Maldives Food and Drug Authority

Ministry of Health

Male', Maldives

Guideline for Product Registration and Approval of Medicines

Guideline for Product Registration and Approval of Medicines is released under the authority of

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Contents

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
FPP	Finished Pharmaceutical Product
BE	Bioequivalence
GMP	Good Manufacturing Practices
CoPP	Ceritificate of Pharmaceutical Product
CTD	Common Technical Document
ICH	International Conference on Harmonization
INN	International Non-Proprietary Name
PH. EUR	European Pharmacopeia
USP	United States Pharmacopeia
BP	British Pharmacopeia
WHO	World Health Organisation
MFDA	Maldives Food and Drug Authority
MTG	Medicine and Therapeutics Goods Division
NPB	National Pharmaceutical Board
ADL	Approved Drugs List
PP	Primordial Products
MA	Market Authorisation
MAH	Market Authorisation Holder

NRA	National Regulatory Authority
SRA	Stringent Regulatory Authority

Definitions

Medicinal Products	Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings. (WHO PQ definition)
	Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product. (The EU 2001/83/EC Directive)
Applicant	The person or Company who submits a registration application or dossier of a product to the Authority and is responsible for the product information, recall etc., availability.
Dossier	A detailed compilation of documents generated from the product manufacturer for the purpose of pharmaceutical product registration.
Market Authorization (MA)	The entire process of reviewing and assessing the evidence to support a medicinal product, in relation to its marketing, finalized by the granting of a license to be sold in Maldives. Please note that the terms market authorizations and registration is used interchangeably in this document.
Marketing Authorization Holder (MAH)	The local representative and/or applicant that has the authorization to market a medicinal product in Maldives
Market Authorization Validity	The duration in which the applicant is allowed to import, distribute and sell the product in Maldives after being granted Market Authorization.
National Regulatory Authority (NRA):	Authorities responsible for ensuring medicinal products released for public distribution are evaluated properly and meet international standards of quality and safety and efficacy.
Stringent Regulatory Authority (SRA)	National Regulatory Authorities that are recognized by WHO as having stringent regulatory practices.

Innovator pharmaceutical product:	Pharmaceutical products that are first authorized for marketing (normally as a patented product) based on documentation of efficacy, safety, and quality.
Active pharmaceutical ingredient (API)	API refers to any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body (WHO Technical Report Series No. 970, 2012).
Dosage Form	Formulation of an active ingredient(s) so that it can be administered to a patient in specified quantity, strength, e.g., tablets, capsules, injection solution, syrups, ointments, suppositories, etc.
Formulation of Medicine	The excipients of the finished pharmaceutical product (FPP) including active pharmaceutical ingredients (API) and non-active ingredients, specifying the Pharmacopeia standard followed i.e., British pharmacopeia (BP), US pharmacopeia (USP).
Manufacturer of the Product	A company that carries out all the operations of production, packaging, labeling and quality assurance of the products.
Product Label	Includes all the written, printed or graphic material of the primary and secondary packaging of the product, excluding any outer shipping container.
Stability	The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. The chemical, physical, microbiological, and biopharmaceutical aspects of stability shall be considered. Information representing this information in stability data.
Bio-equivalence	Two pharmaceutical products are considered bioequivalent if they are pharmaceutically equivalent to their pharmaceutical alternatives, and their bio-availabilities, in terms of peak (Cmax and Tmax) and total exposure (area under the curve (AUC)) after administration of the same molar dose under the same conditions. They are similar to such a degree that their effects can be expected to be essentially the same
Bioavailability	Defined as the fraction of the active form of a drug that reaches systemic circulation unaltered.

Storing	The storage of medicines according to the different storage conditions for different substances according to their individual requirements.
Evaluation	Refers to a comprehensive safety, efficacy and quality analysis of the submitted product for registration.
Good Manufacturing Practices (GMP)	Refers to a system which ensures that products are consistently produced and controlled according to quality standards (WHO).
National Pharmaceutical Board (NPB)	A board assigned by Regulation on National Pharmaceutical Board 2019/R-135 to provide technical advice on regulating medicine and medicinal products.
Approved Drug List (ADL)	A list of all medicinal products approved for import and use in Maldives.
Primordial Products	These are the medicinal products that have been in Approved Drug List from the beginning as approved products but not registered with a full dossier submission. These products are indicated with the letters *"PP"* In ADL.
Registered Products	These are medicinal products that are registered and approved with full dossier submission. These products are indicated with the letter *"R"* in ADL
Batch	A defined quantity of product processed in a single process or series of processes and therefore expected to be homogeneous. In continuous manufacture, the batch must correspond to a defined fraction of production, characterized by its intended homogeneity. Source: World Health Organization WHO Technical Report Series, No. 863, 1996
Expiry Date	The date given on the individual container (usually on the label) of a drug product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture. Source: World Health Organization WHO Technical Report Series, No. 863, 1996
Variation application	A variation application is an application with regard to a change to the terms of an existing registered product which has been previously registered as per the criteria laid down by MFDA
Post market surveillance	Post market surveillance, is the practice of monitoring the safety of a medicine after it has been released on the market and is an important part of the science of pharmacovigilance. Since these medicines are approved on the basis of registration, post-market surveillance can further evaluate

	the safety of a medicine after it is used in the general population by large numbers of people who have a wide variety of medical conditions.
Pharmacovigilance	Pharmacovigilance is the science and activity relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.
Method validation	Validation is the proof needed to ensure that an analytical method can produce results which are reliable and reproducible and which are fit for the purpose intended. Results from method validation can be used to judge the quality, reliability and consistency of analytical results: it is an integral part of any good analytical practice

Guideline for Product Registration and Approval of Medicines

1 INTRODUCTION

As per Chapter 7, point 3 of clause 65 of Health Services act 29/2015 indicates that all medicines have to be registered and approved by MFDA.

As per Chapter 11 of Medicine Regulation No: R-46/2014, medicines manufactured, imported and sold in Maldives shall be registered as per the procedure of Maldives Food and Drug Authority.

The medicine registration process implemented by the Maldives food and drug authority is similar for all international, domestic, public and private sector applicants without any discernment.

The Authority adopts the principle of "Risk- based Approach" for product registration. This includes fast tracking the registration process, requirement of documents etc., based on the level of risk associated with the situation.

To register medicines, a local representative shall be identified and designated by the applicant, who will be responsible for all the communications to the authority from the manufacturer of the product. The local representative or the applicant shall have a valid medicine import license as per the criteria defined by the authority.

The local representative and the applicant can be the same. And this local representative or applicant shall be a Maldivian National.

It is the responsibility of the assigned local representative to furnish all the information required for product registration and all supporting documents as defined by the authority and ensure that these documents are legitimate and valid.

Applicant/local representative shall verify that all of the required documents are submitted by using the checklist provided in **Annex 3** in order to facilitate the acceptance of the documents for registration.

However, the Authority may request additional information not described in this document that is deemed necessary to ensure the quality, safety and efficacy of the product. This will be informed by the authority as a written request to the applicant or the local representative.

Medicine Dossiers are accepted if only the product is categorized as a medicine in the country of origin.

2 Stakeholders

The stakeholders include all medicine importers, market authorization holders, applicants who apply for product registration, pharmacists and consumers

3 Purpose

This guideline shall serve as the guidance for applicants for submitting documents for medicine registration.

4 Scope

The scope of this document pertains to the administrative requirements and procedures for submission, evaluation and approval, of new chemical, re-registration and variation applications with a defined timeline for each procedure.

5 Responsibilities and Accountability

Pharmaceutical officers of Medicine Registration.	Responsible for verifying the documents, accepting the dossiers, evaluating the dossiers, submitting the summary of the evaluation to the National Board for Pharmaceuticals, preparing ad issuing product registration certificates.

	Is also responsible for effective communication with the applicant in a timely manner
Section Head	Responsible for checking and verifying the product evaluation documents and to guide the pharmaceutical officers on evaluating the product.
Division Head	To approve the medicine before it is submitted for Final approval from the national Pharmaceutical Board
Director General (MFDA)	Final authorization of all the activities related to MFDA tasks
National Pharmaceutical Board	For final approval of the medicine

6 Types of Dossier Application

6.1 New Drug Application / New Chemical Entity Application

6.1.1 The registration of a new active pharmaceutical ingredient that have not been previously approved by the authority and present in the most recent Approved Drug list (ADL) , either as a single ingredient drug or as part of a combination product.

6.1.2 These applications will be subject to a high level of scrutiny in terms of efficacy, safety and their contribution to therapeutic improvement.

6.1.3 Refer to section 17 on how to proceed with this application.

6.2 Generic Drug Application (Generic –Generic and branded -Generic)

6.2.1 The registration of a medicine that has the same active ingredient as the innovator or patented medicine, including dosage and having the same safety, efficacy, stability and quality requirements.

6.2.2 Majority of the applications received falls under this category.

6.3 Re-registration application

6.3.1 This is the application for a product that has been registered previously under the criteria set by the authority for medicine registration.

6.3.2 All these registered products will be indicated with the letter "R", in the Approved Drug List. The validity period for the registered product under the previous criteria is 5 years.

6.3.3 Before the expiry of the validity the client shall submit the application for re registration as per the current criteria.

6.4 Variation Application

6.4.1 A variation is a change in the dossier of a product that has already been registered and granted Market Authorization (MA) under the criteria set by the authority for medicine registration.

6.4.2 These changes can include a change in label, shelf-life, excipients and stability data.

6.4.3 Any variation to a product that is listed as a primordial product (PP) or Pre authorization required product (PA) in ADL will not be considered as a variation application.

6.4.4 Variation to a registered medicine can be considered as a new application based on the formulation change, change in the strength of the active ingredient and excipients or any other change as the authority may decide based on the product.

6.5 Registration of products that has already been registered by another party

6.5.1 These are the products that has already undergone full evaluation by assessing the full dossier submitted as per the criteria defined, by another party.

6.5.2 Application for this shall be limited than full dossiers as already the product has been evaluated

6.5.3 The Applicant shall ensure that exact same product is submitted and also shall submit the full pharmaceutical information sheet as mentioned in clause 11.2 B of this document.

