PART X

EAC GUIDELINES ON PROCEDURAL ASPECTS FOR APPLICATIONS FOR MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCTS

ABBREVIATIONS AND ACRONYMS

BMGF	-	Bill and Melinda Gates Foundation
BMR	-	Batch Manufacturing Record
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
EMA	-	European Medicines Agency
FEAPM	-	Federation of East African Pharmaceutical Manufacturers Harmonization
GCP	-	Good Clinical Practice
GMP	-	Good Manufacturing Practice
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	-	Marketing Authorization
MAH	-	Marketing Authorization Holder
MER	-	Medicines Evaluation and Registration
NEPAD	-	New Partnership for African Development
NMRA	-	National Medicines Regulatory Authority
TWG	-	Technical Working Group
WHO	-	World Health Organization

1. INTRODUCTION

All pharmaceutical products in the EAC region are regulated by individual Partner States' NMRA. As a preliminary step, the NMRA issues marketing authorization of all pharmaceutical products for human use prior to their use in the region. The objective of pharmaceutical product marketing authorization is to ensure that pharmaceutical products marketed in the region are safe, efficacious and of good quality and are manufactured in facilities that complies with the requirements prescribed in the EAC Good Manufacturing Practice guidelines. All local manufacturers, wholesalers, distributors and importers of pharmaceutical products must be licensed before they can conduct their businesses.

The guideline covers the steps that are followed from the submission of a dossier to the final outcome, the timeframe and procedure for competent authorities to amend, where necessary the conditions of marketing authorization of a particular product.

2. SCOPE

The guideline is applicable for all types of application submitted to the EAC Partner States National Medicines Regulatory Authorities (NMRAs) that include new application, renewal of application and application for variation of a registered pharmaceutical product.

3. TYPES OF APPLICATIONS

3.1 For purposes of submission to the NMRA, applications are classified into new application, application for variation of a registered pharmaceutical product and renewal application.

3.2 A new application is an application for registration of a pharmaceutical product that is intended to be placed on the market for the first time. A new application may only be made by the applicant and he shall be the person who signs the application form.

3.3 A new application for registration shall include submission of relevant documentation as provided in the main guidelines for registration of pharmaceutical products in use.

4. GENERAL REQUIREMENTS AND APPLICATION PROCEDURES FOR PHARMACEUTICAL PRODUCT REGISTRATION

4.1 All applications and supporting documents shall be in English. All submitted documents which are in any language other than English must be accompanied by a certified or notarized English translation.

4.2 The responsibility of applying for product marketing authorization rests with the company responsible for the introduction of the product into the EAC market, i.e.: the Marketing Authorization Holder (MAH).

4.3 Applications must be duly completed and supported by all of the required documents i.e. Module I to Module V in accordance with the EAC Common Technical Document (CTD) for registration of pharmaceutical products. The submitted application will be screened for completeness within 30 working days. Dossiers which are incomplete will not be accepted for evaluation.

4.4 A dossier is a file that contains detailed scientific information on the chemistry, formulation, manufacturing, quality control and non-clinical and clinical studies that demonstrates quality, safety and efficacy of active pharmaceutical ingredient(s) and the corresponding finished pharmaceutical product.

Different sections of the dossier shall be distinctly marked and page numbered in the style: **page x of y** and have a table of contents indicating the sections and page numbers. Where information is required in the application forms its location shall be cross referenced in dossier. Information for each section shall be printed on both sides of an A-4 paper which will be arranged sequentially on a 1.00 mm or more diameter stainless spring and clamped with a stainless steel binder of not less than 1.0 mm thick in an A4 expandable spring file. The file shall be of cardboard or paper material of not less than 600gsm.

4.5 The covering letter shall be submitted in hard copy and the entire dossier on a CD-ROM or the entire application be electronically submitted to the NMRA.

4.6 Data shall be presented on A4 and 80g/m^2 paper with readily readable letters of at least 12 font sizes. Every page shall be numbered sequentially. Extension sheets, tables, diagrams and other supporting documents shall as far as possible be of the same size, well annotated, numbered and appropriately cross-referenced.

4.7 Application must be accompanied by two samples of the finished product as packaged for sale. The NMRAs may request for additional samples when need arises.

4.8 The processing fee as prescribed in the respective NMRA’s fees and charges schedule must be paid to the NMRA at the point of submission of the application.

5. PROCESSING OF APPLICATIONS (MANAGEMENT OF APPLICATIONS)

5.1 Upon acceptance of an application, an acknowledgement for the receipt of the application will be issued within and a reference number will be generated. The reference number shown in this acknowledgement should be used in all subsequent correspondences relating to the application.

5.2 The NMRA shall complete screening of the dossier for completeness within 30 working days from receiving such application.

5.3 In the event that the dossier is incomplete, it will be rejected. The applicant will be notified of the rejection.

5.4 In case of a positive outcome during screening, the NMRA shall notify the MAH in writing that the screening has been successfully completed and place the dossier in the evaluation queue.

5.5 Review of application for marketing authorization of a product will follow the appropriate evaluation queue. Priority review may be granted where the product is intended for treatment of a serious or life-threatening disease. Evaluation of priority product shall be carried out within 6 months from receiving the application.

