Maldives Food and Drug Authority

Ministry of Health

Male', Maldives

Guideline for Medicine Registration Including Emergency Use Authorization

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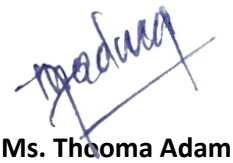

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Contents

ABBREVIATIONS

ADL	Approved Drugs List
API	Active Pharmaceutical Ingredient

BE	Bioequivalence
BP	British Pharmacopeia
CEP	Certification of Suitability
CoA	Certificate of Analysis
CoPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DP	Drug Product
DS	Drug Substance
EUA	Emergency Use Authorization
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
INN	International Non-Proprietary Name
MA	Market Authorization
MAH	Market Authorization Holder
MDI	Metered Dose Inhaler
MFDA	Maldives Food and Drug Authority
MTG	Medicine and Therapeutics Goods Division
NPB	National Pharmaceutical Board
NRA	National Regulatory Authority
PH. EUR	European Pharmacopeia
PIL	Patient Information Leaflet
PP	Primordial Products
PSUR	Periodic Safety Update Report

RMP **SmPC**	Reference Medicinal Product Summary of Product Characteristics
SRA	Stringent Regulatory Authority
USP	United States Pharmacopeia
WHO	World Health Organisation

Definitions

Active Pharmaceutical Ingredient (API) / Drug Substance	A 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. A substance or compound that is intended to be used in the manufacture a drug product as a pharmacologically active compound (ingredient)
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.
Adverse Drug Reaction	A response to a pharmaceutical product that is harmful and unintended and that occurs at doses normally used or tested in humans for prophylaxis, diagnosis, or treatment of disease, or for the modification of physiological function
Approved Drug List	A list of all medicinal products approved as drug product for use in Maldives.
Authority	Authority means Maldives Food and Drug Authority (MFDA)
Batch	A defined quantity of raw material, packaging material, or finished pharmaceutical product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size may be defined either as a fixed quantity or as the amount produced in a fixed time interval Source: World Health Organization WHO Technical Report Series, No. 863, 1996

Bioavailability	The extent to which, following administration of a medicine, fraction of the active form of a drug that reaches systemic circulation unaltered to exert an effect.
Bio-equivalence	Two pharmaceutical products are considered bioequivalent if they are pharmaceutically equivalent to their pharmaceutical alternatives, and their bio-availabilities (rate and extent of availability), 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.
Certification of Analysis	It is a document that describes the list of tests applied to a particular sample with the result obtained and the acceptance criteria applied. It indicates whether the sample complies with the specifications. An authoritative document showing the results of analysis of a particular product batch.
Certification of Suitability	A certificate that certifies compliance of the active pharmaceutical ingredients/ Drug substances or pharmaceutical ingredients as per the monograph of the European Pharmacopoeia (EP)
Composition	Composition in relation to a medicinal product means the ingredients of which it consists, and the proportions, degree of strength, quality, and purity of those ingredients
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging, or repackaging, storage or transport
Container Closure System	a. A primary container closure system is a packaging component (for example, a vial) that is in, or may come into, direct contact with the final product dosage form, or components that contribute to the

container/closure integrity of the primary packaging material for a sterile product.

b. A secondary container closure system is a packaging component (for example, a carton) that is not, and will not be, in direct contact with the dosage form.

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.
Dossier	A detailed compilation of documents generated from the product manufacturer for the purpose of pharmaceutical product registration.
Drug Product / Finished Drug Product / Medicinal Product	Finished Drug Product or drug product or Medicinal Product means a finished dosage form that has undergone all stage of manufacturing including packaging in its final container and labelling. FPP may contains one or more active pharmaceutical ingredient / drug substance.
Emergency Use Authorization / Approval	A risk-based procedure for assessing and listing unlicensed medicines and vaccines with the ultimate aim of expediting the availability of these products in the public health emergency.
Evaluation	Assessment of submitted dossier for product registration based on parameters of safety, efficacy and quality.
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
Excipient / Non-active ingredient	A substance or compound, other than the API and packaging materials, that is intended or designated to be used in the manufacture of a FPP. It also

	means any component of a finished dosage form that has no therapeutic value.
Formulation of Medicine	The validated composition of the finished pharmaceutical products i.e active pharmaceutical ingredients/ drug substance and excepient(s).
Generic Name	A unique name identifying a particular pharmaceutical substance Generic names are officially assigned by international medicines nomenclature commissions, and nowadays mostly conform to those assigned by the WHO program on the selection of INNs.
Good Manufacturing Practices	Good Manufacturing Practices is the aspect of quality assurance that ensures that medicinal product(s) are consistently manufactured and controlled to the quality standards appropriate to their intended use and as required by the product specifications.
Innovator Drug Product	Finished drug (pharmaceutical and biological) products that are first authorized for marketing globally (normally as a patented product) based on parameters of efficacy, safety, and quality.
International Nonproprietary Name	The shortened scientific name (also known as the generic name) of a pharmaceutical substance assigned by the WHO program on the selection of INNs, the INN is recognized worldwide.
Label	A printed text attached to or comprising part of a medicine container or package (primary and secondary excluding any outer shipping container), specifying the name, dosage form, composition, batch number, manufacturing date, and expiry date of the contents as well as the name and address of the manufacturing company and/or importer of the product, the product license holder, the permitted retail price, and other relevant information (e.g., recommended storage conditions).
Manufacturer	A company that carries out any of the operation of manufacturing, packaging, labeling, quality control, final product release and quality assurance of the products.
Market Authorization/ Registration	An official document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product in Maldives after evaluation for safety, efficacy, and quality. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form,

	the quantitative formula (including excipients) per unit dose (using INNs or national generic names, where they exist), the shelf life and storage conditions, and the packaging characteristics. It specifies the information on which authorization is based (e.g., "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence"). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products (the register), and is often said to be "registered" or to "have registration." Market authorization may occasionally also be referred to as a license or product license (Please note that the terms market authorizations and registration is used interchangeably in this document.)
Market Authorization Validity	The duration in which the applicant is allowed to manufacture, import, distribute and market or sell the product in Maldives after being granted Market Authorization.
Marketing Authorization Holder	The local representative and/or applicant / firm that has the authorization to manufacture / import and/or market a medicinal product in Maldives. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or registration.
Medicinal Products / Drug Product	a. 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). b. 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)

Method validation	The documented process by which an analytical procedure (or method) provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.
National Pharmaceutical Board	A board assigned by Regulation on National Pharmaceutical Board 2019/R-135 to provide technical advice on regulating medicine and medicinal products.
National Regulatory Authority	Authority responsible for ensuring medicinal products released for public distribution are evaluated properly and meet international standards of safety, efficacy and quality.
Packaging Material	Any material, including printed material, used in the packaging of a pharmaceutical product, excluding, any outer packaging used for transportation or shipment and packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
Pharmacopeia	A publication issued by an authorized national or international commission / body that specifies quality standards and other properties of pharmaceutical substances and dosage forms
Pharmacovigilance	Pharmacovigilance is the science and activity relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical and biological drug products.
Post-market surveillance	Set of activities following the market authorization of a drug product including maintenance of product authorization and/or registration of variations or renewals; regular inspections of manufacturers, wholesalers, distributors, and retailers; quality control testing; pharmacovigilance; promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products.