6.5.4 The applicant shall ensure the safety, quality and efficacy of the product and shall submit 3 batches of tested reports as per the official monogram published from a WHO pre-qualified laboratory. Refer to the list of such laboratories from:
https://extranet.who.int/pqweb/medicines/prequalified-lists/sf-quality-control-labs

7 Reference Country Categorization for Pharmaceutical Product Registration.

7.1.1 Regardless of the type of dossier application, all applications fall under one of the categories mentioned in **Annex 4:** *"Reference country categorization for pharmaceutical product registration"*

7.1.2 They are categorized according to the country of manufacture of the product under application:

a. Category 1: Countries that have a stringent regulatory authority (SRA) as established by WHO and countries that have strong regulatory procedures as per the recommendations of WHO experts in regulatory systems, are classified in Category 1.

b. Category 2: Countries that import a significant percentage of pharmaceutical products to Maldives and selected based on our market surveillance findings, are classified as Category 2

c. Category 3: Any country that falls outside Category 1 and Category 2 is classified as Category 3

d. Category 4: Products that are WHO Pre-qualified products are classified as Category 4

7.1.3 These categories then dictate the documents to be submitted for the registration of that specific product and the MA validity granted for that product following a successful registration:

a. All pharmaceutical products that fall into Category 1 are able to apply for registration with minimal dossier documents. These documents are indicated in Table 1 of **Annex 4**: "Reference country categorization for pharmaceutical product registration"

b. For pharmaceutical products manufactured by multinational companies where the parent company is from a Category 1 country, the product can be applied for registration under Category 1 Option 1.2, where only minimal dossier documents and proof of standardization document is required as mentioned in Annex 4: "Reference country categorization for pharmaceutical product registration"

c. All pharmaceutical products that fall into Category 2 shall apply for registration with a full dossier. The documents to be submitted in a full dossier and the acceptance criteria of each document is detailed in **Section 11.2**

d. Under Category 2, there are four options available for the applicant to choose from, based on preference and document availability.

e. Each of the four options Under Category 2, detail a condition that shall be fulfilled by the applicant and/or the authority, either before or during import of the product in addition to the submission of a full dossier. These conditions are indicated in Table 2 of **Annex 4**: "Reference country categorization for pharmaceutical product registration"

f. Products that fall into Category 3 can only apply for registration given that the product is registered in a Category 1 country and a full dossier shall be submitted.

g. WHO pre-qualified products that fall into Category 4, can apply for registration with minimal dossier documents, and proof of WHO pre-qualification shall be provided. Same documents shall be submitted as of Category 1 criteria in addition of proof of WHO pre-qualification.

8 Market Authorization / Registration Validity

8.1.1 The duration of registration or Market Authorization (MA) validity is decided based on the strength of the National Regulatory Authority (NRA) in the country of manufacture of the pharmaceutical product.

8.1.2 The table below details the duration for which registration or Market Authorization (MA) is issued as per Reference Country Categorization for Pharmaceutical Product Registration (Annex 4).

Category	Option / Condition	Registration/MA validity
Category 1	Option 1	5 years
Category 1	**Option 2:** Multinational Companies	5 years

Category 2	**Option 1:** To submit a registration certificate of the product under application, in a Category 1 country during application with full dossier	5 years
	Option 2: GMP inspection conducted by MFDA of the manufacturing facility	5 years
	Option 3: To submit analysis reports of 3 batches of the product tested from a WHO prequalified laboratory during application (https://extranet.who.int/pqweb/medicines/prequalified-lists/sf-quality-control-labs) with full dossier	3 years
	Option 4: To submit batch certificates for each individual batches that are imported during import form an accredited laboratory or WHO prequalified laboratory (https://extranet.who.int/pqweb/medicines/prequalified-lists/sf-quality-control-labsrom) in addition to the batch analysis report from the manufacturer.	3 years
Category 3	Full dossier with product registration certificate from category 1 country	5 years
Category 4	WHO Pre-qualified products	5 years

9 Requirement Criteria of Applicants and applications

9.1.1 The manufacturer shall designate a local representative by issuing an authorization letter, indicating that all responsibilities in communicating on behalf of the manufacturer shall be done by the local representative to the authority which include supplying all the relevant information for product registration.

9.1.2 The designated or assigned local representative can then take the responsibility as the applicant in supplying the required information to the authority for the registration procedure.

9.1.3 The applicant shall be registered as an authorized medicine importer under the authority as per the criteria of medicine regulation.

9.1.4 The person or an authorized representative established in Maldives, shall take full responsibility of the medicine that is going to be in the market, which includes, informing the authority of any variations in the product after issuance of MA, recalling the registered medicine if required, and providing PSUR's of the product once placed in the market as per criteria set by the authority. It is the responsibility of the MA holder of the product to ensure that the product comply with the specification of the manufacturer throughout the Supply chain. The evidence of these shall be documented with the applicant and shared with the authority when needed.

9.1.5 The applicant shall have an established system for reporting and handling adverse drug reactions and for these focal points shall be identified and documented. The focal point shall closely liaise with the authority and shall provide the needed information to the authority. This system shall include market safety information of the product as well.

9.1.6 All electronic documents submitted shall be signed and endorsed unless such documents can be verified from the regulatory authorities.

9.1.7 All documents submitted for registration purpose shall be in English language and shall be signed and endorsed.

9.1.8 MFDA shall reject the applications which does not fulfill the criteria as mentioned in this clause.

9.1.9 For in-house methods, other than official methods as per the official pharmacopeias, in house method validation report shall be submitted which shall have the parameters or validation characteristics of:

a. Specificity
b. Accuracy
c. Precision (repeatability, intermediate)
d. Linearity & Range
e. Detection Limit
f. Quantitation Limit
g. Robustness

For:

1.Identification
2.Assay (content & dissolution measurement only)
3.Impurities (quantitative & limit test)

9.1.10 The in-house method shall also provide document evidence for the Identification of sources and quantitation of potential errors, determination if method is acceptable for intended use and Establish proof that a method can be used for decision making

9.1.11 The in-house method validation report shall be endorsed by a third party. The third party can be an accredited laboratory, regulatory authority or any other external or internal assessment body.

10 How to Apply

10.1.1 Application shall be submitted Online via Dhirithi portal 'https://dhirithi.egov.mv'

10.1.2 In order to do so, the applicant shall first register as a user in Dhirithi portal using the form available on the MOH website, under, https://health.gov.mv/dv/downloads/dhirithi-portal-user-registration-form. The form is also available in Dhrithi portal under "Publications". If the applicant is an authorized medicine importer, they would already be registered as a Dhirithi user and hence can directly apply for medicine registeration.

10.1.3 Once the applicant is registered in the Dhirithi portal, the applicant can then select "medicine registration" and submit the dossier.

10.1.4 See **Section 11.1, for** guidance on preparation of dossier.

10.1.5 To ensure all mandatory documents are submitted, the applicant shall refer to **Annex 2** *"Applicant checklist"* and submit it along with the application via Dhirithi portal.

11 Pharmaceutical Product Registration Process

11.1 Preparation of Dossier

11.1.1 A detailed compilation of documents known as a Dossier, is required for product registration in order to assure the product's safety, quality and efficacy. The documents shall be submitted in accordance to the requirements as mentioned in this guideline.

11.1.2 The documents required for the registration of a product differ according to the category the product falls under, as presented in Annex 4: "Reference country categorization for pharmaceutical product registration".

11.1.3 The acceptance criteria of each document are indicated in Section **11.2**, of this guideline. Any application with missing documents or documents that do not meet the criteria set, will be rejected.

11.1.4 The reason for the rejection will be indicated in the Dhirithi portal for the applicant to see.

11.1.5 All documents shall be submitted in English language.

11.1.6 A separate dossier is required for each product i.e., products containing the same ingredients but made to different specifications in terms of strength, content of ingredient(s), dosage form, description and pack size etc.

11.1.7 For tablet and capsules if the it under goes the same production and packing process under the same quality assurance system, it will be considered as a one product regardless of its pack size. Example: A having 12 table per strip and 10 tablet per strip will be considered as one product if the product under goes the same process and have the same labelling information on the product.

11.2 Acceptance Criteria of the Documents Submitted in a Full Dossier

11.2.1 The table below contains a list of documents required in a full dossier and the information that shall be included in each document for it to be accepted by the authority.

11.2.2 As all applications does not require a full dossier, in order to determine the type of dossier application and the required documents, refer to Section 7 and Annex 4: "Reference country categorization for pharmaceutical product registration".

11.2.3 Refer to the table below for the documents and acceptance criteria. The document code and title are the same as they appear on the Dhirithi portal for ease of interpretation.

Code	Document Title	Acceptance Criteria
A1	**Letter of Appointment (Annex 2)**	**Shall be in the format as attached in Annex 1 of this guideline**
B	**Pharmaceutical Information Sheet**	**The pharmaceutical information shall be supplied by the manufacture with signed and endorsed including the following information:** A) API information: Shall include the API information as per one of the following criteria: 1) Confirmation of API Prequalification document (CPQ) as specified in Annex; OR 2) Certificate of suitability of the European Pharmacopoeia (CEP) as specified in Annex; OR

		3) Technical Information on the active pharmaceutical ingredient/s as specified in Annex; B) Brand name, Trade name or Product name: Shall provide this information in the format as provided by the manufacturer 1) The product name shall be entered according to the product label submitted and shall tally with the product name mentioned in Certificate of Pharmaceutical product (CoPP) submitted. 2) The strength of the active ingredient shall generally be included as part of the product name to allow differentiation between different products containing the same active ingredient. C) International Nonproprietary Name (INN) or the Active Pharmaceutical Ingredient (API) or Generic name: Shall provide the information with the details as mentioned below: 1) The name and amount of active ingredients present in the formulation and in the form of salts or chelates shall be clearly stated. Example: *Each film coated tablet contains Calcium carbonate equivalent to elemental calcium 500mg* 2) If more than one active ingredient is present in the preparation, it shall be separated by a + between each active ingredient. *Example.: Calcium carbonate 500mg + Docosahexaenoic Acid 150mg+vitamin D3 200IU* D) Non-active ingredient or Excipient: Shall provide these details as mentioned below: 1) All Non-active ingredients and all proprietary ingredients (e.g., colorants, flavoring agents, etc.) used in the product shall be mentioned with the composition with the grade of the excipients.

		2)In case of cough and cold preparations and paracetamol preparations, the exact grade of the excipients shall be mentioned with supporting documents. 3)For all the pediatric oral formulations including cough, cold and paracetamol formulation the certificate of analysis (COA) shall be submitted for all the excipients used, specifically if glycerin or glycerol or propylene glycol is used, verifying that it does not contain the impurities diethylene glycol (DEG) and ethylene glycol (EG). 4)Manufacture validation protocols of the excipients shall be submitted specifically those that are at a risk for diethylene glycol (DEG) and ethylene glycol (EG) contamination. For such excipients each container of the excipients shall be tested for purity and validity and evidence documents shall be submitted. 5)The test mentioned in point 4 of the clause shall be as per the official monogram for purity. E) Pharmacopeia standard / Formulation of the product: Shall provide the details as mentioned below 1) All Active pharmaceutical ingredients and all excipients in the product shall be listed with their Pharmacopeia standard i.e., British pharmacopeia (BP), US pharmacopeia (USP) or Indian pharmacopeia (IP) or any international accepted pharmacopeia 2) If there is no pharmacopeial formulation as mentioned in point 1), method validation report of the in-house method shall be provided which has to be endorsed by a third party. The third party can be an accredited laboratory, regulatory authority or any other external or internal assessment body.