5.6 Evaluation of the application shall be carried out within 12 months from receiving the application.

5.7 Abridged evaluation will be carried out to pharmaceutical products that are registered in any of the agreed benchmark regulatory agencies.

5.8 During product evaluation, the NMRA may request for further information and additional supporting documents from the applicant. This shall be considered as the first round of evaluation.

5.9 Applicant should make available such information or documentation requested after the first round of evaluation within 180 calendar days from the date of receipt of the request.

5.10 Applicant should make available any information or documentation requested after subsequent rounds of evaluation within 120 calendar days from the date of receipt of the request.

5.11 If no response is received from applicant after the timelines described in 5.9 and 5.10 above, the clock stops and the application will be cancelled if no formal request for extension of deadline has been made to the NMRA. A new application will have to be submitted if the MAH wishes to pursue marketing authorization of the product.

5.12 Evaluation of the additional information shall be carried out within 3 months from receiving such information. This shall be considered as the second round of evaluation and subsequent submission of additional information shall be considered as third round of evaluation and so forth.

5.13 Evaluation of one application shall not exceed four rounds of evaluation with the exception of administrative queries.

5.14 The MAH will be informed of the decision of the NMRA in writing as to whether the application has been approved or rejected.

5.15 A registration number will be given when a product is registered. The registration number is specific for the product registered as specified in the registration documents. A certificate of registration shall be issued for the registered product.

5.16 For a product to be issued MA, it must be manufactured in a GMP compliant facility and studies conducted following GCP.

6. MAINTENANCE OF MARKETING AUTHORIZATION

6.1 The conditions for marketing authorization of pharmaceutical products are as follows:-

6.1.1 The product registered with the marketing authorization number as stated in the marketing authorization certificate shall have the name, composition, characteristics, specifications and origin as specified in the marketing authorization documents.

6.1.2 The holder of the marketing authorization certificate must supply such documents, items, samples, particulars or information as the NMRA may require in relation to the registered product.

6.1.3 Changes in name, composition, characteristics, origin, specifications, manufacturer, packing, indications, labelling, package insert, product literature or any other particulars of the registered product shall not be made without prior approval from the NMRA.

6.1.4 The labels for the registered product must comply with all of the labelling requirements as specified by the guidelines for labelling.

6.1.5 The registered product must only be indicated for use as approved by the NMRA.

6.1.6 The holder of the marketing authorization certificate must inform the NMRA of any adverse reactions or complaints on quality, safety and efficacy of the registered product immediately after he/she becomes aware of such adverse reactions or complaints.

6.1.7 The holder of the registration certificate must notify in writing to the NMRA of any decision to withdraw the marketing authorization of the product and shall state the reasons for the decision.

6.2 MAH shall be required to pay retention fees as specified by the respective NMRA.

6.3 The registration of a product shall be valid for 5 years or such period as specified in the registration certificate (unless sooner suspended or cancelled by the NMRA).

6.4 The renewal of product registration should be done not later than three months prior to expiry. Applications for renewal of registration shall be made by submitting the following:

a) Duly filled in application form for registration.
b) Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.
c) Details of all changes during validity of the registration.
d) Two samples of the finished product as packaged for sale.
e) A site master file that describes the manufacturing facilities.
f) Non-refundable evaluation fee for registration of pharmaceutical product and GMP and GCP inspection fees for facilities not inspected and approved by the NMRA within a period specified by NMRA.

7. CANCELLATION OR SUSPENSION OF MARKETING AUTHORIZATION

7.1 The NMRA may cancel or suspend the marketing authorization of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with the marketing authorization requirements or due to changes in national policies.

7.2 Such products may not be imported and marketed in the country. The holder of the registration certificate shall immediately surrender to the NMRA the marketing authorization certificate upon cancellation or suspension of marketing authorization of the product.

7.3 NMRA shall notify all Partner States on the decision taken by the respective NMRA.

8. APPEALS AGAINST NMRA'S DECISIONS ON PHARMACEUTICAL PRODUCT MARKETING AUTHORIZATION

8.1 For products that have been suspended and cancelled marketing authorization by the NMRA, MAH may make a written appeal to the NMRA to review its decision.

8.2 All notice of appeals must be made within thirty (30) calendar days from the date of the NMRA's notification.

8.3 MAH shall make appeal by giving grounds for review for each reason given for the rejection of his product. The grounds for the request shall be based on the information that was submitted in the product dossier. Any additional or new information that was not earlier submitted will not be accepted. The NMRA may review or uphold its earlier decision.

9. VARIATIONS IN PARTICULARS OF REGISTERED PRODUCTS

All variations to a registered product shall be made according to requirements stipulated in the EAC Application Guidelines for Variation of Registered Pharmaceutical Products.

9.1 EXTENSION APPLICATIONS

9.1.1 An extension application is an application that is a modification of an already registered medicinal products. The modification shall be such that it does not fulfil criteria for minor or major variations but is similar enough to the original product in terms of quality, safety and efficacy.

