures

of other dosage forms, primary and secondary packaging, labeling and insert(s). The packaging and labeling should be in good condition and photos should be provided in color (not black and white). A sample of the product in market ready packaging may be requested, but is not required at submission.

10. Provide proof of therapeutic equivalence submitted to the RA (i.e. bioequivalence/bioavailability studies, when applicable, or comparative in vitro dissolution tests, when applicable).

    Note: for innovative products, provide summaries of relevant clinical data in lieu of therapeutic equivalence data. This requirement can also be fulfilled through ICH Common Technical Document (CTD) module 2 summaries.

11. Provide the most recent periodic safety update report (PSUR)/ periodic benefit risk evaluation report (PBRER).

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

13. The checklist of the technical documents included in the dossier (Annex 1, page 13), should be completed and signed by the appropriate company representative.

Section 4: Additional CARPHA/CRS Rules

1. Production

1.1 Products submitted to the CARPHA/CRS shall conform to the general and product specific guidelines related to production, quality, safety, efficacy and potency adopted by the RA or WHO Expert Committees, if not otherwise specified in the requirements listed above.

- For reference, the 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 changes related to the product submitted for registration to CARPHA/CRS as they are required by the RA. The sponsors shall provide the approval letter of the corresponding RA or WHO regarding the change(s), when they become available.

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.

3. Labeling

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

3.2 Labels shall be in English.

3.3 Product labels must be the same as 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.

4. Adverse events and Substandard and Falsified Medicines

4.1 The sponsor shall notify the CARPHA/CRS of any adverse events and/or substandard and falsified medicines 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 may 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 The 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.

7. Language

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

Section 5: Instructions for Submission of Technical Documents

- The documents set forth in Section 3, Technical Requirements (1 to 13), should be submitted to CRSregistration@carpha.org electronically, and for example, can be made available, through electronic platforms that CRS staff can download. Paper submissions are strongly discouraged. For questions, please consult the CARPHA/CRS staff.
- Documents should correspond to those included in the checklist below and should follow the corresponding nomenclature.
- CARPHA/CRS will consider other formats for dossier submission in order to avoid duplication of efforts by the sponsor. For example, the CARPHA/CRS may consider dossiers prepared according to the format of the ICH CTD or per WHO PQ requirements. Irrespective of the format used for submission of the dossier, all CRS requirements should be satisfied. The sponsor should discuss any plans to submit different formatting with the CARPHA/CRS staff in advance of the submission.

Section 6: Annex 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 and PIL)	
4. Manufacturer(s) API	
5. Manufacturer(s) FPP	
6. Certificate of analysis for FPP	
7. Currently approved FPP specifications	
8. Stabilities studies	
9. Pictures of product	
10. Proof of therapeutic equivalence/clinical summaries	
11. PSUR/PBRER	
12. Public Assessment Report(s)	
13. 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]: _____