		F) Pharmaceutical Dosage Form: Pharmaceutical dosage form is defined as the physical form of the medicine which is intended for administration to the patients: 1) Dosage form shall be as specific as possible with respect to the product's actual dosage form. *Example: Film-coated Tablet instead of Tablet, sustained release tablets instead of tablets* 2) In certain cases, the dosage form may also include information about the container closure system. *Example: pre-filled syringe, spray pump and pressurized container*. G) Strength: Strength is defined as the amount of active pharmaceutical ingredients in the dosage form. 1) Strength shall be provided for all API's including if the product is a combination drug. 2) Each strength shall be separated with a "+" Example.: 500mg + 250mg H) Volume of the preparation: Applicable for liquid and semi solid dosage forms like oral liquids, injectables, creams and ointments etc and the volume shall be clearly mentioned as follows: 1) Volume is not applicable for Tablet and capsules 2) For semi-solid dosage forms (i.e., ointments, pastes, cream, gels), liquid dosage forms (i.e., suspensions, syrup, liquid for injection), powders, suppositories and MDI's, volume shall be indicated as per product label. I) Product description, Container type and Pack sizes: shall provide this information:

		1) Description of primary packaging shall be defined with the pack size. *Example blister pack of 12 tablets* *2)* Description of secondary packaging shall be defined with the pack size. Example *12 tablet blister pack of 10 blisters equal to total 120 tablets in 1 box* 3) Length, width, height of primary and secondary packaging shall be provided in detail 4) Weight of product which is submitted for registration. Shall indicate the deviation level for the weight 5) Odor description of the product submitted for registration shall be submitted 6) Visual description of the product shall be submitted including the shape, size, color any engraving or any other detail of the product. 7) Preparations whose primary packing is plastic or if the preparation comes in direct contact with the plastic container shall provide studies on such containers to demonstrate the safety of the material used to the preparation. J) Route(s) of Administration: 1) All routes of administration proposed for the product shall be included and specified accordingly. K) Indication or Use of the product: 1) The intended use or the indication of the product shall be clearly specified. *Example: Used for upper respiratory infections* L) Therapeutic Class according to WHO ATC Index shall be indicated with: 1) The WHO ATC code 2) WHO ATC classification

		3) Shall be provided for each therapeutic indication proposed for a product. M) Storage conditions of the product shall be provided: *1)* The condition in which product shall be stored and kept shall be clearly specified*. Example temperature, humidity etc. Of the product storage shall be specified* 2) Non-numeral statements such as *"Store in a cool dry place"* is not encouraged. N) Shelf life of the product: The shelf life is the period between the execution of the preparation and its expiry date. 1) Product Shelf life shall be specified in months. O) Dispensing Category in country of origin shall be specified: 1) If the product is a prescription only medicine (POM), over the counter (OTC), Hospital use etc shall be defined as per the registration of the product in the country of origin
C2	**Manufacturer responsible for lot release of the Finished Product**	1) Full address of the manufacturer shall be provided with site and country of origin including the phone number, fax, e-mail 2) Contact details of the manufacturer shall be provided that can be reachable if needed. 3) This contact shall provide further information and verification if needed by the authority and shall be responsive to the queries sent from the authority.
C3	**Manufacturer responsible for packaging of the Finished Product, if different.**	1) Full address of the manufacturer shall be provided with site and country of origin including the phone number, fax, e-mail 2) Contact details of the manufacturer shall be provided that can be reachable if needed.

		3) This contact shall provide further information and verification if needed by the authority and shall be responsive to the queries sent from the authority.
C4	**Manufacturing License**	A manufacturing license is a permit issued by the regulatory authority of the country of origin to manufacture medicine and medicinal preparations. 1) The manufacturing license shall have at least validity of 6 months at the time of submission. 2) The manufacturing g license shall contain date of issue, expiry, identity of issuing authority, the activities or thew products covered under the license and full manufacturing site address 3) The manufacturing license shall be self-attested and notarized copy.
C61	**Valid GMP certificate**	Good Manufacturing Practices (GMP, also referred to as 'cGMP' or 'current Good Manufacturing Practice') is the aspect of quality assurance that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification. GMP defines quality measures for both production and quality control and defines general measures to ensure that processes necessary for production and testing are clearly defined, validated, reviewed, and documented, and that the personnel, premises and materials are suitable for the production of pharmaceuticals and biologicals including vaccines. GMP also has legal components, covering responsibilities for distribution, contract manufacturing and testing, and responses to product defects and complaints. ***Source: WHO*** 1) Proof of GMP compliance (valid GMP certificate) shall be submitted for all the sites relevant to the product 2) A color scanned copy of the original or certified true copy of GMP certification document issued by the relevant drug regulatory agency shall

		be submitted, certifying that the manufacturer concerned complies with current applicable GMP standard. 3) GMP Certificate shall have the following information; date of issue, identity of issuing authority or agency approving GMP certificate, validity of the GMP, manufacturing site address and dosage forms of productions. 4) GMP Certificate shall have the validity of 6 months at the time of submission. 5) If the GMP does not have the 6-month validity, the client shall submit proof document requesting to renew the GMP from the country of origin and hence these applications shall be put on hold till the new GMP is submitted. Once the new GMP certificate is submitted, registration of the product will be issued 6) If the validity period or expiry date is not stated on the GMP Certificate, the applicant shall supply supporting documents to confirm the validity period of the GMP certificate. 7) Commitment letters of GMP renewal are not accepted. 8) The names and addresses of manufacturer(s)/repacked(s)/batch releaser(s) shall be consistent with the information provided in the GMP certificate 9) The specific dosage form applied for registration shall be mentioned in the GMP 10) Shall submit with valid GMP certificate, the most recent GMP inspection report or a summary of the inspection report endorsed by the inspection authority.
C7	**Proof of Validation of the Manufacturing method**	As per ICH recommendations, copies of the validation process of Manufacturing method shall be provided including: 1) Short description of the process with a summary of the critical processing steps or critical process parameters to be monitored during validation.

		2) API validation report 3) Excipients validation report 4) Finished product specification report 5) Finished product specification report, specifically tested for Diethylene Glycol and Ethylene Glycol impurities in oral cough and cold preparations 6) Details of analytical methods 7) In-process controls proposed with acceptance criteria 8) Additional testing intended to be carried out (e.g., with proposed acceptance criteria and analytical validation as appropriate) 9) Sampling plan - where, when and how the samples are taken 10) Details of methods for recording and evaluation of results 11) Proposed timeframe. 12) Any variations from the validation protocol shall be documented with appropriate justification 13) Following completion of the validation, a report containing the following information signed by the authorized person shall be provided: • Batch analytical data • Certificates of analysis • Batch production records • Report on any unusual findings, modifications or changes found necessary with appropriate rationale • Report of the validation studies shall be submitted with a conclusive statement of the results, comments on any deviations observed, including recommending changes to correct deficiencies. 14) Refer to ICH Quality Guidelines Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Section 12 for further reference.

C8	**Standard Batch size Quantity**	1) Shall submit the information specifying Label claim, Batch size, Quantity of all active ingredients and excipients per batch and per dosage form at relevant stages of manufacture, Overages and other adjustments with justification 2) For multiple batch sizes, the batch formula for each batch size is to be provided
C9	**Technical Specification and source of all material(s)**	**Technical specification of all excipients and API(s) shall be provided indicating the pharmacopeial specification followed:** 1) Specification provided shall be consistent with label claim 2) Certificate of analysis (CoA) of all raw materials including all active ingredients and excipients shall be provided along with specifications 3) The quality of the raw materials used in the production of the drug substance (or drug product) shall meet standards appropriate for their intended use. 4) The quality of the excipients used in the drug product formulation (and in some cases, in the drug substance), as well as the container/closure systems, shall meet pharmacopeia standards, where available and appropriate. Otherwise, suitable acceptance criteria shall be established for the non-pharmacopeia excipients. 5) Information on measures taken to ensure the quality and control of these materials shall be provided. 6) Source of all excipients and API shall be listed and the origin or source of the API and excipients shall be approved by the manufacturer and this document shall be provided. 7) Shall submit documents stating that all excipients used are pharmaceutical grade or grade approved for manufacturing the pharmaceutical product. 8) A signed statement shall be provided by the manufacturer indicating that all excipients and API(s) are obtained through approved vendors in the country of origin.

		9) The manufacturer shall submit document evidence on how vendor assessment is done for raw material and excipients.
C10	**Brief profile of Manufacturer(s)**	1) A brief description of the manufacturer, when it was established and the products manufactured shall be submitted 2) Shall Provide a short description of accreditations, achievements and standards practiced of the manufacturer 3) Shall Provide list of products manufactured and specify those currently marketed in the country of origin. 4) Shall provide a list of products manufactured and exported to other countries, specifying which products are exported to which country
CM1	**Company profile**	1) Shall include a detailed profile of the company including but not limited to history, accreditations, and standards practiced. and international/national levels of recognition achieved, company information, staff, organizational chart, equipment used, quality control procedures used, etc for all new companies. 2) A detailed Company profile is not required for companies that already have a pharmaceutical product(s) registered in Maldives. 3) For all new sites also requires company profile documentation. 4) Company profile is also required in instances of a major change brought to a company that has previously registered a product in Maldives 5) Shall also State whether the company is manufacturing under loan license or not. If so, shall include all details.
C11.0	**Manufacturing plant layout and machinery involved**	1) Shall include a list of equipment which is relevant to the product under application

		2) Manufacturing plant lay-out shall be clear, legible and relevant to the product under application
C11.1	**Manufacturing and Packaging process**	1) Process flow chart of the whole process of the manufacturing of the product shall be provided identifying the critical control points at every stage 2) Manufacturing monograph shall be provided 3) An executed Batch Manufacturing Record for the product under application shall be provided
C12	**List of personnel, their responsibilities and qualifications**	1) Name, qualification and experience (in years) of the authorized key personnel shall be provided including: • Head of Quality assurance, Quality Control, Storage and production etc., where possible shall provide signatures of the personnel • These Information shall be up to date.
C13	**Letter from Manufacturer to MFDA**	As mentioned in clause 5.4.1 of this document, the manufacture shall submit a letter to the authority identifying the responsible local representation for the product and this letter shall contain and not limited to: 1) Manufacturer details 2) The name and address of local representative authorized to apply for product registration on the manufacturer's behalf 3) Product details 4) Name, designation and signature of the authorizing personnel of the manufacture
C14	**Regulatory decisions taken on this Finished Product from any drug**	1) A formal, signed statement from the manufacturer and/or MAH is required stating that no regulatory actions such as recalls, bans or alerts have been

	regulatory authorities	issued for any batches of the product under applications by any National Regulatory Authorities including that of the country of origin. 2) If any actions as such have been taken by any National Regulatory Authorities regarding product quality, safety and/or efficacy, shall please provide full details with the endorsed statement of how the issue was resolved.
D3	**Certificate of a Pharmaceutical Product (CoPP)**	1) CoPP shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products. 2) A color scanned copy of the original or certified true copy of CoPP certification document issued by the relevant drug regulatory authority of the country of origin shall be submitted which necessarily does not require to be country specific 3) CoPP shall have the following information: • Date of issue • Expiry date • Product name • Label claim • Excipients (preferred) • Name and address of Manufacturer • Registration status in exporting country • Market availability of product in the exporting country • Name and address of issuing authority 4) CoPP Certificate shall have validity of 6 months from the time of submission of the application 5) If the certificate is nearing its expiry, evidence of application or under process letter for renewal issued by the same licensing authority shall be submitted along with the current CoPP.

		6) If the expiry of the CoPP is not mentioned in the certificate, evidence document shall be submitted for assurance of the validity
D4	**Registration status of Finished Product in countries other than country of origin**	List of countries in which the product is registered, including the country of origin, shall be provided along with registration number and date of issue. For this purpose, a link shall be provided with the documents for further verification.
D5	**Proof of registration of the Finished Product in a Category 1 country**	1) This document shall be mandatory when applying under Category 1 option 2 OR Category 3 as per in Annex 4: "Reference country categorization for pharmaceutical product registration" 2) This document shall have the same product as that of the product under application 3) For ease of application, Registration certificate of the product from the Category 1 country is provided as the document evidence as indicated in 1) of this clause. A link shall be provided for verification. If the documents are not in English an official, signed and endorsed translation shall be provided.
E2	**Copy of the Finished Product specification**	1) The finish product specification report shall be based on a reference to an official monogram and if an in-house method is used it shall be endorsed by a third party. The third party can be an accredited laboratory, regulatory authority or any other external or internal assessment body. 2) As per ICH recommendations, finished product specification shall include the following information: * • Description: a qualitative statement about the state (e.g., solid, liquid), shape and color of the drug substance • Identification: Identification tests shall be specific for the new drug substance. • Assay: A specific, stability-indicating assay to determine strength (content) in % shall be included for all active ingredients.

