EAC/TF-MED/REG/PD/N1R0

EAST AFRICAN COMMUNITY

EAC - GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF HUMAN PHARMACEUTICAL PRODUCTS

PREPARATION OF MARKETING AUTHORIZATION APPLICATION IN TECHNICAL COMMON DOCUMENT (CTD) FORMAT

APPROVED BY THE…….. ORDINARY MEETING OF THE EAC COUNCIL OF MINISTERS
(REF: EAC/CM …../DECISION------/dd/mm/yy)

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3RD DRAFT

EAST AFRICA COMMUNITY SECRETARIAT
EAC CLOSE
P.O.BOX 1096
ARUSHA, TANZANIA.

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I wish to also thank the EAC Secretariat staff for their hard work and coordination of the EAC MRH project implementation. The oversight role of the EAC MRH project Steering Committee is also acknowledged.

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Ambassador Dr. Richard Sezibera,
SECRETARY GENERAL
East African Community

Preface

Access to essential medicines for prevention and treatment of priority disease conditions remains a challenge in the East African region, yet essential medicines are a key element in the provision of primary healthcare in improving public health. The situation is not any different in the rest of Africa, where inefficient medicines regulatory systems have impeded access to quality healthcare for large sections of the population.

Assuring the quality, efficacy and safety of medicines in the EAC region is an important task of Partner States National Medicines Regulatory Authorities (NMRAs). All pharmaceutical products for use within the region have to be subjected to pre-marketing evaluation, marketing authorization/registration and post-marketing review.

Most of the EAC Partner States cannot ensure safety, efficacy and quality of medicines circulating in their markets. The challenges behind include disparate regulations, guidelines and procedures among EAC-Partner States, inadequate or lack of guidelines, laws and regulations. Furthermore, lack of standards, transparent procedures and systems are among of the overwhelming challenges.

To address challenges related to medicine registration procedures, the East African Community Medicines Regulatory Harmonization (EAC-MRH) programme has been created to help Partner States build effective medicines regulation procedures through harmonization and regulatory capacity building. The availability of affordable essential medicines, therefore, can be improved through a simplified, open and transparent regulatory system.

These guidelines have therefore been prepared by the EAC-Partner States to provide harmonized medicines registration procedures using Common Technical Document (CTD) format.

Adherence to guidelines will ensure that all relevant information is provided in the medicinal dossiers submitted for marketing authorization and this will facilitate efficient and effective assessment as well as approval process.

We wish to express our gratitude to all individuals who developed and reviewed the guidelines and call upon all technical experts from EAC-NMRA and EAC Secretariat to use it as a guide for efficient and effective implementation of the medicine registration.

Signed on this .....(*date*) Day of ..... (*month*) 2013 by the Heads of Delegations as:

.....	.....	.....	.....	.....
Ministry of East African Community Affairs	Ministry of East African Community Affairs and Regional Integration	Ministry of East African Affairs, Commerce and Tourism	Ministry of East African Cooperation	Ministry of East African Community Affairs
REPUBLIC OF UGANDA	**REPUBLIC OF BURUNDI**	**REPUBLIC OF KENYA**	**UNITED REPUBLIC OF TANZANIA**	**REPUBLIC OF RWANDA**

Responsibility for Implementation and Legal Framework

These guidelines will be adhered and implemented by applicants intended to seek marketing authorization of human medicinal products in EAC region.

Chapter 21 (Article 118) of the East African Community (EAC) treaty, in the context of cooperation on health issues within the Partner States provides for harmonization of medicines registration procedures so as to achieve good control of medicinal standards without impeding or obstructing the movement of medicinal products within the Community. For this purpose, an application shall be submitted to the EAC Department of Health in accordance with the provisions of Article 118 and the relevant EAC Guidelines.

Abbreviations and acronyms

EAC	East Africa Community
EAC-NMRA	East Africa Partner State National Regulatory Authority
EAC-MRH	East Africa Medicines Registration Harmonization
CEP	Certificate of Suitability to the monograph of Ph Eur monograph
CTD	Common Technical Document
DMF-	Drug Master File
EDQM	European Directorate for the Quality of Medicines
	EU-European Union
GCP-	Good Clinical Practice
GMP-	Good Manufacturing Practice
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
PI	Product Information
SmPC	Summary of Product Characteristics
API	Active Pharmaceutical Ingredient
FPP	Finished Pharmaceutical Product
SDRA	Stringent Drug Regulatory Authority
MAD	Marketing Authorization Dossier

Glossary

The definitions provided below apply to the words and phrases used in these guidelines. The following definitions are provided to facilitate interpretation of the guidelines.

