PROCEDURE ON SUBMISSION OF EAC – ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE (EAC-APIMF)

1. Introduction

The EAC- Medicines Regulation Harmonization Programme is initiating API Certification procedure. Previously, API assessment within EAC has been conducted only as part of FPP assessment as per the EAC guidelines on submission of documentation for registration of Human pharmaceutical Products (EAC/TF-MED/MER/FD/COM/N1R2). The Information on API can be submitted using the following options;

a) Option1: Certificate of suitability of European Pharmacopeia(CEP)
b) Option 2: Active pharmaceutical ingredient pre-qualified by WHO
c) Option 3: EAC Active Pharmaceutical Ingredient Master File (EAC-APIMF)
d) Option 4: Full details in the Product Dossier (PD)

EAC has been implementing options 1, 2 and 4 only. Option 3 has not been previously implemented by EAC.

In the context of globalization, APIs are sourced in a worldwide market and the risk of sourcing substandard or contaminated products is high. A proper system of API certification of suppliers will promote sourcing of active pharmaceutical ingredients of appropriate quality and thereby safeguard public health interests.

API certification is being implemented to avoid duplication of work and minimize different outcomes of assessment in EAC. API certification will be based on submission and assessment of the Active Pharmaceutical Ingredient Master File (EAC – APIMF) –option 3. The EAC – APIMF procedure will facilitate product assessment by NMRAs and thereby shorten the time for marketing authorization of finished pharmaceutical products across the region.

Assessment of an API for APIMF acceptance has two components:

a) Assessment of the API master file (APIMF) to verify compliance with EAC norms and standards; and
b) Verification that the site(s) of API manufacture comply with EAC GMP requirements.

Following successful assessment and acceptance of the APIMF, the API will be included in the EAC approved APIMF data base. Upon API certification, an EAC Certificate of approval (EACCA) will be issued to the applicant. The EACCA shall contain information regarding the certificate holder, API manufacturing site(s), API specifications, claimed standards, standard analytical procedures, primary and secondary container closure system, storage statement and retest period/shelf life. The accepted EAC-APIMF or the EAC Certificate of Approval (EACCA) will be acceptable in supporting marketing authorization of the finished product consisting of the same API within the EAC partner states.

The APIMF holder should provide letter of access along with the open part of the APIMF to the relevant finished product applicant applying for marketing authorization of finished product in the EAC Partner States. The Holder of API Certification should provide the certificate along with its annexures to the relevant finished product applicant applying for marketing authorization of finished product in the EAC Partner States. The certificate should be dully filled in and signed to support the registration of the specified finished product.

2. Objectives of the procedure

The objective of this quality assessment procedure is to assess whether APIs meet the requirements recommended by EAC and are manufactured in compliance with EAC current good manufacturing practices. This will be carried out through standardized quality assessment and inspection procedures.

The quality assessment procedure established by EAC is based on the following principles:

a) a general understanding of the production and quality control activities of the manufacturer of the API
b) assessment of data and information on the API, submitted by the manufacturer, which includes the manufacturing process, material specifications, test data and results, including changes and variations (amendments)
c) assessment of the API manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key starting materials or intermediates and the final APIs during and after purification through compliance with EAC GMP.

3. Information to be submitted for the EAC APIMF procedure

Interested API manufacturers are expected to submit documentation on the APIs as called for in the invitation for Expression of Interest (EOI). Applicants should submit an application package consisting of a cover letter, application form and the APIMF in CTD format, with the required information to the EAC lead country in medicines assessment and registration; Tanzania Medicines and Medical devices Authority.

The content of the APIMF should be aligned to the common technical documentation (CTD) format for the API section; in line with the open and restricted parts of the APIMF as described in the guidelines on submission of documentation for registration of human pharmaceutical products (EAC/TF-MED/MER/FD/COM/N1R1) and EAC guideline on submission of EAC-APIMFs for API certification available on the EAC NMRAs and EAC websites.

Holders of APIMFs with dossiers in CTD format that have been assessed with a positive notified outcome by EAC NMRAs as part of the registration for a finished pharmaceutical product may in response to an invitation for EOI, apply in writing for assessment under this EAC-APIMF procedure with submission of updated version of APIMF. Changes in the manufacture of an API should be documented in the APIMF through appropriate change control procedures and communicated to the lead country in medicines assessment and registration (Tanzania Medicines and Medical Devices Authority).