		• Impurities and Related substance: Acceptance limits shall be stated for specified degradation products, which may include both identified and unidentified degradation products as appropriate. • Water content. • Dissolution. • Uniformity of dosage units. • Microbial limits. • All tests shall specify the pharmacopeial standard used • Shall include reference pharmacopeial standard used for finished pharmaceutical product (FPP) **Please note the tests can vary based on the type of dosage form and additional tests/criteria shall be included in the specification when the tests are relevant to the quality of the drug substance.* Refer to ICH Quality Guidelines Q6A-Q6B Specifications.
E5	**Certificate of Analysis for batch release/Certificate of Analysis of Finished Product (CoA)**	1) This certificate Shall be a notarized true copy 2) This certificate Shall contain the following information: • Name and address of the certifying/notarizing authority • Batch details 3) Batch analyses data from a minimum of 2 batches shall be submitted for the product submitted for registration. 4) Shall include a conclusion specifying that the product is in compliance.
F. 2.1	**Real-Time Stability Data**	1) **Stability** is the ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life.

		2) **Stability tests** are a series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions. 3) **Real-time (long-term) stability studies** refers to experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf-life, to confirm the projected shelf life, and to recommend storage conditions. ***Source: World Health Organization, WHO Technical Report Series, No. 863, 1996*** 4) For registration of the product, the authority shall require the manufacturer to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. The data submitted are obtained from both accelerated and real-time studies. Published and/or recently obtained experimental supporting stability data may also be submitted, e.g. on the stability of active ingredients and related formulations. 5) Both Real time and accelerated stability data shall be submitted **separately.** 6) The objective of stability testing is: 6.1 To select adequate (from the viewpoint of stability) formulations and container closure systems. This is done during the development stage of the product via accelerated stability testing 6.2 To determine shelf-life and storage conditions of the product. This testing is done during the development of the product and for the registration dossier via both Quality assurances in general, including quality control

		6.3 To substantiate the claimed shelf-life of the product. This is done for Registration dossier and is done via real time stability testing. 6.4 To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product. This is done for quality assurance of the product process including quality control and this is done via both Quality assurance in general, including quality control 7) Where the product is to be diluted or reconstituted before being administered to the patient (e.g., a powder for injection or a concentrate for oral suspension), "in use" stability data must be submitted to support the recommended storage time and conditions for those dosage forms. 8) The design of the stability testing program shall take into account the intended market and the climatic conditions in the area in which the drug products will be used. Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows: • Zone I: temperate. • Zone II: subtropical, with possible high humidity. • Zone III: hot/dry. • Zone IV: hot/humid. 9) In a stability study, the effect on the product in question of variations in temperature, time, humidity, light intensity and partial vapors pressure are investigated. The effective or mean kinetic temperature therefore reflects the actual situation better than the measured mean temperature; a product kept for 1 month at 20°C and 1 month at 40°C will differ from one kept for 2 months at 30°C. Moreover, the storage conditions are often such that the temperature is higher than the average meteorological data for a country would indicate.

		10) For registration purposes, test samples of products containing fairly stable active ingredients shall be taken from two different production batches, in contrast, samples shall be taken from three batches of products containing easily degradable active ingredients or substances on which limited stability data are available. The batches to be sampled shall be representative of the manufacturing process, whether pilot plant or full production scale. Where possible, the batches to be tested should be manufactured from different batches of active ingredients. 11) Detailed information on the batches shall be included in the test records, namely the packaging of the drug product, the batch number, the date of manufacture, the batch size, etc. 12) For products containing new APIs, data from stability studies shall be provided on at least three primary batches. Two of the three batches shall be at least pilot-scale batches and the third batch can be smaller, if justified. 13) For products containing existing APIs (e.g., generics), data shall be provided on not less than two batches 14) Long term or Real-time stability data shall be provided for the duration of the proposed shelf life of the product with storage condition of 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH. 15) Accelerated Stability Data shall be provided for minimum 6 months with storage condition of 40 °C ± 2 °C/75% RH ± 5% RH 16) For products intended for storage in a refrigerator: • Long term stability data shall be provided for the duration of proposed shelf life with storage condition of 5°C ± 3°C • Accelerated Stability Data shall be provided for minimum 6 months with storage condition of 25 °C ± 2 °C or 30 °C ± 2 °C 17) For products intended for storage in a freezer:

		• Long term stability data shall be provided for the duration of proposed shelf life with storage condition of –20 °C ± 5 °C • Accelerated Stability Data shall be provided for minimum 6 months with storage condition of 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C . 18) The testing shall cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content and functionality tests (e.g., Appearance, Average weight, Disintegrating time, pH, Dissolution time, Relative substance, Microbial Limit test and Assay) 19) Analytical procedures shall be fully validated including: • The orientation of the product during storage, i.e., upright, on the side or inverted, where relevant. • Date started and end date (Manufactured date/ Expired date) Signature of quality control • Packaging of the product 20) A conclusion statement shall be submitted with both real time and accelerated stability data indicating that the stability data is acceptable. *****The results shall be presented in an appropriate format such as tabular, graphical, or narrative description.*** ***Refer to ICH Quality guidelines Q1A – Q1F Stability***

F12 (2.1)	**Accelerated Stability Data**	1) **Accelerated stability testing** refers to Studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real-time stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. 2) **Accelerated stability tests** provide a means of comparing alternative formulations, packaging materials, and/or manufacturing processes in short-term experiments. As soon as the final formulation and manufacturing process have been established, the manufacturer carries out a series of accelerated stability tests which will enable the stability of the drug product to be predicted and its shelf-life and storage conditions determined. Real-time studies must be started at the same time for confirmation purposes. Suitable measures should be taken to establish the utilization period for preparations in multidose containers, especially for topical use. ***Source: World Health Organization, WHO Technical Report Series, No. 863, 1996***
F3	**Stability Report and statement**	3) A brief summary of stability report shall be established and shall be submitted with the dossier giving details of the design of the study, as well as the results and conclusions. The stability of a given product, and therefore the proposed shelf-life and storage conditions, must be determined on the basis of these results 4) An official statement issued by the manufacturer that all stability tests are performed of the same formula, manufactured at the same site and packed

		in the same packing material as the product shall be provided with the dossier. This statement shall be signed and endorsed by the manufacturer.
G1 (1.1)	**In vivo Bioequivalence Study** • **Required for all immediate release oral solid dosage forms only (i.e., tablets, capsules)**	The Bio equivalence study is the comparative analysis between the innovator or bench mark product with that of the product submit for registration to assure that the product submitted for registration can show the same efficacy as that of the innovator or benchmarked product. 1. The reference product used in the BE study shall be: • An innovator drug OR • A similar drug product with existing BE studies against an innovator drug** **If reference product is not an innovator product, proof shall be provided that the reference product used in study has established bioavailability comparative to the innovator product 2. The study report shall contain the following information: • Information about the reference and test products, such as the product name, strength, dosage form, batch number, manufacturing site, batch size of the test product, etc. The reference product shall have the exact same strength and in the exact same formulation the product submitted for registration. • Certificates of Analysis of the reference and test products used in the BE study, including the batch size of the test product and manufacturing/expiry date of both products (where applicable) • Bioanalytical study report summary and description of the bioanalytical method validation

		3. A complete bioequivalence study report including all appendices and data and conclusive statement of the end results shall be provided. 4. A signed statement confirming that the test product used in the BE study is the same formulation and is manufactured by the same process as the product submitted for registration shall be provided
		5. Bio waiver requests: • The biopharmaceutics classification system (BCS) classified APIs into the following groups based on level of solubility and permeability. • BCS class I HIGH solubility and HIGH permeability • BCS class II LOW solubility and HIGH permeability • BCS class III HIGH solubility and LOW permeability • BCS class IV LOW solubility and LOW permeability • As per criteria set by WHO, products containing API's belonging to BCS class I and BCS class III qualify for a BCS-based biowaiver request, provided that the following criteria is met and surrogate information is submitted. 6. Criteria for biowaiver** • The API shall belong to BCS class I, or BCS class III. • The product shall not be a narrow therapeutic index (NTI) drug. **Please note that biowaivers submitted for pharmaceutical products that do not fit the criteria described will not be accepted even if a comparative dissolution profile is provided. 7. Data to support requests for biowaiver. • Data supporting high solubility of product • Data supporting high permeability of product 8. A satisfactory dissolution study with reference product as per criteria described below:

		• Demonstrate that the excipients used are well-established and do not alter the pharmacokinetics of API. 9. Biowaiver request for multiple strength product • If the test product used in the BE study is of a different strength from that proposed for registration, a signed statement confirming that the test product used in the BE study has the same qualitative composition and quantitatively proportional composition and is manufactured by the same process as that proposed for registration shall be submitted. 10. Additional justifications and relevant supporting documents for biowaiver requests shall be submitted if requested by the authority. 11. A statement signed and endorsed by the manufacturer shall be submitted stating the conclusion of the bioequivalence study indicating that the product applied for registration is bioequivalent to the innovator or the reference product
G1 (1.2)	**In vitro Dissolution Test**	1. **The dissolution profiles shall be submitted by following the method described in the monograph of the relevant pharmacopoeia.** 2. **If in-house method is used it shall be endorsed and validated by a third party** 3. **The following data shall be submitted:** 4. Information about the reference and test products, such as the product name, strength, dosage form, batch number, manufacturing site, batch size of the test product, etc. 5. The dissolution apparatus, media, results and the conditions at which it is operated shall be specified and in accordance with an established pharmacopeia dissolution test guideline. (e.g. European Pharmacopoeia (Ph. Eur.), United States Pharmacopeia (USP) etc.) .

