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مملكة البحرين
Kingdom of Bahrain

الهيئة الوطنية لتنظيم المهن والخدمات الصحية NATIONAL HEALTH REGULATORY AUTHORITY



Medicine Licensing Guideline



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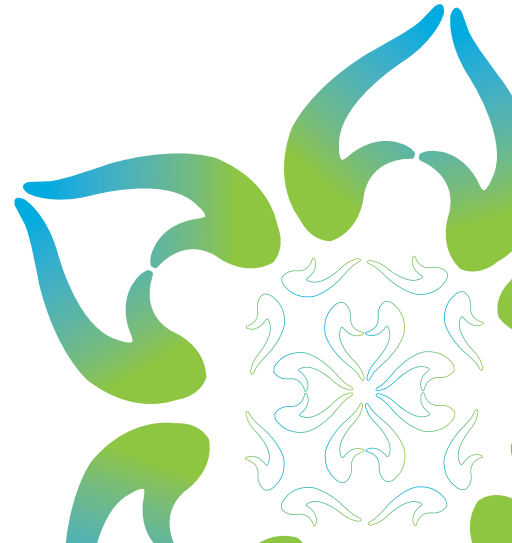
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DEFINITIONS

NHRA

National Health Regulatory Authority.

PPR

Pharmaceutical Product regulation is the responsible department for medicine licensing at NHRA.

Manufacturer

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

Marketing Authorization Holder (MAH)

The pharmaceutical company that legally holds the right and responsibility of marketing the medicine in Bahrain.

Local Agent

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

Country of Origin (COO)

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

ICH

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

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 the applicant for the certificate in the exporting country.

Package Leaflet (PL)

The package leaflet is the medicine information provided in the pack .It should be drawn up in accordance with the summary of the product characteristics.

Summary of Product Characteristics (SmPC)

The definitive description of the product. The SmPC is an integral part of the marketing authorization and should take the form as outlined in Annexes.

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. Medicine licensing is done through PPR department in NHRA.

This guideline has been developed to assist license holders in the preparation and submission of applications for licensing medicines in the Kingdom of Bahrain.

It should be noted that the NHRA has the right to request any information and data within the context of this guideline.

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

2. SCOPE

This guidance document describes the procedures and requirements for submitting an application to obtain a new medicine License in the Kingdom of Bahrain. Applicants are expected to comply with the procedures and requirements laid out in this guidance.

3. MEDICINE LICENSING

Any medicine must be licensed before marketing in Bahrain as per law no. (18) of 1997, medicine Importation and distribution must be done through authorized pharmacy only (Local agent), this agent can be the applicant on behalf of the pharmaceutical company as long as the agreement is prone to NHRA and acknowledged. The local agent must inform NHRA with any agreements made with new pharmaceutical companies for review and approval before starting the licensing process.

Pharmaceutical companies (MAH) should note that they are responsible for the medicines quality, efficacy and safety throughout its life cycle. Responsibilities start with the licensing of the medicine and end when the medicine license is cancelled. Since the medicine quality, efficacy and safety can change at any time during the course of its life cycle, it is the MAH responsibility to inform NHRA when these changes occur as per the current guidelines.

These responsibilities include:

1. To ensure that all of the information given in the application form and supporting documents are true and valid.
2. To notify NHRA if the application submitted to NHRA has been rejected, withdrawn or deferred by any drug regulatory agency, with reasons
3. in each case if applicable, throughout the medicine life cycle in the Bahraini market.
4. To notify NHRA of any change in the information submitted in the application and of any new significant safety information during the course of evaluation and throughout the product's life cycle in the Bahraini market
5. To respond to NHRA queries or requests for more data for review, within the timelines.
6. To ensure that the medicine will be sold, supplied and recommended for use in accordance with the approved PI/PIL and in compliance with all license conditions, applicable legislation and guidelines.

Failure to comply with the above shall render the product registration license cancelled. NHRA, thus reserves the right to, suspended or cancel the registration license of the product anytime during the life cycle of the product, if found non-compliant.