4. Screening of APIMFs submitted through EAC-APIMF procedure

Each APIMF submitted by an applicant shall be screened within a period of two weeks by the lead country in medicines assessment and registration (Tanzania Medicines and Medical Devices Authority) for completeness prior to the beginning of the assessment process.

In the event of the APIMF being incomplete after screening, the applicant will be informed and will be requested to update the APIMF. The response should be submitted within a period of three months. EAC will not consider incomplete APIMFs for assessment. APIMFs that are considered complete as following the screening process will be retained by the lead country for assessment process and the applicant shall be notified of the same.

5. APIMF Assessment

The EAC NMRAs, in accordance with EAC Standard Operating Procedures (SOPs) and guidelines, will conduct the assessment of the APIMF. The APIMF assessment shall be done within a period of four months from the date of successful screening of the APIMF and shall be done concurrently with GMP inspections if applicable.

The outcome of the assessment will be shared with the applicants by the lead country in medicines assessment and registration (Tanzania Medicines and Medical Devices Authority). If any additional information is required, applicants will be required to provide such additional information to the lead country in medicines assessment and registration within 90 days, and any extension beyond the specified period should be justified. Upon receipt of additional information (query responses), the EAC NMRA partner states shall evaluate the query responses within a period of 90 days. If found satisfactory the APIMF will be accepted, if found not satisfactory additional information will be requested and this will be limited to three rounds of assessment of queries responses. If no written responses are received within 90 days from the date indicated on the query letter, it will be deemed that the applicant has withdrawn the application.

In the course of assessment, all measures including signing of confidentiality forms will be taken to ensure that all participating parties protect confidentiality of the information submitted.

6. Inspection of API manufacturing site(s)

Dependent on the outcome of the evaluation of the APIMF, the planning of inspections should take into account the types of API and the results and reports of inspections conducted by regulatory authorities or other competent organizations.

EAC will plan and coordinate the performance of inspections at the manufacturing site(s) of APIs and that of the key intermediate (if relevant) to assess compliance with the relevant sections of EAC GMP guidelines, and will compare the technical information on the manufacturing process given in the APIMF submitted to EAC with the manufacturing process actually carried out on site. The inspections will be performed by a team of inspectors consisting of experts appointed by EAC. Each team will perform the inspections and report on its findings to EAC in accordance with SOPs established by EAC for that purpose so as to ensure a standard harmonized approach.

Each inspection team will finalize its reports according to the established EAC SOP and format, describing the findings and including recommendations to the applicant. The inspection report will be communicated to the applicant. If any additional information is required, or corrective action has to be taken by the manufacturer of the API and/or manufacturer of the key intermediate, EAC will postpone its decision of the acceptability of the respective site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

7. **Outcome of the assessment**

In the event that EAC is satisfied that the quality assessment process is complete for the relevant API, and that the EAC recommended standards are met, the API, as manufactured at the specified manufacturing site(s), will be included in the EAC approved APIMF data base which shall include information as provided in table 1 below. Upon API certification, an EAC Certificate of Approval (EACCA) will be issued to the applicant and the API will be included on the EAC list of certified APIs. The list will be published on the EAC - MRH and NMRAs web sites and will specify the particulars of the certified API as shown in table 2 below.

Table 1: Particulars of the EAC approved APIMF Database

International Non-proprietary Name-(INN) of API	APIMF No. and Version No.	APIMF Holder	API manufacturer and site	Validity (5 years from the date of acceptance)

Table 2: Particulars of the list of EAC certified APIs.

International Non-proprietary Name-(INN) of API	Certificate No.	Certificate Holder	API manufacturer and site	Validity (5 years from the date of acceptance)

Once the API is included in the approved APIMF database or on the list of EAC Certified APIs, applicants shall be required to communicate details to EAC of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the API. It is the applicant's responsibility to provide EAC with the appropriate documentation (referring to relevant parts of the APIMF) to prove that any intended or implemented variation will not have an

impact on the quality of the API that has been certified. EAC will undertake an evaluation of variations according to the established EAC variations guidelines.