		6. The reference product shall have the exact same strength and in the exact same formulation the product submitted for registration. • A complete Dissolution study report including all appendices and data and conclusive statement of the end results shall be provided. • A statement signed and endorsed by the manufacturer shall be submitted stating the conclusion of the dissolution study indicating that the product applied for registration is in compliant with the requirements stated.
H5	**Product Label/Packing insert**	**1. Product label shall contain the following information;** • Brand name, Generic name, strength and dosage form • Full manufacturing site address of the product. Exemptions: In case if the manufacturer is not defined in the label for category 1 manufactured product, a specific code shall be in the label to trace the manufacture name and address and this shall tally with the submitted document. • Direction for use • Special precaution if applicable • Shelf life • Storage condition • Shall be submitted in English **2. The draft artwork of the outer carton labels shall be in the actual format, design and colour that are to be printed.** **3. Separate labels shall be submitted for each pack size of the product.**
		4. **Packing insert/Patient leaflet criteria: Packing** insert/ Patient leaflet/ SmPC shall be clear, concise and shall contain the following information:

		• **Name of the product:** The brand name shall be followed by both the strength and the pharmaceutical form. • The International Nonproprietary Name (INN) or the usual common name of the active substance shall be used when referring to properties of the active substance(s) rather than the brand name. • **Strength: The** strength shall be the relevant quantity for identification and use of the product and shall be consistent throughout other sections of the packing insert/patient leaflet • **Pharmaceutical form/Dosage form:** The dosage form of a product shall be described by a single full standard term according to the relevant pharmacopeia used. • **Composition:** Full details of the qualitative and quantitative composition in terms of the active substance(s) shall be provided as a separate subheading qualitatively, and, quantitatively. • The active substance shall be written in its recommended INN, accompanied by its salt or hydrate form if relevant. • The quantity of the active substance shall be expressed per dosage unit and in an internationally recognized standard term. • **Indication:** The indication(s) shall be stated clearly and concisely and shall define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. • **Where appropriate it shall define the target population especially when restrictions to the patient populations apply.** • **It shall be stated in which age groups the product is indicated, specifying the age limits**

		• **Dosage:** The dosage shall be clearly specified for each method/route of administration and for each indication, as appropriate. • Dosage adjustments or other posology related information in specific patient groups shall be stated where necessary, in well-defined sub-sections, e.g. elderly population, renal impairment and other relevant special population • If the product is indicated in the pediatric population, dosage and administration recommendations shall be given for each of the relevant subsets • **If there is no indication for the product in some or all subsets of the pediatric population, no dosage recommendation can be made, but available information shall be provided using the following standard statements such as *"No data are available"* or *"The safety and efficacy of the product in children aged x to y has not been established"*** • **Administration:** The route of administration and concise relevant instruction for correct administration and use shall be given here. Information on instructions for preparation or reconstitution shall be provided • Any specific recommendation for use related to the dosage form shall be explained e.g., Tablet shall not be crushed due to "xyz" • **Contraindications: All** situations and circumstances where the medicinal product shall not be given for safety reasons shall be clearly defined and explained • **Special warnings and precautions for use:** Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions

		• Any special precautions related to the administration of the product by healthcare professionals, the patient or caregivers • Any need for specific clinical or laboratory monitoring • Any warnings necessary for excipients or residues from the manufacturing process • Any and all particular risks associated with using the medicinal product shall be provided in this section. • If the product is indicated in any subset of the pediatric population or special population, the risk associated with use of the product in the pediatric population or special population shall be present • **Critically important safety information may be included in bold and/or within a box.** • **Drug interactions and other forms of interactions:** This section shall detail recommendations regarding the use of this medicinal product in relation to the potential for drug interactions to occur based on the pharmacodynamics properties and in vivo pharmacokinetic studies of the medicinal product. • Information on other relevant interactions such as with herbal medicinal products, food, alcohol, smoking, or pharmacologically active substances not used for medical purpose, shall also be given. • **If no interaction studies have been performed, this shall be clearly stated** • If there are patient groups in which the impact of an interaction is more severe, the details of such interactions shall be provided • **Fertility, pregnancy and lactation:** Recommendations for use in pregnant or lactating women and in women of childbearing

		potential shall be provided with reasoning and clinical/animal data where available. • Efforts shall be made to update the recommendations for use during pregnancy and lactation on the basis of increasing human experience in exposed pregnancies which eventually supersede the animal data. • **If there is no data available at all, then this shall be clearly stated.** • **Side effects/Undesirable effects:** This section shall include **all** adverse reactions from clinical trials, safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility. This section shall be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product. • **Overdose:** Describe acute symptoms and signs of different dose levels of the medicinal product based on all available information including accidental intake, mistakes and suicide attempts by patients. • Taking into account all relevant evidence, describe the management of an overdose e.g. in relation to monitoring or use of specific agonists/antagonists, antidotes (no dosage recommendations) or methods to increase elimination of the medicinal product such as dialysis. • **Pharmacodynamics/Pharmacokinetic properties: Pharmacokinetic**/Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the

		pharmaceutical formulation marketed shall be given in this section. • **Shelf life** • **Special precautions for storage** • **Date of publication/revision** ***Please note that the information listed above is not meant to be exhaustive and any information that is vital in the safe and effective administration of the product by healthcare professionals shall be included.***
I1	**Cost and Retail price**	1. Cost price (USD) shall be provided **specifying the quantity**. E.g., per tablet or bottle 2. Proposed price for retail in Maldives (USD) be provided **specifying the quantity**. Eg. per tablet or bottle 3. The price structure shall include the name of the product.
J1	**Proof of Standardization**	**1. Only applicable for Category 1 Option 2** 2. A document from the parent company stating the product manufactured from the proposed site is up to the standard of the parent company OR a recent audit or assessment report of the site by the parent company etc.

11.3 Dossier submission and evaluation

11.3.1 Once the dossers are submitted, it will be checked for document completion and legibility. If all the requirements as per the acceptance criteria is fulfilled, then only the dossier will be accepted.

11.3.2 MFDA shall have the right to reject incomplete dossiers and hence it's the applicant's responsibility to ensure that all are in accordance to the requirements as mentioned in point 11.2

11.3.3 If all the requirements are complete, the dossier will be accepted and a submission fee of 100 MVR (hundred Maldivian Rufiyaa) shall be paid via Bandeyri Pay (https://bandeyripay.finance.gov.mv/), within 5 working days from the time of dossier acceptance to Dhirithi portal. If the payment is not made within the given 5 days, the dossier will be rejected. This submission fee is non-refundable

11.3.4 Once the payment is made the evaluation process of the dossiers will be initiated with regards to safety, quality and efficacy of the product. Evaluation and assessment of the dossier will be completed within 30 working days from the date of submission fees received to the authority.

11.3.5 Dossiers that require further clarification will be put to "Need clarification" status on Dhirithi portal. The clarification requested by the authority shall be resolved within 10 working days by the applicant, otherwise the dossier will be rejected.

11.3.6 In the case of a rejection, the reason for the rejection will be specified.

11.3.7 The dossier evaluation process may be prolonged due to the time taken by the applicant to respond to the authority's request to provide additional information or further clarification.

12 Approval by the National Pharmaceutical Board (NPB)

12.1.1 Upon successful evaluation of the dossier, the documents are submitted to the National Pharmaceutical Board (NPB) for final approval or rejection. The status will read as "Pending committee decision" at this stage on Dhirithi portal.

12.1.2 If approved by the NPB, the applicant will be notified to pay a registration fee of 300 MVR via Bandeyri Pay within 5 working days. If the payment is not made within the given five days, the client will be informed through via email. If the payment is not made within 10 working days of the notification, the application will be rejected. The applicant has to process this dossier as a new application again.

12.1.3 If rejected by the NPB, the dossier will be rejected and the applicant will be notified via Dhirithi portal indicating the reason of rejection.

13 Issuing the Certificate of Registration of a Pharmaceutical Product and agreement signing

13.1.1 After the registration fee has been paid, the authority will issue a Certificate of Registration of a Pharmaceutical Product and Agreement to the applicant within 15 working days.

13.1.2 The applicant will be notified via email to report to MFDA 2nd floor for the agreement signing and certificate issuance within this period. The applicant shall bear the responsibility of attending the signing and failure to attend within 15 working days of notification will result in cancellation of the agreement.

13.1.3 The product can only be imported, distributed and sold in the country once it has been registered and added to the Approved Drug List (ADL).

13.1.4 Please refer to Annex 3 “Registration process flow chart” for a summarized version of the complete pharmaceutical product registration process with time lines.

14 Submitting Periodic safety update reports (PSURs) to MFDA

14.1.1 PSURs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorization. These data include reported adverse reactions, any reported unknown side effects, and market analysis data of the product.

14.1.2 For all registered products, PSUR shall be submitted during the renewal of the registration

15 Sample Criteria:

15.1.1 Physical sample of the product is not required for the re-registration if there is no change in the product label or packing. However, it is encouraged to submit 1 sample to verify the product details with the submitted documents.

15.1.2 Samples shall tally with the documents submitted for registration, otherwise the application shall be rejected.

15.1.3 For all new products samples shall be summited. For all solid oral dosage forms 60 units shall be submitted (Eg 60 tablets, 60 capsules etc). For Liquid dosage forms 3 units shall be submitted. (Eg: 2 bottles of oral liquids. 2 vials /ampoules of injections ect)

15.1.4 Samples approval shall be applied through dhirithi portal and requests shall be attended and approval given within 10 working days.

15.1.5 Samples shall only be imported once sample authorization approval has been issued.

15.1.6 The imported sample shall be handed over to MFDA port staff once its cleared from the ports and these samples shall be handed over to product registration unit with the sample release sheet

15.1.7 In case an application is rejected, the samples shall be kept in MFDA for 60 days from the date of rejection and then it will be disposed.

16 Re-Registration Application

16.1.1 A product that has been registered and been in the market for the duration of registration granted without any issue of quality, safety and efficacy, shall be submitted for re-registration at least 30 days before the expiry date of the current MA validity along with the processing fee.

16.1.2 The general procedure for the renewal of the reregistration is the same as the initial registration.

16.1.3 For the purpose of re-registration, there shall not be any change in the product excluding variations that have been notified and approved by the authority for the specific product.

16.1.4 If the registration of the product is expired and the applicant did not apply for re-registration, the product will be removed from ADL within 1 Month after the expiry. If the applicant wants to register it again the application will be treated as a new application as per the criteria mentioned in this guideline.

16.1.5 All products in ADL if not applied for re-registration before the expiry will be removed from ADL after 1 month of the date of expiry of that specific product

16.1.6 For products in category 2 and option 3 and 4, since the initial registration period is 3 years, for renewal or for re registration, along with the requirements of sixteen point 2, a GMP inspection shall be carried out by MFDA. The cost of this inspection shall be boned by the applicant as per the government rules and regulations. After successful GMP inspection the product shall be re-registered for a period of 5 years.

16.1.7 Products which are registered under this criterion BEFORE shall fulfill this current requirement as per category 2 and option 3 and 4 of Annex 4: "Reference country categorization for pharmaceutical product registration" in this document after the validity period.

16.2 Documents required for Re-Registration Application

16.2.1 Please refer to the following table, detailing the documents to be submitted for a re-registration application.

Code	Document Title	Acceptance Criteria
A1	Letter of Appointment	See **Section eleven point** *"Acceptance Criteria of the Documents Submitted in a Full Dossier"* for the required information of each relevant document
B	Pharmaceutical Information Sheet	
C61	Valid GMP certificate	
D3	Valid Certificate of a Pharmaceutical Product (CoPP)	
E2	Copy of the Finished Product specification	
F12	Accelerated Stability Data	

(2.1)		
F12 (2.2)	Real-Time/Long-term Stability Data	
H5	Product Label/Packing insert	
I1	Cost and Retail price	
12	Submitting Periodic safety update reports (PSURs) for the registration period	
13	CoPP issued from MFDA after registering the product	

16.2.2 Those products which has been imported under pre-authorization approval from MFDA for 3 years can undergo this same re-registration process in order to get the registration status for the product with the assigned validity period. The importer shall submit all the documents as mentioned in 16.2.1 to fulfill the re-registration requirements.

16.2.3 For re-registration, the exact product which was registered shall be submitted. Any change in the product name, dosage, formation, manufacturer and new site shall be considered as a new application and shall submit the full documentation as per the registration criteria.

16.2.4 Declaration letters stating otherwise shall not be accepted.

16.3 Variation Application

16.3.1 Type of Variation: Variations are classified according to the extent of impact it has on the finished pharmaceutical product (FPP).

a. Minor variation: A minor variation is defined as changes that may have minor effects on the overall safety, efficacy and quality of the FPP.

b. Major variation: A major variation is defined as changes that could have major effects on the overall safety, efficacy and quality of the FPP.