4. LICENSING PROCEDURE

4.1. Before Submission

Before submission of medicine licensing application the manufacturer license must be valid. The applicant must prepare the file according to requirements laid out in this guideline and assure all the requested documents are available.

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

4.2. Application fees

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

4.3. Data requirement

The data requirement for each application will differ, depending on the drug submission type. However all required data should be in accordance with ICH Common Technical Document (CTD) in eCTD format.

The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions and must be submitted in soft copy according to ICH guideline. Specific details to eCTD submission are mentioned in Annex I. In case of New Chemical Entity (NEC) & Biological all CTD modules are required.

In case of generic products the comparative bioavailability/bioequivalence study report should be present under module 5. This should be in accordance with GCC bioequivalence guideline. It is mandatory that the center conducting bioavailability/bioequivalence study should be approved with GCC-DR. However centers approved from either of the listed authorities shall be considered viz. European Medicine agency (EMA), United stated Food and Drug Administration(USFDA), World Health Organization (WHO) & Ministry of Health, Labour & Welfare Japan (MHLW).

The applicant must refer to GCC approved bioavailability/bioequivalence center list on NHRA website.

MODULE 1 REQUIREMENTS:

1. Cover letter: Original company paper signed and dated.
2. Comprehensive CTD table of contents.
3. 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. Application Form.
 - ii. Check list.
 - iii. Pricing form.
4. 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).
 - v. One finished product sample.
5. Contact details for the Marketing Authorization Holder responsible person for communication with the NHRA on quality issues.
6. Patency Information:

New medicine (Innovator): Declaration about the patency status worldwide, in the Gulf region & Bahrain is required.

Generics: Proof that the innovator patency is expired form Bahrain patency office and GCC patency office is required.

7. Certificates

- i. Certificate of Pharmaceutical Product (CPP) according to WHO format; legalized and issued from the COO (batch releaser country).
- ii. 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, legalized 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 showing, ex-factory price, whole sale and public retail price in the country of origin (legalized by the Ministry of Foreign Affairs & Embassy and issued within the last six months from the submission date). The price certificate must be issued from the Health Authority in the COO of the finished product (i.e. from which it is batch released). If the Health Authority doesn't issue price certificate the company can use NHRA price form (annex V) and it must be filled for all the countries where the product is registered and attested/endorsed by the Health Authority.
- viii. Manufacturer registration certificate in Bahrain (batch releaser).

8. Other Documents

- i. Alcohol content declaration.
- ii. Pork content declaration.
- iii. Worldwide registration status (registered, marketed (date), under registration and rejected).
- iv. Proof of Payment for submission.
- v. Proof of prior registration under SFDA, GCC-DR, FDA(US), TGA(Australia), Health Canada, Japan, Medsafe , Swissmedic or EMA (EU)*.

*Includes medicines licensed by the European Medicines Agency (EMA) under the Centralized Procedure and medicines licensed by one of the following countries Denmark, France, Germany, Italy, Ireland, Netherland, Portugal, Spain, Sweden or UK.

9. Laboratory Analysis:

It is mandatory to analyze the product samples for new registration applications prior to 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:

- i. Samples of the product.
- ii. Certificate of analysis for the sample submitted.
- iii. Reference standard for the active ingredients and related substances along with their certificate of analysis.
- iv. Product composition certificate.
- v. Complete method of analysis.
- v. Product Specification.
- vii. Material safety data.
- viii. 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	Parental solution up to 500ml	5 nos
6	Parental solution above 500ml	1 no
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

4.4. GCC-DR Registered Products

Since the Kingdom of Bahrain is an active member state in the Co-operation Council for the Arab States of the Gulf (GCC), NHRA recognizes and pledges to fast track the assessment of new drug registration applications already approved in GCC-DR.