Primordial Products	These are the medicinal products that have been on 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.
Prescription Only Medicines	Medicines that may only be made available to the consumer through a written order signed by a duly qualified and registered medical prescriber and dispensed by a registered pharmacist.
Over-the-counter medicines	Medicines that are generally regarded as safe for the consumer to use by following the required label directions and warnings, and which may be purchased without a prescription
Pilot scale batch	A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch, for example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale for 100,000 tablets or capsules, whichever is larger, unless otherwise adequately justified
Primary batch	A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, as the case may be. A primary batch of an API should be at least a pilot-scale batch. For an FPP, two of the three batches should be at least pilot-scale batches, and the third batch may be smaller if it is representative of the critical manufacturing steps. However, a primary batch may be a production batch.
Reference Regulatory Authrities	A national or regional authority or a trusted institution as adopted by the Maldives Food and Drug Authority for the purpose of reliance registration pathways.
Reliance	scope of reliance. Reliance is the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and

	information of others. Full reliance means that the authority relies on the entire assessments/inspection and quality control reports performed by another NMRA. Partial reliance means that the authority relies on certain documents/parts of the assessments performed by another NMRA, while for the other part(s) an independent, full assessment of the documentation submitted by the Applicant is conducted. NRA remains independent, responsible, and accountable regarding the decisions taken, even when it relies on the decisions and information of others
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.
Registration Number	A number assigned to a medicinal product after being given marketing authorization.
Comparator / Reference Medicinal Product	A medicinal product that has been authorized for use on the basis of a full dossier, including the results of pre-clinical tests and clinical trials. Such products are used as a comparator for the demonstration of the safety, efficacy and quality of a generic drug product seeking marketing authorization.
Stability	a. The capacity of drug substance or drug product to remain within specification established to ensure its identity, strength, quality, and purity. b. The evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage condition.
Stability study	Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf life) of an API or the shelf life of an FPP
Stability tests (protocol)	

Summary of Product Characteristics	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. A regulatory document of a medicinal product as it serves as the basis of information for healthcare professionals regarding the use of drug products, ensuring their safety, efficacy, and quality.
Ongoing Stability	The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm, and extend the projected re-test period (or shelf life) of the API, or confirm or extend the shelf life of the FPP.
Accelrated Stability Studies	Studies designed to increase the rate of chemical degradation and physical change of an API or FPP by using exaggerated storage conditions as part of the stability testing program. The data thus obtained, in addition to data derived from long-term stability studies, may be used to assess long-term chemical effects under 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 predictive of tentative shelf life of the drug product. Such studies are designed to simulate the rate of chemical and/or physical degradation of an active ingredient or dosage form or product, under exaggerated storage conditions.
Real time/ Ongoing Stability Studies	Experiments on the physical, chemical, biological, biopharmaceutical, and microbiological characteristics of an API or FPP, 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 re-test period or the shelf life, to confirm the projected re-test period or shelf life, and to recommend storage conditions.
Specification	A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which any drug

	substance or any drug product should conform to be considered acceptable for its intended use.
Storing	The storage of drug products according to the different storage conditions for different drug substances according to their individual requirements.
Storage condition	The storage condition that guarantees the maintenance of the quality of the product in relation to its safety, efficacy, and acceptability throughout the shelf life, as may be predicted from the stability studies. The described conditions should indicate the temperature or temperature range in degree Celsius, as well as humidity, light, and other relevant conditions.
Strength	Strength of the medicinal product means the content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or mass or weight, according to the dosage form
Stringent Regulatory Authority	National Regulatory Authorities that are recognized by WHO as having stringent regulatory practices.
Variation	A change to any aspect of a pharmaceutical product safety, efficacy and quality including but not limited to any change including but not limited to starting material, formulation (API/DS and exipients), method and site of manufacture, specifications for the finished product and ingredients, container, labeling, product information etc.
Validation	Documented act of proving that any procedure, process, equipment, material, activity, or system works correctly and actually leads to the expected results.
Variation Application	A variation application is an application for any intended change to already approved conditions of an existing registered product which has been previously registered as per the criteria laid down by MFDA

1 Introduction.

Maldives Food and Drugs Authority (MFDA) is responsible to regulate the medical products in the country under the Health Services Act (29/2015). The Medicine and Therapeutic Goods (MTG) Division of MFDA is mandated to implement a regulatory framework to ensure the accessibility of safe, quality assured and effective medical products for the people of Maldives.

The Health Services Act (29/2015) provides the legal provisions for establishing a national health system and standards for healthcare delivery services. The Health Services Act, Clause 65 (3) states that all medical products that are manufactured, imported, and sold in the country shall be registered by the Maldives Food and Drugs Authority. The Medicine Regulation further explains the procedures implemented for the registration of medicines including pharmaceutical and biological drug products in the country.

This "Guidelines for Medicine Registration including Emergency Use Authorization**"** will serve as the reference guide for the registration process including the pre-registration and post-marketing quality controls. However, this guideline shall be read in conjunction with the currently applicable laws and regulations together with other relevant legislation applicable to pharmaceutical and biological drug products in the Maldives.

2 Objective

This guideline is aimed at supporting applicants for the registration/market authorization of pharmaceutical and biological drug products intended for human use in the Maldives.

3 Scope

The scope of this document encompasses the administrative requirements and procedures for submission, evaluation, and approval of registration applications of New Drug Products and Generic Drug Product (pharmaceutical and biological including vaccines), post-registration variations and renewal of registered drugs. It also covers the procedure for Emergency Use Authorization (EUA) applicable under public health emergency situations.

4 Legal Context

These guidelines shall be read in conjunction with the other applicable legislations on drug product (pharmaceutical and biological products) which include but not limited to: -

a. Medicine Regulation R-46 (2014)
b. Medicine Regulation Amendment R-49 (2016)
c. Health Service Act (29/2015)

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
Senior pharmacist (Regulation Section)	Responsible for checking and verifying the product evaluation documents and to guide the pharmaceutical officers on evaluating the product.
Pharmaceutical Specialist (Medicine Therapeutic Goods Division)	To approve the medicines, after evaluation and verification, 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 Medicine registration

6.1 Pathways for Registration / Marketing Authorization.

6.1.1 Registration pathways: Table 1 below shows the registration pathway for medicines and reliance mechanism is applied to make use of the maximum benefits for the available resources.

6.2 Reliance Approach for Registration / Marketing Authorization.

a. MFDA recognized the reliance approach in regulatory decision making in line with the WHO guidelines for Good Reliance Practices and as per Guidelines on Good Reliance Practices for Regulation of Medicines. It gives consideration and significant weight to the assessments performed by Reference Regulatory Authorities and WHO Prequalification team. The decisions and other related authoritative information from National Regulatory Authorities and other trusted institutions are also considered while reaching the regulatory decision for enhanced access to safe, efficacious and quality assured products.

b. MFDA applies reliance principles for the products registration that has already undergone full evaluation / assessment by the Reference Regulatory Authorities either in the country of origin or where the product is being exported based on the full dossier assessment performed by these reference regulatory authorities. In such cases, applications will be accepted with abridged data / limited dossier as defined in these guidelines.

c. PICs certified manufacturing sites are also included in this reliance process

6.3 Reference Regulatory Authorities (RRAs).

a. MFDA classifies all applications for registration of medicines products into the below mentioned categories as mentioned in the below table, based on the product origin and its approval status from other NRAs.

b. For this purpose, reference countries are identified based on criteria for stringent regulatory authorities, WHO listed regulatory authorities and those regulatory authorities which have achieved maturity level 3 and above. The documentation requirement is detailed for each reliance pathway in the table below with the assessment duration and validity period. Refer to Annexure-II for the reference countries.