Active pharmaceutical ingredient (API)
An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

(USFDA Glossary of terms, it can be found in line at Drugs@FDA Glossary of Terms).

Active pharmaceutical ingredient (API) starting material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. (WHO glossary of terms).

Market Authorization Holder

Is a person resident/domicile to each of the EAC Partner States who holds authorization to place a medicinal product in the EAC Partner Sates and is responsible for that product.

Commitment batches
Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Comparator product
A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

Generic product
Is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
(PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)

Existing API

An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority. (WHO glossary of terms).

Finished pharmaceutical product (FPP)
A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture, including packaging in its final container and labelling. (WHO glossary of terms)

Innovator medicinal product
Generally the medicinal product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality. (WHO glossary of terms)

Manufacturer
A manufacturer is a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. It involves operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals.
(PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)

Officially recognized pharmacopoeia (or compendium)
Those pharmacopoeias recognized in the EAC-MRH (i.e. *British Pharmacopoeia* (BP), *European Pharmacopoeia* (Ph.Eur.), *The International Pharmacopoeia* (Ph.Int.), *Japanese Pharmacopoeia* (JP) and *United States Pharmacopeia* (USP)).
(WHO glossary of terms).

Ongoing stability study
The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP. (WHO glossary of terms).

Pilot-scale batch
A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example,
for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified. (WHO glossary of terms).

Primary batch
A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. (WHO glossary of terms).

Production batch
A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

A stringent drug regulatory authority (SDRA)
A National Medicine Regulatory Authority which is strict, precise, exact with effective and well functioning systems.

Among others, it includes a regulatory authority which is:
A member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
An ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, and Health Canada (as may be updated from time to time); or
A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

For more terms refer EAC Common Glossary of Terms (Link).

Introduction

1.1 Background

This guideline provides guidance for applicants preparing a Common Technical Document for the Registration of Medicines for Human Use (CTD) for submission to the EAC-NMRA. The document describes how to organise applications based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD.

According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements which is region specific. The Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5, respectively. Applicants should not modify the overall organisation of the CTD.

If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview.

Information in these Modules should be present in relevant sections.

For application procedures see EAC Guidelines on Procedural Aspects for Application for Market Authorization for Human Medicinal Products. (Link)

1.2 Scope

These guidelines will assist applicants to prepare applications to register medicinal products for human use in East Africa Partner States. The format for applications is the Common Technical Document (CTD).

These guidelines apply to MA applications for medicinal products containing APIs of synthetic or semi-synthetic origin. Biological, biotechnological and herbal products are not covered by these guidelines.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRODUCT

INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments, antibiotic resistance and overseas evaluation reports), as needed. Documents should be organised in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes.

1.1 Comprehensive table of contents for all modules

1.2 Cover letter

Applicant s should include a *Letter of Application* with all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter shall be signed by Market Authorization Holder. *(Appendix I).*

1. 3. Comprehensive table of content

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module. In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document.

1.4 Application form

An application to register a medicinal product for human use must be accompanied by a completed application form *(Appendix II),* together with all the relevant annexes.

1.5 Product Information

Provide copies of all package inserts, labels and any information intended for distribution with the product to the patient.

If the SmPC, has not been approved from SDRA at the time the application is submitted in EAC, a draft document may be included. The approved SmPC from SDRA should then be supplied to the EAC-NMRA as they become available.

1.5.1 Prescribing information (Summary of products characteristics)

All prescription medicines should be accompanied by Summary Product Characteristics.

See EAC Guidelines on Summary of Products Characteristics for guidance on preparation of SmPC. (Link).

1.5.2 Container labelling

See EAC Guidelines on container labelling for guidance on preparation of product labelling (Link)

1.5.3 Patient information leaflet (PIL)

All medicinal preparations with potential for long term use and self-administered injections and Over the Counter (OTC) must contain a patient information leaflet.

See EAC Guidelines on PIL for guidance on preparation of PIL. (Link).

1.5.4. Mock-ups and specimens

If the product applicant has a specimen or mock-up of the sales presentation of the medicine available at the time of initial application, it should be included in Module1.4.4.

A *mock-up* is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging / labelling of the medicine. It is also referred to as a *paper copy* or *computer generated version*.

