مملكة البحرين
Kingdom of Bahrain

الهيئة الوطنية لتنظيم المهن والخدمات الصحية
NATIONAL HEALTH REGULATORY AUTHORITY

Medicines Renewals Guideline

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TABLE OF CONTENTS

1. INTRODUCTION

Guideline documents are meant to provide assistance to industry and professionals on how to comply with governing statutes and regulations. Guideline documents also provide assistance to staff on how NHRA mandates and objectives should be implemented in a manner that is fair, consistent and effective.

The purpose of this guideline is to provide clear instruction on the NHRA procedure for renewal of a marketing authorization (MA) once every 5 years from the date of first licensing of a medicine in the Kingdom of Bahrain.

The renewal process is designed to provide for a periodic review by the NHRA of all available data to support an existing MA and therefore to ensure that the benefits of medicines holding MAs issued by the NHRA continue to outweigh any known risks.

Renewal applications should be submitted within 3 months of the expiry date of the MA to ensure that the assessment can be carried out before the date of expiry. In addition, renewal applications should contain all the data/documentation as outlined in this guideline in order to facilitate efficient and timely assessment.

As per Bahrain pharmacy Law 18 of 1997, all product should have a valid medicine license for importation and distribution in the Kingdom of Bahrain. Thus product with expired license shall be allowed for importation or distribution by NHRA.

All products due for renewal are subject to laboratory analysis, thus a laboratory file should be submitted upon request.

It should be noted that the NHRA has the right to request any information and data within the context of this guidance in order to assess adequately the safety, efficacy and quality of any medicines at the time of renewal. The NHRA is committed to ensuring that such requests are justifiable and decisions are clearly documented.

NHRA has the right to review the price of the medicine upon renewal.

Approval of a renewal by NHRA should be consistent with the NHRA requirement, that the interest of consumers and users of approved medicines are protected, notably in the following areas:

- A pharmaceutical product should be of appropriate quality such that its contents and its pharmaceutical performance should con form to acceptable standards.

- The risk of using the product should be acceptable and reasonable, taking into account that the use of any medicine carries a risk, which should be considered in the light of the likely benefit.

- There should be a demonstrable benefit for pharmaceutical products. If a medicinal claim is made, the consumer is entitled to expect a benefit.

This document should be read in conjunction with other applicable guideline documents.

2. DEFINITIONS

Certificate of pharmaceutical product (CPP)

A certificate issued in the format recommended by the World Health Organization (WHO), which establishes the status of the pharmaceutical product and of the applicant for this certificate in the exporting country.

Competent Authority (CA)

Regulatory authority recognized by the NHRA in the Kingdom of Bahrain for the purposes of recognition of their regulatory activities as follows:

- Gulf Cooperation Council – Central Drug Registration (GCC-DR)
- Saudi Food and Drug Authority (SFDA)
- European Medicines Agency (EMA)
- National regulatory agencies of the European Union Member States
- United States Food and Drug Administration (FDA)
- Health Canada
- Australian Therapeutic Goods Administration (TGA)
- New Zealand Medsafe
- Swissmedic
- Japanese Ministry of Health

Country of origin

It is the country where the pharmaceutical product has been released with certificate of analysis signed by the responsible qualified person.

Local agent

The licensed pharmacy in Bahrain; designated by the MAH to act on its behalf in communication with NHRA.

Label (immediate)

The immediate label (or primary packaging) is the label in direct contact with the product and, where there is a secondary label (see below), should contain at a minimum the following information:

Blister

- Product name
- Active substance(s) – International non-proprietary name (INN) or common name
- MAH name
- Batch number
- Expiry date (month/year)

Small containers

- Product name
- Active substance(s) – INN or common name
- Strength
- Pharmaceutical form
- Contents by weight, volume or number of dosage units
- Method and, if necessary, route of administration
- MAH name
- Batch number
- Expiry date (month/year)

Label (outer)

The outer label (or secondary packaging) is the label on the carton or box containing the finished product and should contain the following information:

- Product name
- Active substance (s) – INN or common name
- Pharmaceutical form
- Strength
- Contents by weight, volume or number of dosage units
- List of excipients
- Method and, if necessary, route of administration.
- Dose
- Special warning that the medicinal product should be stored out of the reach and sight of children
- Other special warnings, if this is necessary for the individual product
- Expiry date (month/year)
- Storage precautions
- Specific precautions relating to the disposal of unused products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place
- MAH name & address
- Batch number
- In the case of non-prescription medicinal products, instructions for use

Please note that in the absence of a secondary label, all the above information should appear on the immediate label.