Table 1

General requirement for all applications	All Applications shall have this following information: • Cover letter signed by applicant's responsible officer; • Application form (product, manufacturers, and applicant details); • Applicant business registration/licence information. • Contract between applicant and finished product manufacturer authorizing applicant to submit application and undertake related regulatory work during and after assessment is completed. • Product information as per the information mentioned in section 12.3 B and Manufacturer information as per section C2 and C3 • Samples /artwork, full package picture

#	Registration Pathways			Requirements	Assessment duration	Registration validity
A	**1.Reliance**	**1.1Reliance on MA (approved by reference NRAs)**	**1.1.1 Verification**	**•Evidence of approval and marketing in one or more reference country including the country of manufacture, with detailed description of the product approved. For this, providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Stability study report covering applicable climatic zone as mentioned in section F 2.1, F12, (2.1) and F3**	**Working 45 days**	**5 years**

		1.2Abridge	**1.2.1 GMP verification (manufacturing site certified by PIC/S member NRA)**	**•Evidence of PIC/S-GMP compliance for the site where the finished dosage form is manufactured and batch release takes place.** **PICs certified manufacturing sites can be verified using the following links:** **1. http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=VSj9l6duvYdgIizmjw5ojlLTiRKH5-EwIbnUqabF2Ks1lh8NuukA!-1996855337** **2. https://datadashboard.fda.gov/ora/index.htm** **•Evidence of approval by the NRA of the country where the finished dosage form is manufactured, and batch release takes place. For this, providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Verifiable declaration of approval by at least 3 other NRAs. Providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Stability study report covering applicable climatic zone as mentioned in section F 2.1, F12, (2.1) and F3**	**Working 45 days**	**5 years**

			1.2.2 WHO prequalified products/manufacturers	**Evidence of WHO prequalification of the product and site where the finished dosage form is manufactured, and batch release takes place.** **https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products** **•Evidence of approval by the NRA of the country where the finished dosage form is manufactured, and batch release takes place. For this, providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Verifiable declaration of approval by at least 3 other NRAs. Providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Stability study report covering applicable climatic zone as mentioned in section F 2.1, F12, (2.1) and F3**	**Working 45 days**	**5 years**
		1.3 Collaborative registration procedure (CRP)	**1.3.1CRP-PQ**	**Letter of manufacturer showing interest in going for this pathway. Once letter is received from the manufacturer the information of the dossier will be retrieved from the relevant authorities/organization by MFDA to process the registration of the product**	**Working 90 days**	**5 years**
			1.3.2 CRP-SRA	**Letter of manufacturer showing interest in going for this pathway. Once letter is received from the manufacturer the information of the dossier will be retrieved from the relevant authorities/organization by MFDA to process the registration of the product**	**Working 90 days**	**5 years**

B.	**1.Full procedure**	**1.1 Full dossier**	**• Product full dossier with the document requirement in section 8.3** **• Declaration of regulatory status in other countries.** **•Full ICH M2 and M3 dossier parts.**	**Working 90 days**	**5 years**
		1.2 Full dossier (CTD format)	**• Product full dossier with the document requirement in section 8.3** **• Marketing Authorization certificate from the country of manufacture** **• Marketing authorization certificate from 2 or more reference NRAs**	**Working 90 days**	**5 years**
C.	**1.Notification**	**These are for low-risk medicines like vitamins and vitamin preparation that are categorized as medicines.**	**•Evidence of approval by the NRA of the country where the finished dosage form is manufactured and batch release takes place. For this, providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Verifiable declaration of regulatory status in at least 3 other NRAs. Providing a link to trace the evidence or registration or marketing authorization certificate is sufficient.** **•Stability study report covering applicable climatic zone as mentioned in section F 2.1, F12, (2.1) and F3**	**Working 90 days**	**5 years**

D.	**Products for exclusive use in public health or disease control programmes**			**•Copy of appeal, procurement, or request issued by the concerned programme. •Declaration of regulatory status in other countries; •Proof of approval and marketing in one or more reference country. Detailed description of the product approved in the mentioned reference country OR evidence of PIC/S-GMP compliance for the site where the finished dosage form is manufactured and batch release takes place AND evidence of approval by the NRA of the country where the finished dosage form is manufactured and batch release takes place; •Stability study report covering applicable climatic zone as mentioned in section F 2.1, F12,(2.1) and F3**		
E.	**Donations**			**•Copy of appeal or request for donation issued by a national institution. •Copy of marketing authorisation in the donating country or declaration of conformity with national regulatory requirements by the NRA of the donating country. •Document describing profile of donating entity. •Copy of contract between donating entity and product supplier**		

7 Types of Application

7.1 New Drug Application / New Chemical Entity Application

7.1.1 The registration of a new active pharmaceutical ingredient that has 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.

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

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

7.2.1 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.

7.2.2 Majority of the applications received falls under this category. Registration of products that has already been registered by another party.

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

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

7.2.5 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.

7.2.6 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-labsrom

7.3 Re-registration Application

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

7.3.2 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.

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

7.4 Variation Application

7.4.1 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.

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

7.4.3 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.

7.4.4 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.

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

7.5.1 These are the products that have already undergone full assessment as per the criteria defined in one of the regulatory pathways.

7.5.2 Application for this shall be limited as already the product has been evaluated.

7.5.3 The Applicant shall ensure that exact same product is submitted and also shall submit the full pharmaceutical information sheet as mentioned in clause 12.3B

7.5.4 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

7.5.5 The applicant shall submit the most recent stability data as per the criteria defined in F 2.1, F12, (2.1) and F3 of this document.

8 Non-Routine Registration Pathways.

8.1.1 MFDA recognizes that there are circumstances in which standard requirement and procedure for registration / market authorization may be challenging to fulfil and there is an unmet need of such drugs in the country. In such situations, MFDA supports the availability through registration of drug products that address the unmet medical needs in special situations. In such cases, application dossier submission is considered for priority review or applicants may be granted a conditional registration / marketing authorization or emergency use authorization for such drug products / applications where the benefits of immediate availability outweigh the risk of less comprehensive data than normally required.

8.2 Eligibility Criteria.

8.2.1 MFDA has developed special approvals procedure for drugs and vaccines during public health emergency and extra ordinary situation. Applicant firms are required to submit "Letter of intent" to MFDA for consideration under appropriate expedited pathways for registration / market authorization/emergency use authorization, if the products fulfill any of the following criteria:

a. The benefit-risk balance of the product is positive.
b. Unmet medical needs will be followed.
c. The benefit to public health of the drug product's immediate availability on the market outweighs the risk.
d. It is likely that the applicant will be able to provide comprehensive data.