A specimen is a sample of the actual printed outer and inner packaging materials and package leaflet. If there are multiple strengths and/or pack sizes, one representative specimen or mock-up will be sufficient. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mock-ups or specimens are not available at the time of initial application, a text version may be submitted, however, mock-ups or specimens must be submitted to the EAC-NMRA, during the evaluation process and prior to finalisation of the application.

1.6. Information about the experts

Experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5.

The requirement for these signed Expert Reports may be met by providing:

- The Quality Overall Summary, Non-clinical Overview / Summary and
- Clinical Overview / Summary in Module 2,
- A declaration signed by the experts in Module 1.6.
- Brief information on the educational background, training and occupational experience of the experts in Module 1.6.

Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the applicant / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Reports should be based on an independent

assessment of the dossier and references must be provided for any additional claims not supported by the dossier. A sample declaration form is provided as *Appendix III.*

1.7. Certificates of suitability of monographs of the European pharmacopoeia (CEP)/ EAC-APIMF

If CEP is available, the finished product applicant should present copy of CEP in module 1.7.

Applicant should provide the *Letter of Access to EAC-APIMF* or *Letter of Access to CEP,* as appropriate from API manufacturer. These letters should be included in Module 1.7.

1.8 Good Manufacturing Practice

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient ingredients and finished pharmaceutical products must be performed in plants that comply with EAC GMP guidelines. Attach a WHO-type certificate of GMP. For more information on GMP requirements and application for GMP inspection; *See EAC Guidelines on Good Manufacturing Practice for more guidance.*

If available at the time of submission of application, GMP certificates for EAC-NMRA and/or SDRA or an evidence for application for GMP inspection should be submitted in module 1.8.

1.9 Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)

Provide evidence such as accredited certificate for GLP or GLP for the sites participating in the clinical studies

1.10 Regulatory status from countries with SDRA

1.10.1 Registration status in EAC Partner States

Provide registration status of the medicinal product applied for registration.

1.10.2 List of countries in which a similar application has been submitted

The applicant should provide, in Module 1.9.1 of the dossier, a list of countries in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case.

1.10.3 Statement on whether an application for the product has been previously rejected, withdrawn or repeatedly deferred in the EAC- Partner States

Applicant must declare whether a marketing application for the medicine has been rejected prior to submission of the application in EAC. If the medicine has been rejected, repeatedly deferred, withdrawn or suspended then reasons must be stated. If rejection occurs during the EAC evaluation process, the EAC-NMRA should be informed.

1.11 Evaluation reports from SDRA

At least one independent evaluation report from countries with SDRA, where the product is already approved, is required to be provided at the time of application.

Copy of this evaluation report should be provided as to Module 1.10

1.12 Evidence of API and/or FPP prequalified by WHO

If available evidence indicating that the active pharmaceutical ingredient and/or finished pharmaceutical product have been prequalified by WHO should be presented in Module 1.14

1.13 Evaluation reports from EAC-NMRA

Provide copy of evaluation report from EAC-NMRA should be provided in Module 1.11

1.14 Manufacturing and Marketing authorization

Submit a Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production. If available, evidence for prequalification of medicinal product by WHO should be submitted.

1.15 Product samples

Sufficient number of samples should be submitted together with the application. The quantity of samples should be adequate to carry out full specification analysis plus one repeat.

MODULE 2: OVERVIEW & SUMMARIES

2.1 Table of contents of Module 2

A table of contents for module 2 should be provided.

2.2 Body of data

2.3 Quality overall summary (QOS)

The quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3 (*See EAC – Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products: Quality overall Summary of Module 2 and Module 3-Quality*). The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the common technical document (CTD).

2.3.S Active pharmaceutical ingredient (name, manufacturer)

2.3.S.1 General Information (name, manufacturer)

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, manufacturer)

Information from 3.2.S.2 should be included:

Information on the manufacturer;

- A brief description of the manufacturing process and the controls
- *A flow diagram, as provided in 3.2.S.2.2;*
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the API, as described in 3.2.S.2.3;
- Highlight critical process intermediates, as described in 3.2.S.2.4;
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.

2.3.S.3 Characterisation (name, manufacturer)

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance (name, manufacturer)

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3. S.5 Reference Standards or Materials (name, manufacturer)

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (name, manufacturer)

A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (name, manufacturer)

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P Finished Pharmaceutical Product (name, dosage form)

2.3. P.1 Description and Composition of the Drug Product (name, dosage form)

Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (name, dosage form)

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, dosage form)

Information from 3.2.P.3 should include:

Information on the manufacturer.