Manufacturer
Manufacturing site of batch release, the final manufacturing site from which the medicine is dispatched to Bahrain.

Marketing authorization (MA)
The license issued by the NHRA to place a medicine on the market in Bahrain.

Marketing authorization holder (MAH)
The pharmaceutical company that legally holds the right and responsibility of marketing the medicine in Bahrain

Package leaflet (PIL)
The package leaflet is the product information provided with every licensed product. It should be drawn up in accordance with the summary of the product characteristics and it should include, in the following order:

- Product name
- Active substance(s) – INN or common name
- Strength
- Pharmaceutical form
- Contents in weight, volume or number of dosage units
- Intended population (babies, children, adolescents, adults, elderly)
- Pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient
- Therapeutic indications
- Contra-indications
- Precautions for use
- Interactions with other medicines and other forms of interaction (e.g. alcohol, tobacco, foodstuffs)
- Special warnings
- Dosage
- Method and, if necessary, route of administration
- Frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered

- As appropriate, depending on the nature of the product the following additional details should be provided:
    - Duration of treatment, where it should be limited
    - Action to be taken in case of an overdose (such as symptoms, emergency procedures)
    - What to do when one or more doses have not been taken
    - Risk of withdrawal effects
- Specific recommendation to consult a healthcare professional for any clarification on the use of the product
- A description of the adverse reactions which may occur under normal use and, if necessary, the action to be taken in such a case. The patient should be expressly asked to communicate any adverse reaction which is not mentioned in the package leaflet to his healthcare professional
- Reference to the expiry date indicated on the label, with a warning against using the product after that date
- Storage precautions, including a warning concerning certain visible signs of deterioration, if relevant
- Full qualitative composition (active substances and excipients)
- MAH name & address
- Name and address of the MAH appointed representative in Bahrain
- Name and address of the manufacturer responsible for batch release

In the absence of a package leaflet, the above information should appear on the product label (immediate and/or outer).

Summary of product characteristics (SmPC)

The definitive description of the product both in terms of its properties, chemical, pharmacological and pharmaceutical etc. and the clinical use. The SmPC is an integral part of the MA.

Laboratory File

As per the Bahrain pharmacy law # 18 of the year 1997, it is mandatory to analyze the product samples for re- registration/renewal applications prior to re- issuance of license.

3. LICENSE RENEWAL PROCEDURE

3.1 Before submission

Applicants should prepare a renewal application including all documents listed in medicine renewal checklist; the medicine renewal form must be filled and signed stamped by the MAH Company for all renewals applications.

Please note that for each application the most up to date version of these forms should be downloaded directly from NHRA website.

Compounding variations applications with renewal applications is not accepted. The applicant must get the approval for any variation before submitting renewal application.

The manufacturing site registration must be valid before submitting renewal application.

3.1.1 Application fees

As per resolution 17 of 2016, application fees and service fees is chargeable for each medicine renewal application submitted to NHRA. The applicant must refer to the latest fee structure from NHRA website.

3.1.2 Data requirements

All required data should be in accordance with ICH Common Technical Document (CTD) in eCTD format. Module 1 is region specific. Specific details to eCTD submission are mentioned in Annex I.
Additional documents to be part of Module 1 requirements:

1. Cover letter: Original company paper signed and dated.
2. Forms: Completed forms must be included in this section. The latest version of the below forms must be filled, signed and stamped with date by the MAH Company.

i. Medicine renewal application form.
ii. Check list.