8.2.2 A determination process will be used to assess the eligibility of a product for the expedited pathway, however the designation of an application to the expedited pathways does not necessarily mean that the product will be approved after evaluation and registered by the MFDA.

8.2.3 In public health emergencies or under special circumstances, the applications for registration of drug products, biologicals and vaccines may be considered under following pathways:

8.3 Priority Review Program.

8.3.1 The Priority Review of drug registration application is an expedited pathway to address local unmet medical needs in the best interest of public health. This program is aimed at providing enhanced access to vital lifesaving drug products and to address extra ordinary situations like public health emergencies. The program is appropriate only for those products for which the benefit-risk balance of immediate availability outweighs the associated risks.

8.3.2 The applicant is responsible for providing all the necessary information in a timely manner to the MFDA. If the applicant cannot meet this requirement, the application can be converted to the standard registration route.

8.3.3 National Pharmaceutical Board (NPB) considers application under priority review pathways with the intent to provide patients and healthcare professional with faster access to new drug products and advanced drugs/therapies. Priority review is based on a full dossier along with substantial evidence of quality, safety and efficacy.

8.3.4 The following types of products are generally considered under priority review pathway:

a. Orphan medicines for the treatment of rare diseases
b. New drug molecule / New indication drug
c. Drugs products in short availability
d. Serious condition e.g. outbreak of a disease etc.

8.4 Application submission and Review Process.

8.4.1 Applicant must justify applicability of priority review scheme in the cover letter of registration application, providing brief justification for fulfilling the eligibility criteria for consideration under non-routine pathway along with the approval status in other regulatory authorities.

8.4.2 The Priority review application submission requires similar data as applicable for routine registration pathways based on approval status of product as per categorization described. However, the timeline for assessment and evaluation of dossier is aimed to reduce within a target timeframe of 15 working days.

8.4.3 The timeframe is calculated after priority determination process, from acceptance of application dossier for evaluation through to the decision of MFDA. A mutual stop-clock will be applied during evaluations / assessment rounds and the applicant is expected to submit responses for the queries raised by the evaluators within 14 working days.

9 Conditional Marketing Approval.

9.1.1 Conditional marketing approval is a fast-track procedure for availability of new medicine and vaccines with a positive benefit-risk balance and has the potential to address unmet medical needs in the country. This program intends to provide a time limited approval to new drugs and vaccines for serious or life-threatening diseases that have no alternative treatments, based on the conditional or special approval in the reference authorities with limited clinical data or less comprehensive clinical data.

9.1.2 The conditional marketing approval can be converted to full registration on the basis of the submission and review of full data and full registration status in reference countries.

9.1.3 The National Pharmaceutical Board (NPB) considers application under conditional marketing approval pathway with the intent to provides patients and healthcare professional with faster access to new drug products.

9.2 Application submission and Review Process.

9.2.1 Applicants must justify applicability of conditional marketing approval pathway in the cover letter of registration application, providing brief justification for fulfilling the eligibility criteria for consideration under this non-routine pathway along with the approval status in other regulatory authorities.

9.2.2 The MFDA evaluators will review the application, validate and assesses the application and gives a positive or negative opinion on the application within 120 days, taking into account the urgency and the public health need. Application may be rejected if the benefit-risk ratio is negative.

9.2.3 The applicant must fulfill the specific obligations and conditions attached to the authorization for submission of remaining data on completion of studies.

9.2.4 The MFDA will review the conditional authorization at least once a year, based on the data submitted by the applicant, and decide whether to renew, vary, suspend, or revoke it.

10 Emergency Use Authorization (EUA)

10.1.1 Emergency Use Authorization (EUA) is grant of conditional registration for a medical product on priority basis during declared health emergency situations.

10.1.2 As the routine registration regulatory process require complete clinical trials as per international harmonized requirements (like ICH guidelines) which cannot be followed in emergency health situation, thus EUA enables expedited authorization of an unapproved medical product and risk-benefit analysis depicts that its use will be helpful in reducing fatalities / mortality due to instant health emergency.

10.1.3 The procedure for granting EUA has been adopted by Reference Regulatory Authorities and also recommended by the World Health Organization.

10.1.4 To obtain EUA, a manufacturer / importer shall submit a request to MFDA with evidence from clinical trials or other adequate and well-controlled clinical investigations or approval of any Reference Regulatory Authority that suggests that the product can be effective in preventing, diagnosing, or treating the serious or life-threatening disease or condition.

10.1.5 After reviewing such evidence and being satisfied, MFDA may authorize the conditional use of the product under EUA once it is proven that the known and potential benefits outweigh the known and potential risks.

10.1.6 EUA is a temporary authorization and EUA holder shall continue to collect evidence of the safety, efficacy, and quality of the product along with updated status by Reference Regulatory Authorities and submit such data to MFDA for review and appropriate decision.

10.2 Criteria for consideration of Emergency Use Authorization application

Criteria for consideration of Emergency Use Authorization is as follows:

10.2.1 A declaration of a public health emergency by the relevant authorities of Maldives such as pandemics or natural disasters or rare diseases with no approved treatment options or life-threatening diseases with limited treatment options.

10.2.2 Medical products already registered by MFDA either cannot be used in prevailing health emergencies in the country or very limited alternative medical products are available for diagnosis, prevention, or treatment of disease.

10.2.3 If any Reference Regulatory Authority has registered any medicine for treatment and use in prevailing health emergency which has not been yet registered by MFDA, then MFDA will process case for priority consideration of registration of such medicine and will convene special meetings of National Pharmaceutical Board for priority decision.

10.2.4 If any Reference Regulatory Authority has not yet registered any medical products for use in prevailing health emergency but granted Emergency Use Authorization (at least completed or on-going Phase III that clearly demonstrates the safety and efficacy of the product), then these guidelines will enable MFDA to authorize the use of unapproved medical either through verification or Abridged pathway (as the case may be) by following Guidelines for Good Reliance Practices for Regulation of Medicines. Moreover, the applicant has provided sufficient data of demonstrated appropriate efficacy and safety in preliminary trials and risk-benefit analysis allows use of medicinal product with certain conditions.

10.2.5 Applicant of EUA (Manufacturer/importer) has adequate plan for monitoring the safety and efficacy of the product i.e. Risk Assessment Plan and Risk Management Plan.

10.3 Procedure for Processing of EUA Applications.

10.3.1 The initiation of the EUA by MFDA is based on the notification of emergency declaration by relevant authorities of Maldives.

10.3.2 Once the relevant authority notifies the nature of health emergency, MFDA will nominate a focal person for coordinating EUA procedures.

10.3.3 Establishment of a dedicated hotline and email address for manufacturers/importers to facilitate EUA submissions.

10.3.4 Focal point will be coordinating all activities regarding EUA application including coordination with stakeholders, Ministry of Public Health, and other government agencies to implement EUA procedures, submission of application by the company, prioritizing product dossier by MFDA, application assessment by Medicine Therapeutic Goods Division, convening of National Pharmaceutical Board and priority decision.