16.3.2 Type of notification

a. Immediate notification (IN): Changes that require notification to the authority upon implementation of the change by the manufacturer are given IN status. For IN variations the manufacturer shall submit all required documentation at the time of the variation application submission.

b. Annual notification (AN): Changes that require notification to the authority within 12 months of implementation of the changes by the manufacturer are given AN status and the supporting documentation shall be provided when requested by the authority.

16.3.3 Procedure

16.3.3.1 Variation applications can be submitted through Dhrithi portal or through email. If applying via email, please indicate "Variation application" in the subject column.

16.3.3.2 The relevant information once received is evaluated and submitted to the technical committee of the authority for final approval or rejection. Once approved, the information is updated and the applicant is informed via email or through Dhirithi portal.

16.3.3.3 Depending on the type of variation application it will take 5 to 15 working days for approval of the variation.

16.3.4 Documents and Information required for Variation Application

16.3.4.1 Depending on the type of variation, the documentation to be submitted and method of notification differ. Please refer to the table below detailing the documents to be submitted for different variations.

1. Administrative changes			
Type of variation	**Description of change**	**Documentation required**	**Reporting type**

Minor	Change in the name and/or address of a manufacturer of the FPP. *Note: There shall be no change in the location of the manufacturing site and in the manufacturing operations.*	1. Updated CoPP 2. Updated manufacturing license 3. Updated GMP certificate	IN
Minor	Change in the name or address of a manufacturer/supplier of an API or raw material *Note: There shall be no change in the location of the manufacturing site and in the manufacturing operations.*	1. A formal document from the manufacturer in which the new name and/or address is mentioned.	IN
2. Changes regarding production of API			
Type of variation	**Description of change**	**Documentation required**	**Reporting type**
Major	Replacement or addition of a new manufacturing site or manufacturer of an API	1. A valid testing authorization or a certificate of GMP compliance of the new manufacturer 2. A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and new manufacturing site and tabulated summary of differences 3. Description of batches, copies of certificate of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and new manufacturers and/or sites	IN

		4. A copy of the FPP manufacturer's API specifications 5. A declaration from the supplier of FPP that the route of synthesis, materials, quality control procedures and the specification of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.	
Minor	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer	1. A copy of the old API specifications (of the FPP manufacturer) dated and signed by authorized personnel and a comparative table of changed specifications 2. Justification of the change in API specifications (e.g. test parameters, acceptance criteria, or analytical procedures). 3. Copies or summaries of analytical procedures, if new analytical procedures are used 4. Description of batches, copies of certificate of analysis and batch analysis data and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.	

3. Changes regarding production of FPP			
Type of variation	**Description of change**	**Documentation required**	**Reporting type**
Major	Change in the manufacturing process of the FPP	1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study 2. Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation 3. Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the new process 4. Results of stability testing, generated on at least two pilot batches with a minimum of 3 months of accelerated study and 3 months of long-term study with a stability commitment letter for proposed shelf-life 5. Copies of relevant sections of blank master production documents with changes highlighted and confirmation that there are no changes to the currently accepted production documents other than those highlighted.	IN

Minor	Change in the specifications of the FPP involving test parameters and acceptance criteria	1. Justification for the new FPP specifications 2. Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and changed specifications. 3. Copies or summaries of analytical procedures, if new analytical procedures are used 4. Copies or summaries of validation reports, if new analytical procedures are used. 5. Description of batches, copies of certificate of analysis and batch analysis data and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.	IN
4. Change in the shelf-life of the FPP			
Type of variation	**Description of change**	**Documentation required**	**Reporting type**
Major	1. Extension of shelf life *Note: There shall be no change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage.* 2. Reduction of shelf life *Note: the reduction shall not be necessitated by unexpected events*	1. Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and long-term stability test results for a minimum of two pilot- or production-scale batches for a period sufficient to support the proposed shelf-life.	IN

	arising during manufacture or because of stability concerns	2. Updated post-acceptance stability protocol and stability commitment and justification of change.	
5. Changes regarding label/IPL/packaging of FPP			
Type of variation	**Description of change**	**Documentation required**	**Reporting type**
Major	Replacement or addition of a primary packaging type	1. For sterile FPPs, process validation and/or evaluation studies. 2. Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications) 3. Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photo stability studies, along with stability test commitment letter	IN
Minor	Change in label/IPL	1. Document that highlights/annotates the changes brought to the label/IPL specifying the changes brought 2. Document justifying the change (where applicable)	IN
6. Regarding different pack sizes of the same FPP			

1. Variations in pack size, for oral solid dosage forms (i.e., tablets, capsules) different pack sizes (e.g., 14 tablets and 30 tablets) can be registered in a single application given that all available pack sizes are indicated in the application. Therefore, different pack sizes need not be registered separately nor as variation applications.

2. As for all other dosage forms, a difference in pack size/volume will require a separate application per pack size. (i.e., cream dosage form 10g and 15g)

16.3.4.2 Variations that are not listed in the table will be reviewed and processed by the authority using a risk-based approach and under the recommended guidance of WHO "Guidance on variations to a prequalified product dossier".

16.3.4.3 The list of documentation in the table is meant for guidance purposes and it shall be noted that the authority reserves the right to request further information not explicitly described in the guideline.

16.3.4.4 For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative impact on the safety, efficacy or quality of the finished pharmaceutical product.

17 Documents required for New Drug / New Chemical Entity application

17.1.1 In addition to the general documents in a dossier, documents that are specific to NCE applications which shall be submitted, are listed below:

#	Document	Required Information
1.	Background information and origin of the discovery	– Origin and background of the discovery – Use in foreign countries – Characteristics and comparison with existing drugs

2.	Pharmaceutical and Pharmacological Data	– Studies that demonstrate efficacy and safety over existing medication – Secondary/safety pharmacological studies – Other relevant pharmacological studies
3.	Pharmacokinetic Data	– Absorption, distribution, metabolism and excretion profiles of the NME
4.	Toxicity studies	– Single dose toxicity studies – Repeated dose toxicity studies Genotoxicity studies – Reproductive and developmental toxicity studies
5.	Data from clinical studies	
6.	Information and any decisions taken by other drug regulatory authorities	
7	Post marketing data and any observed adverse events.	

18 Classification of medicine registration.

18.1.1 Registration will be issued under the following classifications which determine the level of access control.

Classification	Remark
Restricted for Hospital and institutional use only: (HI)	– Medicinal products restricted to special expertise and Health facilities and clinics with registered medical practitioners. – These products cannot be kept for sale in pharmacies. – These products can only be imported by designated parties.
Restricted for Hospital use only: (HO)	– These medicinal products can only be imported and registered by designated parties. – These products cannot be kept for sale in pharmacies. – These products are restricted to special expertise for hospitals only

Controlled Drug: C	– These medicinal products are controlled and can only be imported by designated parties. – Within this class, Narcotics cannot be kept in pharmacies for sale. – Controlled Drugs include Narcotics and Psychotropic drugs (Internationally and Nationally Controlled).
Over the counter medicine (OTC)	– These medicinal products can be sold without prescriptions.
Prescription-Only Medicines (POM):	– These medicinal products can only be prescribed by a registered medical practitioner. This product can only be sold with a valid prescription.

19 Rejection, Cancellation or Suspension of Registration

19.1.1 The Maldives Food and Drug Authority reserves the right to reject, cancel or suspend the registration of any product if:

a. There are deficiencies in safety, quality, or efficacy of the product

b. Failure to comply with conditions of registration.

c. Any of the conditions of registration of the product has been contravened.

d. Any report on adverse drug reactions of serious nature has been received from national or international sources.

e. For any other matters as specified by the National Pharmaceutical Board at the time of cancellation.

20 Temporary and permanent ban of the product and/or manufacturer

20.1.1 A company or manufacturer can be temporarily or permanently banned if repeated incidents of quality failure are identified from their products. If the company or manufacturer is permanently banned, the particular company will not be allowed to enter the Maldives market until a period of minimum **5** years have passed. After **5** years from the date of ban, they can apply for the registration with the registration certificate of any regulatory Authority in Category 1 of Reference country categorization for pharmaceutical product registration and the decision will be made by the National Pharmaceutical Board.

20.1.2 If a company or manufacturer is temporarily banned, the products of that company can only enter back into the market as a new applicant under the current procedure. All products of that company shall be registered as per the criteria established by the MFDA.

21 Special approvals and exemptions given by the MFDA

21.1.1 Exemptions in Preauthorization is in reference to the Guideline for Pre-Authorization Approval of Medicines (MTG-RE-PA/GLN-TE 010)

21.1.2 For hospitals to import and use hospital use medicines in their facilities:

a. For hospital use medicines that are essential and low in volume and quantity due to difficulties in acquiring the required documentation for registration, exemption approvals will be given to hospitals to import that specific product.

b. The approvals will be given under a set of conditions by means of a signed agreement between MFDA and the importing hospital.

22 Vaccine approval process during emergencies

22.1.1 Special approvals shall be given for vaccines during emergency after reviewing.

22.1.2 Refer to the regulation requirement for product registration and approval of vaccine in emergency number: MTG/RE-LA/STD-TE 003.

23 Clinician's Request for Approval of New Medicine

23.1.1 This form is introduced to the doctors to request to add new chemicals, new dosage form or new strengths, to the Approved Drug List upon the requirement of the patients, and to make sure to maintain the uninterrupted availability of the medicines.

23.2 Required Documents

a. A completely filled "Clinician's Request for Approval of New Medicine" signed by the requesting doctor and approved by head of the applicants' organization/Health facility.

b. Additional information and the picture shots of the product.

c. Research Paper of the product.

23.3 Process of clinician form

23.3.1 If the application is for a new chemical, new strength and new dosage form, and the form is filled in completely and provides the required document the application will be accepted.

23.3.2 The evaluation will be carried out within the next 45 (Forty-five) working days.

23.3.3 Once the product has been approved by NPB the product will be added to ADL and inform the client within 7 working days.

23.4 Rejection of form

23.4.1 If the application is incomplete or if the application is form for an existing medicine in the ADL, the application will be rejected and informed to the applicant during working 7 days via email.

24 Pre market and Post Market Testing

24.1.1 Once the product is registered, imported and introduced to the market, the product shall be on surveillance as to ensure that the same product registered is in the market and if the product is safe, of good quality and efficacy in accordance to the applied documents for registration.

24.1.2 National Health Laboratory (NHL) is the designated national laboratory for testing pharmaceuticals. Samples which are submitted with the dossiers are also tested from NHL depending on the testing capacity of the product.

24.1.3 Once registered, as part of the post market surveillance, samples will be collected from the market and tested from NHL as well as the designated laboratory from abroad and these results will be published.

25 Legal basis

1. Medicine Regulation R-46 (2014)
2. Medicine Regulation Amendment R-49 (2016)
3. Health Service Act (29/2015)

26 References

1. World Health Organization. (n.d.). *List of stringent regulatory authorities*. World Health Organization. Retrieved from https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs#:~:text=The%20concept%20of%20a%20stringent,international%20regulatory%20and%20procurement%20community.