A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

A flow diagram, as provided under 3.2.P.3.3.

A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (name, dosage form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (name, dosage form)

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (name, dosage form)

A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (name, dosage form)

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

2.4 Non-Clinical overview

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

The Nonclinical Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

See ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.5. Clinical overview

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of

those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarisation of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information.

The clinical Overview should be presented in the following sequence

- Product Development Rationale
- Overview of Biopharmaceutics
- Overview of Clinical Pharmacology
- Overview of Efficacy
- Overview of Safety
- Benefits and Risks Conclusions
- Literature References

See ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the format and the content of this part.

2.6 Nonclinical Written and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetcs
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

See ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.7 Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions.

See ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy for guidance on the content of this section.

The following order is recommended:

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods: Generic applications

The objective of CTD Module 2.7.1 is to summarize all relevant information in the product dossier with regard to bioequivalence studies and/or comparative dissolution and associated analytical methods.

The appendix--- *of the EAC Guideline on the Bioequivalence studies: Presentation of Biopharmaceutical and Bio-analytical Data* contains a set of template tables to assist applicants in the preparation of Module 2.7.1 providing guidance with regard to data to be presented. Furthermore, it is anticipated that a standardized presentation will facilitate the evaluation process.

See the EAC Guideline on the Bioequivalence studies requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance

2.7.2 Summary of Clinical Pharmacology Studies

See also the EAC Guideline on the Bioequivalence studies: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance

2.7.3 Summary of Clinical Efficacy

See also the EAC Guideline on the Bioequivalence studies: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance

2.7.4 Summary of Clinical Safety

See also the EAC Guideline on the Bioequivalence studies: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance

2.7.5 Literature References

2.7.6 Synopses of Individual Studies

MODULE 3: QUALITY

For Module 3.2.S Drug substance (or active pharmaceutical ingredient (API)), there are four options to present the information requirements for APIs within the EAC. These are:-

- Option 1: EAC-Active pharmaceutical ingredient master file (EAC-APIMF)
- Option 2: Full details in the Marketing Application Dossier (MAD).

All options require the submission of information in CTD format (3.2.S). The document *EAC – Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products: Quality overall Summary of Module 2 and Module 3: Quality part* described detailed guidance on this issue and on the preparation of the FPP information by the applicant.

MODULE 4: NON CLINICAL STUDY REPORTS

This chapter presents an agreed format for the organisation of the nonclinical reports in the Common Technical Document for applications that will be submitted to EAC- National Medicines Regulatory Authorities.

This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired and provide references to other guideline which may be used for populating this format.

4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology

See ICH Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorization for Pharmaceuticals (M3) for the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

See ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals (S7A) for the definition, objectives and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of Phase 1 clinical studies as well as information needed for marketing.

See ICH Guideline on The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (S7B) for a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. This Guideline includes information concerning non-clinical assays and integrated risk assessments.

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4 2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

See ICH Guideline on Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies (S3B) for guidance on circumstances when repeated dose tissue distribution studies should be considered (i.e., when appropriate data cannot be derived from other sources). It also gives recommendations on the conduct of such studies.

4.2.3 Toxicology

See ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.

4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

See The Committee for Human Medicinal Products (CHMP) Guideline on repeated dose toxicity for guidance on the conduct of repeated dose toxicity studies of active substances intended for human use.

see ICH Guideline on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) (S4) for the considerations that apply to chronic toxicity testing in rodents and non rodents as part of the safety evaluation of a medicinal product. The text incorporates the guidance for repeat-dose toxicity tests.

4.2.3.3 Genotoxicity

See ICH Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (S2) for specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results. This document addressed two fundamental areas of genotoxicity testing: the identification of a standard set of assays to be conducted for registration, and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.

See The committee for medicinal products for human use (CHMP) guideline on the limits of genotoxic impurities for a general framework and practical approaches on how to deal with genotoxic impurities in new active substances. It also relates to new applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new or higher levels of genotoxic impurities are introduced as compared to products currently authorised in the EU containing the same active substance. The same also applies to variations to existing Marketing Authorisations pertaining to the synthesis.

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

See ICH Guideline on Need for Carcinogenicity Studies of Pharmaceuticals (S1A) for a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs. These recommendations take into account the known risk factors as well as the intended indications and duration of exposure.