10.3.5 Medicine Therapeutic Goods Division, MFDA shall evaluate all EUA applications and will convey shortcomings (if any) to applicant on priority. After reply of the applicant, Medicine Therapeutic Goods Division will prepare agenda of National Pharmaceutical Board meeting and will mention all details of application, assessment report and any other relevant information in agenda for the consideration of National Pharmaceutical Board.

10.3.6 The National Pharmaceutical Board may co-opt relevant experts (if needed) like experts in pharmaceutical and vaccine regulation and manufacturing, medical experts, epidemiologists, clinical and pharmacovigilance experts etc.

10.3.7 National Pharmaceutical Board may exempt any requirement in registration application which in its opinion cannot be fulfilled in such health emergency situations and it has no or very limited impact or can be confirmed by MFDA through some other means like online data or communication with another NRA via email etc.

10.3.8 An EUA will only be granted if MFDA, after complete review, finds that the product meets all the applicable criteria of safety, efficacy, and quality. In the event of approval, letter will be issued immediately.

10.4 Process Timeline

10.4.1 Applications for pharmaceutical products during health emergency fulfilling conditions get priority review in 07 working days after complete application received.

10.5 EUA Validity

10.5.1 Emergency Use Authorization will be reviewed by the National Pharmaceutical Board every three months based on available safety, efficacy and quality data. Thereafter, the applicant will be required to submit the applicable data as per the routine registration pathway for conversion to full registration status and renewal accordingly.

10.6 Data Requirement for EUA

10.6.1 The minimum requirement for registration of drug products, biological and vaccines will be as specified in the Guidelines for regulation requirement for product registration and approval of vaccine in emergency (Doc Number: MTG/RE-LA/STD-TE 003) or as determined by National Pharmaceutical Board on case-to-case basis.

All Applications for registration in Maldives are accepted if only the product is categorized as a medicine in the country of origin.

11 Pre-Application Process for medicine registration.

11.1 Applicant for Product Registration.

11.1.1 For registration of a product in Maldives, the manufacturing company shall have a local representative, or a locally incorporated company authorized by the manufacturer or Marketing Authorization Holder in the country of origin, who will be responsible for all the communications to the Authority. The local representative or the applicant shall have a valid medicine import license as per the criteria defined by the Authority.

11.1.2 The local representative and the applicant can be the same, but local representative or applicant shall be a Maldivian National.

11.1.3 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.

11.1.4 Applicant/local representative shall verify that all the required documents are submitted by using the checklist provided in Annexure-III to facilitate the acceptance of the documents for registration.

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

11.2 Responsibilities of Applicants.

11.2.1 The manufacturer or Marketing Authorization Holder in the country of origin, shall designate a local representative by issuing an authorization letter, indicating that all responsibilities in communicating on behalf of the manufacturer or Marketing Authorization Holder shall be done by the local representative to the Authority which includes supplying all the relevant information for product registration.

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

11.2.3 The key responsibilities of applicants are as follows:

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

11.2.5 The person or an authorized representative established in Maldives, shall take full responsibility of the medicine that they supply to 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 MAH of the product to ensure that the drug product complies with the specification as approved by MFDA throughout the supply chain. The evidence of these shall be documented with the applicant and shared with the authority when needed.

11.2.6 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 drug product as well.

12 Pre-Approval Process

12.1 Preparation of Dossier

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

12.2 General Considerations

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

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

12.2.3 The documents required for the registration of a product differ according to the Registration pathways as described in Table 1 of this document.

12.2.4 The acceptance criteria of each document are indicated in Section 9.3 of this guideline. Any application with missing documents or documents that do not meet the criteria set will be rejected.

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

12.2.6 A separate dossier is required for each drug product i.e., products containing the same ingredients but made to different specifications in terms of strength, content of API/DS, dosage form, description and pack size etc.

12.2.7 For tablets and capsules if it undergoes the same production and packing process under the same quality assurance system, it will be considered as a one drug product regardless of its pack size. Example: A having 12 tablets per strip and 10 tablets per strip will be considered as one product if the product undergoes the same process and has the same labelling information on the product.

12.2.8 MFDA shall reject the applications which do not fulfill the criteria as per applicable guidelines.

12.3 Data Requirement and Acceptance Criteria for full Dossier Preparation.

12.3.1 The table below contains a list of documents and required data in a full dossier along with the information that shall be included in each document for it to be accepted by the Authority.

12.3.2 As all applications do not require a full dossier, to determine the type of dossier application and the required documents, see Annexure-II to determine product application category.

12.3.3 The codes and document title stated under column-I and II respectively in the following table are consistent as they appear on the Dhirithi portal for ease of interpretation.

Code	Document Title	Acceptance Criteria
A1	**Letter of Appointment (Annex 1)**	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: i. Confirmation of API Prequalification document (CPQ) as specified in Annexure-IV. ii. Certificate of suitability of the European Pharmacopoeia (CEP) as specified in Annexure-V. iii. Technical Information on the active pharmaceutical ingredient/s as specified in Annexure-VI; **b. Brand name, Trade name or Product name:** Shall provide this information in the format as provided by the manufacturer i. The product name shall be entered according to the submitted product label and shall be same with the product name mentioned in submitted Certificate of Pharmaceutical product (CoPP). ii. The strength of the active pharmaceutical ingredient / Drug substance shall generally be included as part of the product name to allow differentiation between different

Code	Document Title	Acceptance Criteria
		products containing the same active pharmaceutical ingredient / Drug substance. **c. International Nonproprietary Name (INN)** or the Active Pharmaceutical Ingredient (API) or Generic name: Shall provide the information with the details as mentioned below: i. The name and amount of active pharmaceutical ingredient(s) / Drug substance(s) 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*. ii. 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: i. 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. ii. In case of cough and cold preparations and paracetamol preparations, the exact grade of the excipients shall be mentioned with supporting documents. iii. 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).

Code	Document Title	Acceptance Criteria
		iv. 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. v. The test mentioned in point 4 of the clause shall be as per the official monogram for purity. vi. Registration holder will ensure that the manufacturer will perform impurity testing as identified by the manufacturer of innovator drug product like N-Nitroso dimethylamine (NDMA), N-Nitroso diethylamine (NDEA) in valsartan, metformin etc. **e. Pharmacopeia standard / Formulation of the product:** Shall provide the details as mentioned below i. All Active pharmaceutical ingredient(s) / drug substance(s) 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 pharmacopeia of stringent regulatory authorities. ii. 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 as nominated by the Authority. **f. Pharmaceutical Dosage Form**: Pharmaceutical dosage form is defined as the physical form of the drug product which is intended for administration to the patients: i. 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*.

Code	Document Title	Acceptance Criteria
		ii. 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 ingredient(s) / Drug substance(s) in the dosage form. Strength shall be provided for all APIs/DS including if the product is a combination drug. 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: i. Volume is not applicable for Tablet and capsules ii. 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: i. Description of primary packaging shall be defined with the pack size. *Example blister pack of 12 tablets* *ii.* 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* iii. Length, width, height of primary and secondary packaging shall be provided in detail.