9.1.2 A marketing authorization holder may apply for extension of marketing authorization of an already registered product as an extension application. Such an application should be submitted as a new application however an abridged evaluation will be carried out.

9.1.3 Extension applications shall be applicable in the following situations:-

a) Changes or addition of a pharmaceutical form from multi-dose to single-dose of the finished product or vice versa.

b) Change or addition of strength of the finished product.

c) Change or addition of a route of administration of the finished product for products of the same pharmaceutical form.

d) Inclusion of medical devices that result in change of strength, pharmaceutical form or route of administration of the finished product.

9.1.4 An extension application shall be accompanied by the following:-

a) A dully filled in applicant form with the extension application box clearly marked (ticked).

b) The applicable registration fees for applications for registration of new applications.

c) A full dossier submitted in accordance to the requirements stipulated in the guidelines for submission of documentation for registration of human medicinal products.

d) A cover letter declaring the following:
   i. The name and registration number of the relevant product from which the extension is applied.
   ii. The marketing authorization holder for both products shall remain the same.

e) An overview of the nature of the extension being made.

f) Supporting data related to the proposed extension.

9.1.5 The NMRA final decision on whether an application meets the criteria for extension applications will lie with the NMRA. In case of any doubt the MAH may contact the NMRAs before filling for an extension application.

9.2 Duplicate Licensing

9.2.1 The NMRA shall authorize the same applicant to submit more than one application for a finished product when there are objective verifiable reasons on public health grounds regarding the availability of finished products to health-care professionals and/or patients, or for co-marketing reasons and/or for Export purposes.

9.2.2 Additionally, the holder of a marketing authorization can grant the use of product information to another marketing authorization holder, whereby the original marketing authorization holder acts as a contract manufacturer.

9.2.3 The assessment on whether the conditions of a duplicate application are met shall be done on a case-by-case basis, having regard to the facts of each application. The overall objectives being preservation of public health.

9.2.4 To assess whether an application refers to a particular finished product that has already been granted a marketing authorization, and consequently, whose application for a marketing authorization qualifies for a duplicate license, the composition in active substance(s) and the pharmaceutical form shall be considered. Thus, any finished product with the same qualitative and quantitative

composition in active pharmaceutical ingredient (i.e. the same strength) and the same pharmaceutical form are to be considered as the same relevant product.

9.2.5 A duplicate product shall be identical in all marketing authorization requirements with the exception of brand name and any other specific requirements on labelling. Additionally, any variation made to the original marketing authorization should be applied for the duplicate license.

9.2.6 Conditions for a Duplicate Marketing Authorization are outlined hereafter:-

a) That the duplicate application shall be submitted by the same applicant that submitted and/or holds the marketing authorization/application that is being duplicated (hereafter “original marketing authorization/application”).

b) That the original marketing authorization is valid. This step does not apply in case of duplicate applications that are submitted in parallel with the original marketing authorization application (i.e. in cases where the application for the original marketing authorization is still pending).

c) In cases where the duplicate marketing authorization is submitted on the basis of an informed consent application, there should be a letter of consent from the marketing authorization holder that owns the dossier that is referred to.

d) The original marketing authorizations to which the duplicate application relates has to be valid at the time of the submission of the duplicate application.

9.2.7 The applicant for a duplicate license may fall under the following categories:-

a) Applicant is the same entity that applied for the original marketing authorization.

b) Applicant belongs to the same group of companies as the applicant of the original marketing authorization.

c) Applicant is an independent entity that has agreed to placing on the market the product with the applicant of the original marketing authorization (evidence of license agreement or other agreement that can be identified are required).

d) Applicant is an independent entity whereby there are license agreements with the marketing authorization holder of the product in respect of which the duplicate is asked but not for the placing on the market of that product.

e) Applicant is an independent entity that has got an agreement to purchase and/or use data from the company that has applied for a marketing authorization for the product for the first time but there is not an agreement regarding the placing on the market of the product.

9.2.8 All documents in accordance to the guidelines on submission of documentation for new applications should be submitted however an abridged evaluation shall be applied. In addition, the following shall be submitted when making a duplicate license application:

a) A dully filled in application form (Annex II) with the duplicate license box clearly marked (ticked).

b) A cover letter detailing the following:

i. The name of the marketing authorization holder relevant for the duplicate application.
ii. The name of the product relevant for the duplicate application.
iii. The proposed brand name for the duplicate license.
iv. The proposed marketing authorization holder for the duplicate license.

c) The applicable registration fees for applications for registration of new applications.

d) For co-marketing reasons, the evidence co-marketing (contract or letter of agreement between the companies).

e) For duplicates asked on grounds of the existence of patents protecting certain therapeutic indications or pharmaceutical forms, the applicant shall provide a commitment undertaking to extend the therapeutic indication(s)/ pharmaceutical form(s) of the duplicate marketing authorization as soon as the patent restrictions no longer exist. Alternatively, the applicant may also commit to withdraw the marketing authorization with restricted indications/pharmaceutical forms after the relevant patents are no longer in force. The SmPC shall be harmonized. The commitment letter shall be submitted alongside the Marketing authorization Application Dossier.

f) Letter of consent in the case of an "informed consent application".