3. Product Information

i. Summary of product characteristics (SmPC): the template for this document is part of the application form however in Module 1 a declaration from the MAH that the SmPC submitted is correct and similar to the one approved in COO is included in this section (if there is any differences the company shall declare it).
ii. Label text (immediate and secondary packaging).
iii. Package leaflet (bilingual English/Arabic).
iv. Artwork (outer pack, inner pack and package leaflet).

4. Contact details for the Marketing Authorization Holder responsible person for communication with the NHRA on quality issues.

5. Certificates

i. Certificate of Pharmaceutical Product (CPP) according to WHO format; legalized and issued from the COO (batch releaser country).
ii. Copy of valid Good manufacturing practice (GMP) certificates or proof of inspection by a recognized health authority for all finished product manufacturer(s) including bulk manufacturer, primary packager, and secondary packager.
iii. Certificate of suitability for the active substance, if available. If not, copy of valid good manufacturing practice (GMP) certificates or proof of inspection by a recognized health authority for API manufacturer(s).
iv. Certificate of suitability for TSE.
v. Certificate of analysis for the drug substance from the API supplier.
vi. Certificate of analysis for the finished product.
vii. Price certificate
viii. Manufacturer registration certificate in Bahrain (batch releaser).

6. Other Documents

i. Worldwide registration status (registered, marketed (date), under registration and rejected).
ii. Proof of Payment.
iii. Statement that the quality dossier is 'up-to-date' with all relevant legislation and guidance.
iv. Signed and dated by an appropriate expert showing full name and qualification.
v. Confirmation that any quality changes (i.e. Module3) made were approved by variation.
vi. Include currently authorized test specifications for the active substance & the finished product.
vii. Include the qualitative & quantitative composition in terms of the active substance(s) & excipient(s).
viii. Composition, specification (including test methods) should be approved.
ix. Any necessary revision of specification must be made/have been made variation.

Above listed documents are to be part of module1 and should only be submitted as soft copy. Documents to be submitted as original hard copy are listed in Medicine Renewal checklist Annex II.

3.2 Laboratory Analysis

As per the Bahrain pharmacy law # 18 of the year 1997, It is mandatory to analyze the product samples for re- registration/renewal applications prior to re -issuance of license. Thus a request to submission of the laboratory analysis documents with sample will be sent upon assessment.

Documents to be submitted are as follows:

1. Samples of the product
2. Certificate of analysis for the sample submitted
3. Reference standard for the active ingredients and related substances along with their certificate of analysis
4. Product composition certificate
5. Complete method of analysis
6. Product Specification
7. Material safety data
8. Documents in CD

Minimum quantity of sample required for analysis:

Sl.N	Dosage form	Quantity
1	Capsules & Tablets	100 nos
2	Oral liquids	10 bottles
3	Parenteral (ampoule)	50 nos
4	Parenteral (vials)	20 nos
5	Suppositories	50 nos
6	Creams and ointments	10 nos
7	Inhalers	10 nos
8	Powders	20 nos
9	Ophthalmic preparations	20 nos
10	Nasal drops	10 nos
11	Ear drops	10 nos

3.3 Submission & Validation

In order to submit a renewal application, the applicant must request an appointment with PPR department on a designated day and time. Appointment are assigned on a first–come first basis. Valid application (i.e. complete applications that meet the NHRA requirement for renewal) are accepted; a stamped signed copy of the renewal checklist is returned to the applicant. Invalid applications are rejected and resubmission is required.

3.4 Assessment & queries

Each application is assessed in accordance with NHRA standard operating procedures and relevant technical guidelines and, where queries arise, a request for further information will be sent to the MAH.

3.5 Approval

A renewal certificate will be issued upon successful assessment.

4. POST APPROVAL CHANGES

Any change to the approved medicine information must be approved by NHRA. Please refer to NHRA variation guideline for more information.

ANNEX I

Electronic Common Technical Document (eCTD)

I. Introduction

According to NHRA's eCTD implementation plan, the renewal submission in eCTD format is mandatory from the 2ndof May 2017. This applies only to human medicine applications.

The ICH M4 Expert Working Group (EWG) has defined the Common Technical Document (CTD). The ICH M2 EWG has defined, in the current document, the specification for the Electronic Common Technical Document (eCTD). The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission.