2. World Health Organization. (2017). (Technical Report Series). *WHO Expert Committee on Specifications for Pharmaceutical Preparations* (Fifty first, Ser. no. 1003, pp. 13–252) Retrieved from https://www.who.int/publications/i/item/9789241210034

3. World Health Organization. (2022). *WHO-Listed Authority (WLA)*. World Health Organization. Retrieved from https://www.who.int/initiatives/who-listed-authority-reg-authorities#:~:text=The%20introduction%20of%20a%20framework,to%20be%20globally%20recognized%2C%20thereby

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5. European Commission Pharmaceuticals. (2009). *A Guideline on Summary of Product Characteristics.* Retrieved from https://www.ema.europa.eu/en/glossary/summary-product-characteristics#:~:text=A%20document%20describing%20the%20properties,Abbreviated%20as%20SmPC.

6. ICH Expert Working Group. (2003). *Stability Guidelines Q1A-Q1F*. International Conference on Harmonization. Retrieved from https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf

7. ICH Expert Working Group. (1999). *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products Q6A.* International Conference on Harmonization. Retrieved from https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf

8. ICH Expert Working Group. (2000). *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7*. International Conference on Harmonization. Retrieved from https://database.ich.org/sites/default/files/Q7%20Guideline.pdf

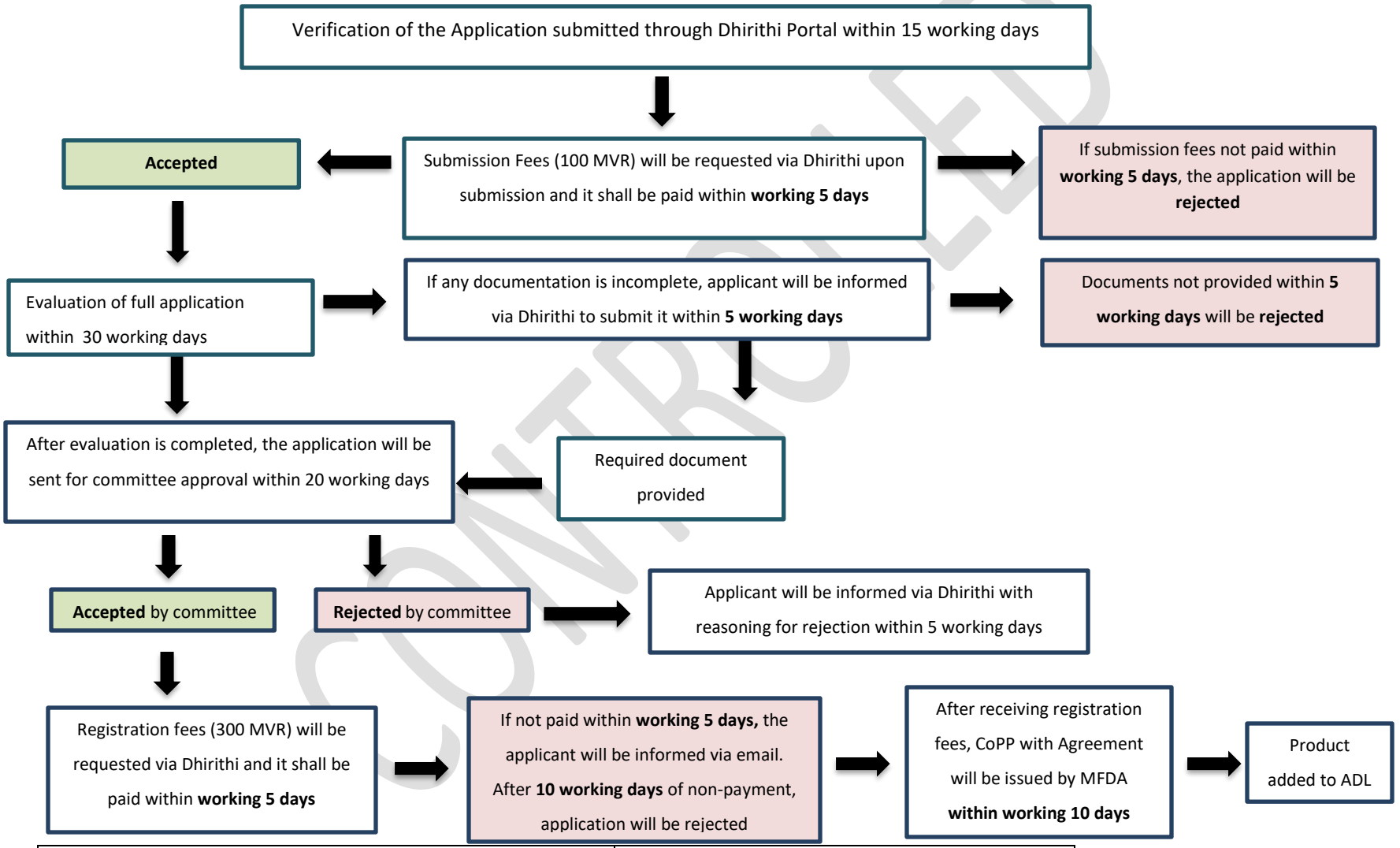
27 Records

1. Reference county categorization for pharmaceutical product registration (MTG/RE-RP/Li 0015)
2. Standard Operating Procedure for Product Registration and Approval of Medicine (MTG/RE-RP/SOP-TE 001)

28 Annexes

1. Annex 1: Registration process flow chart
2. Annex 2: Letter of Appointment
3. Annex 3: Applicant Checklist
4. Annex 4: Reference country categorization for pharmaceutical product registration
5. Annex 5: Confirmation of API Prequalification document
6. Annex 6: Certificates of Suitability
7. Annex 7: Technical Information on the Active Pharmaceutical Ingredients

Annex 1 Registration process flow chart



Annex 2 Letter of Appointment

Maldives Food and Drug Authority
Ministry of Health and Family
Male`, Republic of Maldives

Statement by the Local Applicant for submission of dossier

1) I have received and accepted the entire dossier from **Company name and address** for the product **Name of the product, Brand/ Generic/ Dosage Form/ Strength.**

This dossier includes all data in support of the original documents as per the format of MFDA.

2) I hereby agree that I have sole responsibility for the mentioned product including obtaining approvals for any subsequent product variation and maintenance of the product registration.

3) I declare that information submitted in this application is correct and complete. I authorize the Maldives Food and Drug Authority to obtain information from any institution previously or currently associated with my company. If any information supplied by me is considered to be false, incomplete or misleading in any aspect, Maldives Food and Drug Authority has the right to take action as it believes necessary including the disclosure of the information to any person or body the Maldives Food and Drug Authority considers has a legitimate interest in receiving it and I consent to such disclosure. I understand the Maldives Food and Drug Authority reserves the right to vary or revoke any decision made on the basis of untrue, incomplete or misleading information. Moreover, I will co-operate with any person representing the Maldives Food and Drug Authority, by providing additional information or making the manufacturing premises available for inspection as required.

4) I also acknowledge the responsibility in the event of pharmacovigilance issues or quality defects associated with the product that may occur after the registration.

5) The information provided to the Maldives Food and Drug Authority contain confidential information that can hinder our business and hence this information shall be kept confidential and shall not be disclosed to any third party without our consent.

6)I shall take the responsibility for updating any information relevant to the product/application and will take the initiative to inform MFDA in a timely manner any change in product information during the course of evaluation, and after product registration, especially if the information pertains to rejection/withdrawal and will provide, additional data on product efficacy and safety or current Good Manufacturing Practice (cGMP) compliance of the manufacturers (and repackers, if applicable).

7) I will also supply relevant information in case where the manufacturing facility is sold, merged or changed to another.

8) *As the local agent for marketing the product, I shall take full responsibility for assuring the quality, safety and efficacy of this product throughout the supply chain.*

Applicant representative information (whom MFDA will contact);

Name:
Phone number
Email:

Signed:
Full Name:
Identity Card Number:
Full Address:
Status of the signatory:
(To be signed by the managing director/president/CEO or an equivalent person who has overall responsibility for the company or organization)
Official company stamp:
Fax Number/Telephone Number:
E mail contact details:
Date:

Annex 3 Applicant Checklist

All documents submitted in support of the application shall be in English. For documents not in English, a certified translation or a verified translation shall be provided.

1. This Application Checklist shall be used to ensure the submission of a complete dossier to MFDA.
2. Please note that not all documents mentioned in the checklist are mandatory and the required documents is dependent on the type pf application and the Category the product is applying under.
3. All documents required shall be submitted in softcopy via Dhirithi portal. However, MFDA reserves the rights to request for the original or certified true copy of submitted documents if there is any doubt that a submitted scanned document is not an accurate reflection of the original document.
    - If there is any issue uploading large files, the applicant can submit the hard copy to MFDA or electronic copy to MFDA, via e mail. It will be accepted every Monday and Thursday from 10:00 AM to 13:00 PM. Shared documents will not be accepted.
4. The initial acceptance of the application after screening does not ensure that all information provided are within the acceptance criteria. MFDA has the right to requests for additional documents or changes to the information/documents during evaluation.
5. This checklist shall be completed by ticking each document submitted, according to the application type relevant for your submission.
6. Application checklist shall be submitted to Dhirithi portal along with the application.
7. If a mandatory document and the required information is not submitted, MFDA will reject the dossier.
8. **Please refer to the "*Guidelines on Product Registration and Approval of Medicines Guidelines on Product Registration and Approval of Medicines*" for explanatory notes on the preparation of documents for an application**

Please dictate application type:

Application Type

New API Application /New Chemical	
Re-registration Application	
Variation Application	

Section	Documents/ Required Information	To be filled by the Applicant	To be filled by the MFDA	
		Submitted?	Submitted?	Remarks
Applicant	Letter of appointment (Annex 2)	☐		
Pharmaceutical Product Information	Brand name, Trade name or Product name	☐		
	International Non-proprietary Name (INN) of the Active with Pharmacopeia standard.	☐		
	Non- active ingredient, Excipient	☐		
	Pharmaceutical Dosage Form	☐		
	Strength	☐		
	Volume	☐		
	Product description, container type and pack size	☐		
	Route(s) of Administration	☐		
	Indication/use	☐		
	Therapeutic Class according to WHO ATC Index	☐		
	Storage conditions	☐		

	Shelf life	☐		
	Dispensing category in country of origin	☐		
Manufacturer details	Manufacturer responsible for lot release of the finished dosage form Full details of name, address, phone, fax, e-mail and contact details shall be provided	☐		
	Manufacturer responsible for packaging of the finished dosage form, if different from the above. Full details of name, address, phone, fax, e-mail and contact details shall be provided	☐		
	Brief profile of manufacturer			
	Range of products manufactured and marketed in country of origin.			
	Manufacturing license with validity of 6 months	☐		
	Company profile of manufacturer shall be provided for **newly registering manufacturers**	☐		
	Manufacturing and packaging process	☐		
	Manufacturing plant lay-out and machinery employed	☐		

	Name and qualification of the authorized key personnel	☐		
	Letter from manufacturer to MFDA	☐		
Regulatory decisions taken on this FPP from any drug regulatory authorities	**A formal, signed statement** from the manufacturer and/or MAH is required stating that no regulatory actions such as **recalls, bans or alerts** have been issued for any batches of the product under applications by any National Regulatory Authorities Provide details if such an action has been taken.	☐		
GMP Certificate	A colour scanned copy of the original or certified true copy of GMP certification containing: • **Date of issue/Expiry date** • **Identifying authority** • **Manufacturing site address** • **Dosage form of production** • **Latest inspection date** Validity of GMP Certificate Compliance **shall have the validity of 6 months from the time of submission.** The names and addresses of manufacturer(s)/repacked(s)/batch releaser(s) shall be consistent with the information provided in the Proof of GMP Compliance submitted.	☐		