Code	Document Title	Acceptance Criteria
		iv. Weight of drug product which is submitted for registration and shall also indicate the deviation level for the weight. v. Odor description of the product submitted for registration shall be submitted. vi. A visual description of the product shall be submitted including the shape, size, color any engraving or any other detail of the product. vii. 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:** All routes of administration proposed for the product shall be included and specified accordingly. **k. Indication or Use of the product:** 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: i. The WHO ATC code ii. WHO ATC classification iii. Shall be provided for each therapeutic indication proposed for a product. **m. Storage conditions** of the product shall be provided: i. The condition in which the drug product shall be stored and kept shall be clearly specified. Example temperature, humidity etc. Of the product storage shall be specified ii. Non-numeral statements such as *"Store in a cool dry place"* is not encouraged.

Code	Document Title	Acceptance Criteria
		n. Shelf life of the product: The shelf life is the period between the execution of the preparation and its expiry date. Product Shelf life shall be specified in months. **o. Dispensing Category** in country of origin shall be specified. 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**	i. Full address of the manufacturer(s) shall be provided with site and country of origin including the phone number, fax, e-mail. ii. Contact details of the manufacturer(s) shall be provided that can be reachable if needed. iii. This contact shall provide further information and verification if needed by the authority and shall be responsive to the queries sent by the authority.
C3	**Manufacturer responsible for packaging / final batch release of the Finished Product, if different.**	i. Full address of the manufacturer shall be provided with site and country of origin including the phone number, fax, e-mail. ii. Contact details of the manufacturer shall be provided that can be reachable if needed. iii. This contact shall provide further information and verification if needed by the authority and shall be responsive to the queries sent by the authority.
C4	**Manufacturing License**	A manufacturing license is a permit issued by the regulatory authority of the country of origin to manufacture drug product. i. The manufacturing license shall be at least 6 months valid at the time of submission. ii. The manufacturing license shall contain date of issue, expiry, identity of issuing authority, the activities or the products covered under the license and full manufacturing site address.

Code	Document Title	Acceptance Criteria
		iii. 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 manufacturing 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. Following documents related to GMP need to be provided. i. Proof of GMP compliance (valid GMP certificate) shall be submitted for all the sites involved in any step of manufacturing of the product ii. 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. iii. 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.

Code	Document Title	Acceptance Criteria
		iv. GMP Certificate shall have the validity of 6 months at the time of submission. v. If the GMP does not have the 6-month validity, the applicant 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. vi. 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. vii. Commitment letters of GMP renewal are not accepted. viii. The names and addresses of manufacturer(s)/repacked(s)/batch releaser(s) shall be consistent with the information provided in the GMP certificate ix. The specific dosage form applied for registration shall be mentioned in the GMP x. The applicant 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: i. Short description of the process with a summary of the critical processing steps or critical process parameters to be monitored during validation. ii. API /DS validation report iii. Excipients validation report iv. Finished product specification report

Code	Document Title	Acceptance Criteria
		v. Finished product specification report, specifically tested for Diethylene Glycol and Ethylene Glycol impurities in oral cough and cold preparations vi. Details of analytical methods vii. In-process controls proposed with acceptance criteria viii. Additional testing intended to be carried out (e.g., with proposed acceptance criteria and analytical validation as appropriate) ix. Sampling plan - where, when and how the samples are taken x. Details of methods for recording and evaluation of results xi. Proposed timeframe. xii. Any variation from the validation protocol shall be documented with appropriate justification xiii. 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. xiv. Refer to ICH Quality Guidelines Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Section 12 for further reference.
C8	**Standard Batch size Quantity**	i. 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

Code	Document Title	Acceptance Criteria
		ii. 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:** i. Specification provided shall be consistent with label claim ii. Certificate of analysis (CoA) of all ingredients (APIs/DS and excipients) shall be provided along with specifications iii. The quality of the ingredients used in the production of the drug substance (or drug product) shall meet standards appropriate for their intended use. iv. 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 applicable and suitable acceptance criteria shall be established for the non-pharmacopeial excipients. v. Information on measures taken to ensure the quality and control of these materials shall be provided. vi. Source(s) of all excipients and API/DS shall be listed and the origin or source of the API/DS and excipients shall be approved by the manufacturer and this document shall be provided. vii. Shall submit documents stating that all excipients used are of pharmaceutical grade or grade approved for manufacturing the pharmaceutical product. viii. A signed `statement shall be provided by the manufacturer indicating that all excipients and API(s)/DS are obtained through approved vendor(s) in the country of origin. ix. The manufacturer shall submit document evidence on how vendor assessment is done for API/DS and excipients.

Code	Document Title	Acceptance Criteria
C10	**Brief profile of Manufacturer(s)**	i. A brief description of the manufacturer, when it was established and the products approved / manufactured shall be submitted. ii. Shall Provide a short description of accreditations, achievements and standards practices of the manufacturer. iii. Shall Provide list of products manufactured and specify those currently marketed in the country of origin. iv. Shall provide a list of products manufactured and exported to other countries, specifying which products are exported to which country.
CM1	**Company profile**	i. Shall include a detailed profile of the company including but not limited to history, accreditations, and standards practices and international/national levels of recognition achieved, company information, staff, organizational chart, equipment used, quality control procedures used, etc for all new companies/applying first time to MFDA. ii. A detailed Company profile is not required for companies that already have a drug product(s) registered in Maldives. iii. For all new sites involved in any step of manufacturing also require company profile documentation. iv. Company profile is also required in instances of a major change brought to a company that has previously registered a product in Maldives v. Shall also state whether the company is manufacturing under loan license or not. If so, shall include all details of loan manufacturer including regulatory details of approving NRA.
C11.0	**Manufacturing plant layout and machinery involved**	i. Shall include a list of equipment which is relevant to the product under application along with details of water treatment, HVAC and waste disposal systems.

Code	Document Title	Acceptance Criteria
		ii. Manufacturing plant lay-out shall be clear, legible and relevant to the product under application
C11.1	**Manufacturing and Packaging process**	i. Process flow chart of the whole process of the manufacturing of the product shall be provided identifying the critical control points at every stage ii. Manufacturing monograph shall be provided iii. 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 • All such Information shall be up to date.
C13	**Letter from Manufacturer to MFDA**	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: i. Manufacturer details ii. The name and address of local representative authorized to apply for product registration on the manufacturer's behalf iii. Product details iv. Name, designation and signature of the authorizing personnel of the manufacture
C14	**Regulatory decisions taken on this Finished Product from any drug regulatory authorities**	i. 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

Code	Document Title	Acceptance Criteria
		under applications by any National Regulatory Authorities including that of the country of origin. ii. 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)**	i. CoPP shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products. ii. 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 iii. 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 iv. CoPP Certificate shall have validity of 6 months from the time of submission of the application v. 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. vi. If the expiry of the CoPP is not mentioned in the certificate, evidence document shall be submitted for assurance of the validity

Code	Document Title	Acceptance Criteria
D4	**Registration status of Finished Product in countries other than country of origin**	A 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, preferably a weblink shall be provided with the documents for further verification.
D5	**Proof of registration of the Finished Product in Reference regulatory authority/ies**	i. This document shall be mandatory when applying under the criteria as mentioned in table 1 of this document. ii. This document shall have the same product as that of the product under application iii. For ease of application, a registration certificate of the product or preferably a weblink 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**	i. The finished product specification report shall be based on a reference to an official monograph 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 notified by the authority. ii. As per ICH recommendations, finished product specification shall include the following information: * a. Description: a qualitative statement about the state (e.g., solid, liquid), shape and color of the drug substance b. Identification: Identification tests shall be specific for all API(s)/DS. c. Assay: A specific, stability-indicating assay to determine strength (content) in % shall be included for all active pharmaceutical Ingredient(s)/DS. d. Impurities and related substance: Acceptance limits shall be stated for specified degradation products, which may include both identified and unidentified degradation products as appropriate. e. Water content. f. Dissolution. g. Uniformity of dosage units. h. Microbial limits.