See ICH Guideline on Testing for Carcinogenicity of Pharmaceuticals (S1B) for guidance on the need to carry out carcinogenicity studies in both mice and rats, and guidance is also given on alternative testing procedures which may be applied without jeopardizing safety.

See ICH Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (S1C) for the criteria for selection of the high dose for carcinogenicity studies of therapeutics. The use of other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design should be considered based on scientific rationale and individual merits.

4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

See ICH Guidance on Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (S5) for guidance on tests for reproductive toxicity. It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.

See committee for medicinal products for human use (CHMP) guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications for guidance on the need for, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use.

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

See Committee for medicinal products for human use (CHMP) guideline on Non-clinical local tolerance testing of medicinal products for recommendations on the evaluation of local tolerance to be performed prior to human exposure to the product. The purpose of these studies is to ascertain whether medicinal

products are tolerated at sites in the body, which may come into contact with products as he result of its administration in clinical use.

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

See ICH Guideline on Immunotoxicity Studies for Human Pharmaceuticals (S8) for the recommendations on nonclinical testing for immunosuppression induced by low molecular weight drugs (non-biologicals). It applies to new pharmaceuticals intended for use in humans, as well as to marketed drug products proposed for different indications or other variations on the current product label in which the change could result in unaddressed and relevant toxicologic issues. In addition, the Guideline might also apply to drugs in which clinical signs of immunosuppression are observed during clinical trials and following approval to market.

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other toxicity studies

4.2.3.7.7.1 Photosafety evaluation

A harmonised guideline on photosafety evaluation of pharmaceuticals is to be published through the ICH process.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

For specific products

See ICH Guideline on clinical Evaluation for Anticancer Pharmaceuticals (S9) for information for pharmaceuticals that are only intended to treat cancer in patients with late stage or advanced disease regardless of the route of administration, including both small molecule and biotechnology-derived pharmaceuticals. It describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals and references other guidance as appropriate.

See ICH Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6) for the pre-clinical safety testing requirements for

biotechnological products. It addresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed, and the impact of antibody formation on duration of toxicology studies.

See committee for medicinal products for human use (CHMP) guideline on Non-clinical development of fixed combinations of medicinal products for guidance on the non-clinical strategies to be considered when developing a fixed combination based on the different data available in order to support the safe human use as well as avoid unnecessary repetition of animal studies.

MODULE 5: CLINICAL STUDY REPORTS

5.1 Table of Contents of Module 5

A Table of Contents for study reports should be provided.

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

See ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the content of this section.

See ICH guidelines for the structure and content of clinical study report (E3).

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

For Generic product

See EAC Guidelines on bioequivalence requirements and bio-wavers.

See EAC list of comparators.

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

For Generic product

See EAC Guidelines on bioequivalence requirements and bio-wavers.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

For Generic product

See EAC Guidelines on bioequivalence requirements and biowavers

See EAC Guidelines on bio-analytical method validation

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience if available

5.3.7 Case Report Forms and Individual Patient Listings

See EAC Guidelines on bioequivalence requirements and bio-wavers.

5.4 Literature References

See list of the ICH guidelines on clinical studies

Version History

Version	Date of changes	Changes applied
0	24/07/2012	Initial draft
1st	Jan, 2013	1st draft
2nd	May, 2013	2nd draft

Appendix I – Cover Letter

Ref.
<Applicant>
<Address>
<Address>
<Post code> <Town>
<Country

<Date>
<Reference>

<National Agency>
<Address>
<Address>
<Post code> <Town>
<Country>

Subject: Submission of Application Dossier(s) for Marketing Authorisation of <Product Name(s) and strength(s)

Dear Sir,

We are pleased to submit our Application Dossier(s) for a registration of human medicines which details are as follows:

Name of the medicinal product(s): ……
Pharmaceutical form(s) and strength(s): ……
INN/active substance(s):……**ATC Code(s):** ……

You will find enclosed the electronic submission dossier (CD rom) in CTD format as specified hereafter:

☐ Module 1

☐ Module 2

☐ Module 3

☐ Module 4

☐ Module 5

☐ Summaries and application form in word format and body data in pdf format

☐ We confirm that all future submissions for this specific product will be submitted in this same format

☐ We confirm that the electronic submission has been checked with an up-to-date and state-of-the-art virus checker.

