Caribbean Regulatory System

Guidance Document:
Requirements for the Preparation of a Dossier for Medicine Registration

Effective: 7/25/2016

Foreword

The following are the Caribbean Regulatory System (CRS) requirements for the preparation of a dossier for medicine registration. Guidance documents are intended to provide industry with needed information on how to engage with the policies and procedures of the 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 CRS staff in advance.

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

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Section 1

Introduction, background, objectives, and scope

The 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 (CARPHA). 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 and 2015.

The objective of this document is to provide industry with the necessary guidance to submit dossiers to the CRS. The scope applies to priority generic medicines.

The guidance was developed using standards from multiple recognized sources around the world, 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).

Section 2

Eligibility Criteria

Major eligibility criteria for submission to the CRS include:

1. That the submission represents a priority generic (multisource) medicine for the region (derived via periodic surveys of CARICOM Member States) and that;

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 States, or;

3. The product has been prequalified by the WHO prequalification program (WHO PQP).

Section 3

Technical Requirements

All documents submitted by the sponsor as part of the technical requirements must 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 below 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 product, including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information- will at the time of submission and after, in all respects be the same as the product registered with the reference authority (RA);
    c. A statement indicating that the product is actually on the market in the RA country or region;

2. A copy of the marketing authorization, or the equivalent, issued by the RA to demonstrate that the product is registered in accordance with the RA requirements.

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 finished product, including manufacturers of intermediates, primary packaging sites and release-testing sites, with the physical address of the manufacturing site(s). Attach the

corresponding Good Manufacturing Practices (GMP) certificate.

5. A list of the RA approved manufactures of the active pharmaceutical ingredient (API) used in the manufacture of the finished product, with the physical address of the manufacturing site. Attach the corresponding GMP certificate.

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

7. A current batch certificate of analysis is required. A sample of the product in market packaging may be requested.

8. A copy of the currently approved finished product specifications (release and shelf-life), dated and signed or certified by authorized personnel with the analytical test procedure.

9. 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).

10. A summary of the stability studies for natural and accelerated storage conditions performed according to international recommended standards for the offered product category. The summary should include result tables and conclusions for three different batches offered.

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

12. List of 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.

13. Quality information summaries to include:

    a. API specifications, description of the API container closure system, proposed storage conditions and re-test period of API;
    b. Description and composition of the finished product, including any accompanying diluent, description of the manufacturing process, summary of controls performed at the critical steps, summary of process validation, specifications of the finished product, and description of the container closer system;

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
    a. Products submitted to the CRS shall conform to the following:
        i. General and product specific guidelines related to production, quality, safety, efficacy and potency adopted by the RA or WHO Expert Committees.
            1. **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/

    b. Changes in production, formulation, packaging or labeling of products
        i. The sponsor shall inform the CRS of any changes in the production, formulation, packaging or labeling of products submitted for registration to CRS. The sponsors shall provide the authorization of the corresponding RA or WHO regarding the formulation or other production changes.

2. Marketing Authorization
    a. Products submitted to the 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 CRS.

b. The sponsor must be willing to provide the following documents if requested by the CRS:
    i. Quality control methodology (pharmacopoeial method or other compendial monograph/validated method (see Section 3 Technical Requirements)
    ii. 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
    a. Product labels shall conform to RA requirements or WHO guidance documents (as Specified in Section 4, 1. Production) and any additional requirements indicated in Chapter 4, Section 1 (Packaging and Labeling).
    b. Labels shall be in the language of the country(ies) of destination, which will be specified in the dossier. Languages can be discussed with CRS staff.
    c. Product labels must be consistent with the label evaluated by the responsible RA or the WHO Prequalification Programme, as applicable.
    d. Under no circumstances shall labels include any of the following: “donation” or “free medicine.”
    e. Re-labeling or over-labeling is not acceptable, unless agreed to in writing by the CRS.

4. Adverse events

a. The sponsor shall notify the 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

    a. Unless otherwise indicated by CRS, all submitted dossiers can be subject to random quality control testing by the CRS and/or an independent third party reference laboratory selected by the 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 goods may be rejected at CRS's discretion. The 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 CRS member states

    a. CRS at its sole discretion may share with the corresponding 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 13), must be submitted as individual files via email and each file must be sent as a PDF to CRSregistration@CARPHA.org.
- All documents submitted must correspond to the documents included in the checklist 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;

Section 6

Annexes to Be Submitted By Sponsors

Annex 1

This annex is both a form that should be submitted to the CRS as a technical requirement (requirement #14) and a guide for naming files. Regarding the latter point, nomenclature assigned for technical requirements must follow the indications in the table below. Please include the sponsor name and product name in the file name. For the product name, please use the international non-proprietary name (INN).

Technical Requirement	File Name (PDF required)	Submitted
Number	Technical requirement name X sponsor name product name	☑ or N/A
1	1. Cover letter	
2	2. Marketing authorization of RA	
3	3. RA approved product information (SmPC, PIL, labeling)	
4	4. RA approved manufacturers/GMP finished product	
5	5. RA approved manufacturers/GMP API	
6	6. Public assessment report by RA	
7	7. Batch certificate of analysis	
8	8. Currently approved finished product specifications	
9	9. Proof of therapeutic equivalence submitted to RA	
10	10.Stability studies	
11	11. PSUR/PBRER	
12	12. Countries of marketing authorization	
13	13. Quality information summaries	
14	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: (*INSERT DAY/MONTH/YEAR*)