Code	Document Title	Acceptance Criteria
		i. All tests shall specify the pharmacopeial standard used j. 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)**	i. This certificate shall be a notarized true copy ii. This certificate shall contain the following information: • Name and address of the certifying/notarizing authority • Batch details iii. Batch analyses data from a minimum of 2 batches shall be submitted for the product submitted for registration. iv. Shall include a conclusion specifying that the product is in compliance. v. CoA should include result data, reference range and pharmacopeial references for each test parameter. For non-pharmacopeial test parameter, analysis of the samples will be performed using the analytical method and specifications as per validated method of analysis.
F. 2.1	**Real-Time Stability Data**	1) **Stability** is the ability of a drug 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 drug 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

Code	Document Title	Acceptance Criteria
		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. 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 is 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

Code	Document Title	Acceptance Criteria
		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. As per ICH zones, following climatic zones are 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 A: Hot humid / Tropical • Zone IV B: Hot/Higher humidity 9) In a stability study, the effect on the product in question of variations in temperature, time, humidity, light intensity and partial vapors pressure (in special cases) 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

Code	Document Title	Acceptance Criteria
		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/DS, 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 (one tenth of full production scale or 100 000 tablets or capsules, whichever is the larger, 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 (2-8°C): • 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

Code	Document Title	Acceptance Criteria
		• Accelerated Stability Data shall be provided for minimum 6 months with storage condition of 5 °C ± 3 °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.***
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.

Code	Document Title	Acceptance Criteria
		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.
F3	**Stability Report and statement**	1) 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 2) An official statement issued by the manufacturer that all stability tests are performed of the same formula, manufactured at the same site(s) 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 comparator or reference drug 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 comparator or reference drug 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**

Code	Document Title	Acceptance Criteria
		**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 drug 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

Code	Document Title	Acceptance Criteria
		• 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. Bio waiver 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.

Code	Document Title	Acceptance Criteria
		10. Additional justifications and relevant supporting documents for bio waiver 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. The third party can be an accredited laboratory, regulatory authority or any other external or internal assessment body as nominated by the Authority. **3. The following data shall be submitted:** 4. Information about the reference/innovator/comparator drug product 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/innovator/comparator drug 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.

Code	Document Title	Acceptance Criteria
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 the manufacturer is not defined in the label, a specific code (bar code or QR code) shall be in the label to trace the manufacture name and address, and this shall be same as 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 API/DS 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.

Code	Document Title	Acceptance Criteria
		• **Composition:** Full details of the qualitative and quantitative composition in terms of the APIs/DS 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 required, 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

Code	Document Title	Acceptance Criteria
		• 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 drug 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 or use of the drug product by the 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

Code	Document Title	Acceptance Criteria
		• All particular risks associated with using the drug 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 have detail recommendations regarding the use of this drug 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

Code	Document Title	Acceptance Criteria
		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**

Code	Document Title	Acceptance Criteria
		• **Date of publication/revision** **5. Innovator drug products shall follow the above information as per approval of SRA.** **6. Generic drug products shall follow and maintain the consistency in above information with the innovator drug products as approved by SRAs.** ***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 per 5ml composition. 2. Proposed price for retail in Maldives (USD) be provided specifying the quantity. Eg. per tablet or per 5ml composition 3. The price structure shall include the name of the product.

12.4 Additional Requirements for New Drug Product/ New Chemical Entity

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	a. Origin and background of the discovery b. Use in foreign countries including SRA status c. Characteristics and comparison with existing drugs
2.	Pharmaceutical and Pharmacological Data	a. Studies that demonstrate efficacy and safety over existing medication b. Secondary/safety pharmacological studies c. Other relevant pharmacological studies
3.	Pharmacokinetic Data	– Absorption, distribution, metabolism and excretion profiles of the NCE
4.	Toxicity studies	a. Single dose toxicity studies b. Repeated dose toxicity studies Genotoxicity studies c. Reproductive and developmental toxicity studies
5.	Data from clinical studies	a. For the registration applications of formulations which have been approved by any of the RRA, traceable references shall be provided to establish the safety and efficacy of the applied formulation. b. In case the applied formulation has not been approved by any of the RRA, then authentic clinical data shall be submitted as per relevant international guidelines
6.	Information and any decisions taken by other drug regulatory authorities	a. Approval status of formulation by NRAs mentioned in Annexure-II
7	Post marketing data and any observed adverse events.	a. Data from NRAs mentioned in Annexure-II

12.5 Additional Requirements for Non-Pharmacopeial Products.

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 for testing methods as under:

Testing Methods	Validation Parameters
1) Identification 2) Assay (content and dissolution measurement only) 3) Impurities (quantitative & limit test)	a. Specificity b. Accuracy c. Precision (repeatability, intermediate) d. Linearity & Range e. Detection Limit f. Quantitation Limit g. Robustness

12.5.1 In addition to method validation report, in-house method shall also provide documentary evidence for the identification of sources and quantitation of potential errors, determine if the method is acceptable for intended use and establish proof that a method can be used for decision-making.

12.5.2 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 as approved by NRA.

12.6 Submission of Product Samples.

12.6.1 Applicants are required to submit the product samples to the MFDA for all new products in the quantities as described below for each type. However, MFDA can require more quantities if required for analysis or as notified from time to time for various dosage forms,

Type	Description	Quantity
Liquid dosage forms	These include solutions, syrups, elixirs, suspensions, emulsions etc.,	03 units shall be submitted. (e.g. 03 bottles of liquids.)
Solid dosage forms	These include tablets, capsules, , lozenges, etc.	60 units shall be submitted (e.g. 60 tablets, 60 capsules).
Semisolid dosage forms	These include creams, ointments, gels, pastes, and suppositories.	
Parental Preparations	These include ampules, vials, infusions, etc.	03 units shall be submitted (e.g. 03 vials or ampoules of injections)
Inhalational products	These include inhalers, nebulizers	
Others	Transdermal patches,	

12.6.2 Request for sample import shall be applied online through Dhirithi portal. MFDA considers requests for grant approval within 10 working days. Samples shall only be imported once sample authorization approval has been issued.

12.6.3 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 the product registration unit with the sample release sheet.

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

12.6.5 In case an application is rejected, the samples shall be kept in MFDA for 60 days from the date of rejection and then they will be disposed of as per recommended method.

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

12.6.7 However, a 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.

13 Application Submission and Review Process

13.1 Submission of Application

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

13.1.2 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 registration.

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

13.1.4 To ensure all mandatory documents are submitted, the applicant shall refer to Application checklist (Annexure-III) / section 9.3 of these guidelines and submit it along with the application via Dhirithi portal.

13.2 Submission of Assessment Fee.

13.2.1 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.

13.2.2 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.