Documents required for submission:

1. Covering letter from the MAH and agent
2. Medicine license application form
3. Medicine license checklist
4. Valid registration certificated by GCC-DR for the product
5. Patent status in Bahrain
6. Legalized price certificate form
7. Modules 2-5 shall be requested on a CD containing all queries and responses.
8. A signed and stamped declaration letter to be submitted for no change or update in the information submitted, from that approved in GCC-DR by the MAH.

NHRA, reserves the rights to request for more information if required.

4.5. Submission & Validation

In order to submit new medicine licensing application the applicant must request an appointment by duly filing an appointment request form (Annex III) and sending to the PPR department by email. Appointments are assigned on a first-come basis.

On the appointment day NHRA staff will check the file to make sure all the requested documents are available only valid applications will be accepted as per the checklist (Annex IV). If the application is accepted, the applicant has to pay the required fees. A stamped and signed copy of the medicine licensing checklist is returned to the applicant and the file will be added to the new medicines files record.

4.6. Assessment & Queries

Each application is assessed in accordance with NHRA standard operating procedures and where queries arise, a request for further information will be sent to the applicant. The applicant is requested to respond to such requests in a timely manner and in accordance with any decided timeline.

NHRA will not be held responsible for the delay of registration process if the applicant fails to respond to NHRA request in a timely manner. Failure to respond to NHRA request for information will result in rejection of the application.

4.7. Approval

After completion of assessment and pricing of medicine a decision to approve or disapprove a product for licensing is done by the licensing committee. Upon approval from the committee the applicant has to pay the required fees prior to collection of the license. Medicine license is valid for 5 years.

4.8. General notes

1. Medicine License is specific to a particular name, formulation, dosage form, strength, pack size with a particular set of approved indications and directions for use.
2. The medicine must be licensed and marketed in the country of origin for at least one year before submission of the medicine licensing application.
3. When required Bioequivalence study must be according to GCC guidelines.
4. When required Stability study must be according to GCC guidelines.
5. Two API sources will be accepted upon the first registration addition or deletion of source can be submitted later through variations.
6. Two Bulk manufacturers will be accepted at the time of registration, after that any addition or deletion will be through variation application and will be studied case by case.
7. Medicines can be classified into one of the following categories at the time of licensing (method of sale):
 - i. Prescription Only Medicines (POM) – available only on a prescription.
 - ii. Over-the –counter but Pharmacy only (P) – available under the supervision of a pharmacist.
 - iii. General Sale (GS) – available in general retail outlets.

5. IMPORTATION & INVOICE CLEARANCE

Importation of medicine is governed by Bahrain Pharmacy law no. (18) Of 1997/2015 which states that “the importation of medicines must be through authorized legal entity”.

The following details must be included in the invoice and will be checked against the PPR Medicine database:

1. Medicine name - strength.
2. Pack size - dosage form.
3. Importer name and address (local agent)
4. Manufacturer name and country.
5. MAH name.
6. CIF (Cost, Insurance & Freight) price.
7. Batch number.
8. Manufacturing date - expiry date.

When all the invoice particulars are complying with the approved medicine information the invoice will be approved.

ANNEX I

Electronic Common Technical Document (eCTD)

I. Introduction

According to NHRA's eCTD implementation plan, the eCTD is mandatory from the 1st of November 2016. 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>

Documents to be submitted as hard copy for new registration application are listed in Appendix I.

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

1. 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.

2. For products submitted as eCTD for renewal or variation

Products submitted as eCTD submission, and are approved by NHRA with no ongoing regulatory activity, the baseline sequence may continue from the last one. Table 2 demonstrates more on this case.

Sequence No.	Submission Description	Submission Type	Submission Unit	Related Sequence
0000	Renewal	Renewal	-	-
0001	Response to Questions	Renewal	-	0000
0002	Response to Questions	Renewal	-	0000
0003	Variation	Var	-	-
0004	Response to Questions	Var	-	0003
0005	Baseline Submission	None	Reformat	-

Table 2: Example for starting a baseline with a regulatory activity.

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).
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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