The CTD as defined by the M4 EWG does not cover the full submission that is to be made in a region. It describes only modules 2 to 5, which are common across all regions. The regional Administrative Information and Prescribing Information is described in Module 1. The CTD does not describe the content of module 1 because it is regional specific, nor does it describe documents that can be submitted as amendments or variations to the initial application. Module 1 Specifications of the electronic Common Technical Document (eCTD) for Gulf Cooperation Council (GCC) are described in "GCC module 1 specifications."

This document should be read together with ICH eCTD specifications and with GCC module 1 specifications to prepare a valid eCTD submission to NHRA. The latest version of the ICH eCTD Specification can be found at: http://estri.ich.org and of GCC module 1 specification can be found at: http://www.sfda.gov.sa

NHRA will show all the cases and scenarios of eCTD submissions especially the baseline eCTD submissions.

II. Technical Baseline Application

A baseline submission is a compiled submission of the current status of the dossier, i.e. resubmission of currently valid documents that have already been provided to NHRA but in another format. Where an eCTD application is being used for the first time as variation or renewal application, applicants are obliged to submit a technical baseline for the product as this will greatly facilitate the review process.

It should be clearly stated in the cover letter of the "baseline eCTD sequence" that the content of the previously submitted dossier has not been changed, only the format. There is no need for the NHRA to assess baseline submissions and hyperlinks between documents are not necessary. The submission unit 'reformat' should be used in the envelope for the baseline sequence and submission type should be "none".

III. Baseline eCTD Submission

One of the principles of eCTD is that with the use of the operation attributes, it is possible to manage the lifecycle of a product and generate a view of the "current dossier".

To convert from CTD format to eCTD, a baseline needs to be submitted. A baseline submission is the resubmission of currently valid documents to start the eCTD life cycle.

An eCTD baseline should not contain any new information as it will not be subject to review by NHRA.

Submission of a baseline shall be after the end of a regulatory activity, i.e. the company will follow the same original submission for products under assessment until the end of the regulatory activity.

IV. Baseline Starting as Sequence 0000

For product files that are submitted as CTD, the baseline submission should be submitted as sequence (0000). However, in some cases e.g. renewal and variation submitted as eCTD, the submission could continue to the next sequence of the submission life cycle. The baseline should always be a separate submission and should never include new applications.

V. Baseline Cases

For products submitted as CTD:

If the product was submitted as CTD and has no regulatory activity or complete regulatory activity, a baseline shall be submitted as sequence 0000. The first regulatory activity after baseline (for example a variation request) shall be submitted as sequence 0001. For the next submissions, the sequence number will advance, 0002, 0003, etc. See table below:

Sequence No.	Submission Description	Submission Type	Submission Unit	Related Sequence
0005	Response to Question	CTD	-	-
0000	Baseline submission	None	Reformat	-
0001	Variation Var-Type2	Var-Type2	-	-
0002	Response to Questions	Var-Type2	Response	0001

Table 1: Example for starting an eCTD with a baseline sequence.

VI. Components of an eCTD Baseline Submission:

It is composed of the currently valid documents in an eCTD format. Refer to Appendix I for more details.
The cover letter should include declaration that indicates there is no new information, only the format dossier has changed.

Notes:
1. NHRA encourage applicants to move to a full eCTD (m1 to m5) at least full M1 and M3 should be submitted.
2. The applicant can submit the eCTD dossier for currently registered product in which it requires the submission of a baseline. However, once eCTD is submitted going back to other format will not be accepted.

Appendix I: Components of an eCTD Baseline Submission

Section	Requirements
Module 1	***Regional Administrative Information***
1.0	Cover letter
1.2	Application Form
1.3	Product Information
1.3.1	Summary of Product Characteristics (SPC)
1.3.2	Labeling
1.3.3	Patient information leaflet (PIL)
1.3.3.1	Arabic leaflet
1.3.3.2	English leaflet
1.3.4	Artwork
1.4	Certificates and Documents
1.4.1	CPP
Module 3	***Quality***
3.2.S	Drug Substance
3.2.P	Drug Product
3.2.A	Appendices

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