<- The relevant fees have been paid.>

Yours sincerely,

<Signature>
<Name>
<Title>
<phonenumber>
<Email address>

Appendix II: Application Form

Application Number	EAC use only
Date of submission of th dossier	EAC use only
MODULE 1: ADMINISTRATIVE INFORMATION	
1.0 PARTICULARS OF THE PRODUCT	
1.1	Type of the medicinal product application New Generic Renewal* * If variation has been made, information supporting the changes should be submitted. See EAC variation guidelines for registered medicinal products.
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API)
1.4	Strength of Active Pharmaceutical Ingredient (API) per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name:	

Address: Country: Telephone: Telefax: E-Mail:	
1.6	Pharmaceutical Dosage form* and route of administration* * List of standard terms for dosage forms and routes of administration is available in the EAC the guidelines on submission of documentation for registration of human medicinal products
1.6.1	Dosage form:
1.6.2	Route(s) of administration (use current list of standard terms)
1.7	Packing/pack size:
1.8	Visual description (Add as many rows as necessary)
1.9	Proposed shelf life (in months):
1.9.1	Proposed shelf life (after reconstitution or dilution):
1.9.2	Proposed shelf life (after first opening container):
1.9.3	Proposed storage conditions:
1.9.4	Proposed storage conditions after first opening:
1.10	Other sister medicinal products registered or applied for registration
1.10.1	Do you hold Marketing Authorization (s) of other medicinal product (s) containing the same active substance (s) in the EAC? If yes state; ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Partner States where product is authorised: ▪ Marketing authorisation number(s): ▪ Indication(s):

1.10.2	Have you applied for Marketing Authorization medicinal product (s) containing the same active substance (s) in the EAC? ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Indication(s):
1.11	Pharmacotherapeutic group and ATC Code
1.11.1	Pharmacotherapeutic group:
1.11.2	ATC Code: (Please use current ATC code)
1.11.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.12	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, the NMRAs reserve the right to change and/or apply only those categories provided for in their national legislation)
1.13	Country of origin:
1.14	Product Marketing Authorisation in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons

☐Authorised Country: Date of authorisation (dd-mm-yyyy): Proprietary name: Authorisation number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ Withdrawn (by applicant after authorisation) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation:

	Proprietary name:
1.15	List ICH and Observers where the product is approved.
1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	**Name(s) and physical address(es) of the manufacturing site of the finished pharmaceutical product (FPP), including the final product release if different from the manufacturer**. **Alternative sites should be also declared here**. All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.16.2	**Name(s) and physical address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s) (API)** (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.
Name: Company name: Address:	

Country: Telephone: Telefax: E-Mail:	
1.17	Name and address (physical and postal) of the Brokers and Suppliers (if applicable)
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.18	Name and address (physical and postal) of the person or company responsible for pharmacovigelance
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.19	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Finished Medicinal Product.

1.20	Qualitative and Quantitative composition of the active substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

Name of active ingredient(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph standard
1.			
2.			
3.			
e.t.c			
Name Excipient(s)			
1.			
2.			
3			
e.t.c			

Note: * Only one name for each substance should be given in the following order of priority: INN**, Pharmacopoeia, common name, scientific name

** The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

Details of averages should not be included in the formulation columns but should be stated below:

- Active substance(s):

- Excipient(s):

	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted or

1.21	name and address of laboratory where comparative dissolution studies in support of bio-waiver were conducted. (If applicable)

Name:

Company name:

Address:

Country:

Telephone:

Telefax:

E-Mail:

2.0 DECLARATION BY AN APPLICANT

I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge.

I further confirm that the information referred to in my application dossier is available for verification during GMP inspection.

I also agree that I shall carry out pharmacovigelance to monitor the safety of the product in the market and provide safety update reports to the National Medicines Regulatory Authority of the EAC Partners States.

I further agree that I am obliged to follow the requirements of the Partner States

Legislations and Regulations which are applicable to medicinal products.

I also consent to the processing of information provided by the EAC Partner

States.

It is hereby confirmed that fees will be paid/have been paid according to the national/Community rules*

Name: ……

Position in the company:……

Signature: ……

	Date:…… Official stamp:…… * Note: If fees have been paid, attach proof of payment

Appendix III: Declaration form

The following is an example of a suitable declaration form:

Quality /Non-clinical / Clinical (delete those not appropriate)
I, the undersigned, declare that I have:

- the suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed *curriculum vitae*).
- fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.
- provided a report based on my independent assessment of the data provided
- based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

I further declare that this expert report represents my own view.

Further, I declare the following to be the full extent of the professional relationship between myself and the applicant:

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