Certificate of Pharmaceutical Product (CoPP)	A colour scanned copy of the original or certified true copy of CoPP document issued by the relevant drug regulatory agency shall be submitted, certifying that the product is registered in country of origin or the country the medicine is registered. Validity of CoPP Certificate **shall have the validity of 6 months from the time of submission.** **Shall contain all information as per "*Guidelines on Product Registration and Approval of Medicines"* Section 5.8**	☐		
Registration status in countries other than country of origin	List of countries where the product is registered shall be provided with date of registration and number	☐		
	Proof of registration of the finished product in a category one country **Only applicable when applying under Category 2 Option 1**	☐		
Proof of validation of the manufacturing method	Refer to **"*Guidelines on Product Registration and Approval of Medicines"* Section 5.8**	☐		
Materials used in the manufacture of the product	Technical specification of all excipients and API's shall be provided with reference to pharmacopeia standard used For in house reference standards, the specifications of the reference standard shall be submitted.	☐		
	CoA of all excipients and API's shall be submitted	☐		

	Source of all materials shall be listed Signed statement by manufacturer that all materials are obtained from an approved vendor	☐		
Certificate of Analysis of Finished product (CoA)	Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**			
Finished product specification	Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		
Standard batch size quantity	Quantity of all active ingredients and excipients per batch and per dosage form at relevant stages of manufacture shall be provided	☐		
Stability Data	Real Time Stability Data Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		
	Accelerated Stability Data Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		
	Stability Data statement Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		
Bioequivalence (BE) Data	Required for **immediate release solid oral dosage forms only** Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		
	Biowaiver request if applicable Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		

Dissolution Test	Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8**	☐		
Product label	Shall contain • **Brand name, Generic name, strength and dosage form** • **Full manufacturing site address of the product** • **Direction for use** • **Special precaution if applicable** • **Shelf life** • **Storage condition** Shall be submitted in English	☐		
Packing insert / Patient leaflet	Shall contain the following information: • **Name, strength, pharmaceutical dosage form of product** • **Composition** • **Indication** • **Dosage** • **Administration** • **Contraindication** • **Special warning and precautions for use** • **Drug interactions** • **Fertility, pregnancy and lactation** • **Side effects/ undesirable effects** • **Overdose** • **Pharmacokinetic/pharmacodynamic properties** • **Shelf life** • **Special precautions for storage** • **Date of publication/revision** Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.8** for detailed information under each heading.	☐		

Proof of standardization	**Only applicable when applying under Category 1 Option 2**	☐		
Price	Cost price in USD specifying quantity i.e. per tablet, per vial Proposed price for retail in Maldives in USD specifying quantity i.e. per tablet, per vial	☐		
FOR NCE's ONLY:				
Background information and origin of the discovery	Refer to ***"Guidelines on Product Registration and Approval of Medicines"*** **Section 5.14**	☐		
Pharmaceutical and pharmacological Data		☐		
Pharmacokinetic Data		☐		
Toxicity studies		☐		
Data from clinical studies		☐		
Information and any decisions taken by other drug regulatory authorities		☐		

Post marketing data and any observed adverse events.		☐		

Annex 4 Reference country categorization for pharmaceutical product registration

Table 1

CATEGORY 1		
Country of Manufacture	**Required Documents for registration**	**Validity of Registration/MA**
1. **United states Food and Drug Administration (US FDA) United states of America** 2. **European Medicines Agency (EMA) European Union** 3. **Health Canada Canada** 4. **Therapeutic Goods Administration (TGA) Australia** 5. **Ministry of Health, Labour and Welfare Japan** 6. **Icelandic Medicines Agency Iceland** 7. **Medicines and Medical Devices Safety Authority (MEDSAFE) New Zealand** 8. **Health Science Authority (HSA) Singapore** 9. **Argentinean Health Authority Argentina** 10. **Medicines and Medical Devices Regulatory Authority South Africa** 11. **Swissmedic Switzerland**	1. **Letter of Appointment (Annex 2)** 2. **Pharmaceutical Information Sheet** 3. **Product Label/Packing insert** 4. **Valid GMP certificate** 5. **Certificate of Pharmaceutical Product (CoPP)** 6. **Real-time Stability Data** 7. **Accelerated Stability Data** 8. **Certificate of Analysis for batch release/Certificate of Analysis of Finished Product** 9. **Cost and Retail price**	**5 years**

12. **The National Agency of Drug and Food Control Indonesia** 13. **National Pharmaceutical Regulatory Agency Malaysia** 14. **Ministry of Health Israel** 15. **Norwegian Medicines Agency Norway** 16. **The National Health Surveillance Agency or ANVISA Brazil** 17. **Ministry of Food and Drug Safety (MFDS) South Korea** 18. **Ministry of Public Health Qatar**		
CATEGORY 1 OPTION 2		
Country of Manufacture	**Required Documents for registration**	**Validity of registration/MA**

Any country of manufacture but parent country is a CATEGORY 1 country	1. **All documents required for CATEGORY 1** 2. **A document from the parent company stating the product manufactured from the proposed site is up to the standard of the parent company OR a recent audit or assessment report of the site by the parent company etc.**	**5 years**

Table 2

CATEGORY 2			
Country of Manufacture	**Option**	**Required Documents for registration**	**Validity of registration/MA**
	1	1. **Full Dossier** **Condition: To submit a registration certificate of the product under application, in a CATEGORY 1 country during application**	**5 years**
	2	1. **Full dossier**	**5 years**

1. **National Medicines Regulatory Authority (NMRA) Sri lanka** 2. **Food and Drug Administration (Thai FDA) Thailand** 3. **Food and Drug Administration Philippines** 4. **The Central Drugs Standard Control Organization (CDSCO) India** 5. **Directorate General of Drug Administration (DGDA) Bangladesh** 6. **Drug Regulatory Authority of Pakistan (DRAP) Pakistan**		**Condition: GMP inspection conducted by MFDA of the manufacturing facility**	
	3	1. **Full dossier** **condition: To submit analysis reports of 3 batches of the product tested from a WHO prequalified laboratory during application** **(https://extranet.who.int/pqweb/medicines/prequalified-lists/sf-quality-control-labs)**	**3 years**
	4	1. **Full dossier** **Condition: To submit batch certificates for each individual batches that are imported during import form an accredited laboratory or WHO prequalified laboratory (https://extranet.who.int/pqweb/medicines/prequalified-lists/sf-quality-control-labs) in addition to the batch analysis report from the manufacturer.**	**3 year**

Table 3

CATEGORY 3		
Country of Manufacture	**Required Documents for registration**	**Validity of registration/MA**
Include all other countries other than those mentioned in CATEGORY 1 and 2.	1. **Full dossier** 2. **Second country registration certificate in any of the countries in CATEGORY 1**	**5 years**

Table 4

CATEGORY 4: WHO Pre-qualified Products		
Country of Manufacture	**Required Documents for registration**	**Validity of registration/MA**
All Countries	1. **All documents mentioned in CATEGORY 1** 2. **Proof that the product is WHO prequalified.**	**5 years**

Annex 5 Confirmation of API Prequalification document

Confirmation of API Prequalification document.

A complete copy of the Confirmation of API Prequalification document shall be provided and it shall contain the following information

General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications e.g., solubilities and polymorphs

- If the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data shall be provided.
- Specification - the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
- Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- Reference standards or materials – information on the FPP manufacturer's reference standards.
- Stability - data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a lower temperature or humidity to that of the Prequalified API.

Annex 6 Certificates of Suitability (CEP)

Certificates of Suitability (CEP)

CEP stands for certification of suitability of European Pharmacopoeia monographs/Certificate of Pharmacopoeia.

The CEP is a document that used to demonstrate the purity of a given API produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia. By demonstrating grant a CEP for given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and Regulatory authority .

Certificate of Suitability of the European Pharmacopoeia (CEP) A complete copy of the CEP (including any annexes) shall be provided. The declaration of access for the CEP shall be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant who refers to the CEP.

In addition, a written commitment shall be included that the applicant will inform MFDA in the event that the CEP is withdrawn. It shall also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements to support the application. The written commitment shall accompany the copy of the CEP .
Along with the CEP, the applicant shall supply the following information

- General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs

- Specification - the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer‟s API specifications.
- Reference standards or materials – information on the FPP manufacturer's reference standards.
- Container closure system - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the applicant declares to use the same container closure system.
- Stability - exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as

proposed by the applicant. In the case of sterile APIs, data on the sterilization process of the API, including validation data, shall be included

Annex 7

TECHNICAL INFORMATION ON THE ACTIVE PHARMACEUTICAL INGREDIENT

The documentation shall also contain the following information:

. General information:

a) the International Non-Proprietary Name.
C) Chemical name
d) Synonyms with complete reference
e) Molecular and structural formulas
f) Molecular weight
g) Physical form
h) Melting or boiling point
i) Solubility
j) Loss on drying
k) Physical characteristics (crystalline, amorphous, particle size, solvation, etc.)
l) pka and pH
m) Preservation measures
n) Organoleptic properties

API manufacturing process:

a) Manufacturer(s): name, full address, company responsible for each manufacturing process step and quality
control (including contracted companies, third-parties).
b) Description of the production process, including materials, equipment and operating conditions (for example,
temperature, pressure, pH, time ranges, stirring speed, etc.); and of the in-process controls.
c) Identification of the critical steps including the respective tests and acceptance criteria

d) Production process flowchart indicating the formation of intermediates and possible impurities, including the
clarification of the respective chemical structures.
e) Indication of the raw materials, solvents, catalysts, etc…
f) Indicate the production scale and yield.
g) Specifications of the raw materials and packaging materials.

Characterization:

Physicochemical tests allowing elucidation of the API structure:
a) Analyses of an industrial batch evidencing the functional groups, the chemical structure and the molecular formula expected for the API.
b) Possible Isomers.

c) Polymorphism, describing the characteristics of the polymorph used and of others related to the active pharmaceutical ingredient.

Impurity profile:

a) Description of the potential impurities, resulting from the synthesis, with a brief description and indicating the origin.

b) Organic Impurities (of the process and related substances): raw materials (starting), related products,
intermediate products, degradation products, reagents and catalysts.

c) Inorganic Impurities: reagents and catalysts, heavy metals, inorganic salts.

d) Residual solvents.

Quality Control of the API:

b) Appearance

c) Identification

d) Assay

e) Impurities (organic, inorganic and residual solvents)

f) Physicochemical properties (pH, melting point, etc.).

g) Particle size distribution.

h) Polymorphism, including the adopted analytical methodology and results of the tests intended to determinethe probable polymorphs of the ingredient.

i) For chiral ingredients, data on the stereoisomers content.

j) Water determination

k) Microbiological limits: sterility, endotoxins (if applicable).

l) Specific optical rotation (if applicable

Description of the analytical methodology:

Validation of analytical methodology according to the current specific technical regulation for the validation of analytical and bioanalytical methods when the pharmacopeial methodology is not used.

In case of pharmacopeial methodology, the company shall submit the method covalidation.

Packaging Material:

description and specification of the primary packaging

Stability and Photostability Report

The stability and photostability studies shall be conducted in compliance with the specific technical regulation /standard