13.3 Pre-Screening of Dossier

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

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

13.3.3 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.

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

13.3.5 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.

13.4 Assessment of Application

13.4.1 Pharmaceutical officers of Medicine Registration act as assessors and verify the required documents, accept the dossiers, and evaluating the dossiers as per approved criteria. In case further clarification is required, these officers are also responsible for effective communication with the applicant in a timely manner.

13.4.2 A summary of the evaluation is generated in the approved format by the Assessors and submitted before the National Pharmaceutical Board for Pharmaceuticals for decision-making.

13.4.3 The Director, Pharmaceuticals (Enforcement Section) is responsible for cross-review by checking and verifying the product evaluation documents submitted in the dossiers, and to guide the pharmaceutical officers on evaluating the product.

13.4.4 The Deputy Director General (Medicine Therapeutic Goods Division) is responsible to review the evaluation summary before it is submitted for approval from National Pharmaceutical Board.

13.5 Decision by the National Pharmaceutical Board (NPB).

13.5.1 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.

13.5.2 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 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.

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

13.6 Issuance of Registration Certificate

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

13.6.2 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.

13.6.3 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).

13.7 Validity of Registration

13.7.1 The validity period of the registration is mentioned in the table 1 of this document.

13.8 Classification of Medicine Registration

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

Classification	Remark
Restricted for Hospital and Institutional (HI) use only	a. Medicinal products restricted to special expertise and Health facilities and clinics with registered medical practitioners. b. These products cannot be kept for sale in pharmacies. c. These products can only be imported by designated parties.
Restricted for Hospital use only (HO)	a. These medicinal products can only be imported and registered by designated parties. b. These products cannot be kept for sale in pharmacies. c. These products are restricted to special expertise for hospitals only
Controlled Drug C	a. These medicinal products are controlled and can only be imported by designated parties. b. Within this class, Narcotics cannot be kept in pharmacies for sale. c. Controlled Drugs include Narcotics and Psychotropic drugs (Internationally and Nationally Controlled).
Over The Counter Medicine (OTC)	a. These medicinal products can be sold without prescriptions.
Prescription Only Medicines (POM)	a. These medicinal products can only be prescribed by a registered medical practitioner. This product can only be sold with a valid prescription.

14 Renewal of Registration.

14.1.1 Application for renewal of registered product shall be submitted at least 30 days before the expiry date of the current MA validity along with the processing fee.

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

14.1.3 For renewal, there shall not be any change in the product excluding variations that have been notified and approved by the Authority for the specific product.

14.1.4 If the registration of the product is expired and the applicant did not apply for renewal, then 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.

14.1.5 All products in ADL if not applied for renewal before the expiry will be removed from ADL after 1 month of the date of expiry of that specific product.

14.1.6 For products in category 2 and option 3 and 4, since the initial registration period is 3 years, for renewal, along with the requirements as specified in below section, a GMP inspection shall be carried out by MFDA if not exempted as per Guidelines on Good Reliance Practices for Regulation of Medicines. The cost of this inspection shall be borne by the applicant as per the government rules and regulations. After successful GMP inspection the product shall be renewed for a period of 5 years.

14.1.7 Existing products which were registered prior to the implementation of this guideline under category 2 (options 3, and 4) as defined in Annexure-II, will fulfil the current criteria after completion of their validity period.

Note: Physical samples of the product are 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.

14.2 Application for Renewal of Registration and Required Documentation

14.2.1 The application for renewal of registration will also be submitted Online via the Dhirithi portal 'https://dhirithi.egov.mv. Please see section 10.1 for guidance on making an application via the Dhirithi portal.

14.2.2 For products registered under the reliance process, the same documents shall be submitted for re registration.

14.2.3 The following table provides details of the documents to be submitted for a re-registration application for those products in which full dosser were submitted for initial registration.

Code	Document Title	Acceptance Criteria
A1	Letter of Appointment	See *"Acceptance Criteria of the Documents Submitted in a Full Dossier"* for the required information on 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 (2.1)	Accelerated Stability Data	
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 / approval letter issued from MFDA after registering the product	

14.2.4 Those products which have been imported under pre-authorization approval from MFDA for 3 years can undergo this same registration process to get the registration status for the product with the assigned validity period. The importer shall submit all requisite documents to fulfill the registration requirements.

14.2.5 For registration, the exact product which was registered shall be submitted. Any change in the product name, dosage, formulation, manufacture and new site(s) shall be considered as a new application and shall submit the full documentation as per the registration criteria.

14.2.6 Declaration letters stating otherwise shall not be accepted.

14.3 Cancellation, Suspension, Revocation of Registration

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. If the product is removed from Approved Drug List due to any reason including safety and efficacy.

d. The information provided at the time of the submission of the application is later found to be false or insufficient.

e. If it is substantiated that the formulation has serious side effects and any of Reference Regulatory Authority or WHO or other national and international agency prohibited used of such formulation.

f. If it is found that the manufacturer is not in compliance with Good Manufacturing Practices (GMP), or for any other reasons, that the manufacturer has repeated violations like manufacturing of sub-standard drug products.

g. If any adverse regulatory action is taken against the manufacturer abroad by the regulatory authority of country of origin.

h. If the MAH fail to inform the MFDA of any serious adverse reactions of the registered product upon receipt of such reports.

i. If any post-registration variation has been done including the composition, label, packaging, manufacturing method, drug product specifications, indication or any other particulars of the product has been changed without the approval of the MFDA.

j. If foreign manufacturer of the registered product has decided to withdraw and not to sell the product.

k. Any of the conditions of registration of the product have been contravened.

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

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

14.4 Temporary and Permanent Ban of a Product and/or Manufacturer

14.4.1 A company or manufacturer can be temporarily or permanently banned if repeated incidents of quality failure are identified from their products.

14.4.2 If the company or manufacturer is permanently banned, the company will not be allowed to enter the Maldives market until a period of a minimum 5 years has passed. After 5 years from the date of the ban, they can apply for 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.

14.4.3 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.

15 Post Registration Variations

15.1 Classification of Variations

15.1.1 Following are the basis of classification of post-registration variations.

a. An administrative change such as a change of company name and/or address.

b. A change to the characteristics of drug product that can affect its quality like change of storage condition.

c. A change to the safety, efficacy or pharmacovigilance of the product.

15.1.2 Types of variations for a registered drug product are classified as Minor and Major.

15.2 Minor Variations (MiV)

15.2.1 Variation to a registered finished product in terms of changes which has minimal or insignificant impact on the aspects of safety, efficacy and quality. Minor variations are further divided into following sub types: -

1) Minor Variations – Notification (MiV-N)

a. Minor Variations – Notification (MiV-N) have little or no impact on the safety, efficacy and quality of registered drug product e.g. administrative modifications.

b. MiV-N procedures are classed a 'do-and-tell' procedure, means registration holder should implement the change and intimate / notify to MFDA by fulfilling the conditions and supporting documents.

c. Applicant should ensure this notification/intimation must reach relevant section of MFDA within 30 days of implementation of change for MFDA's record and it can be considered accepted if an objection is not issued by the MFDA within 30 working days of the date of submission of variation application.

1) Minor Variations – Prior Approval (MiV-PA)

a. If the change is more significant than (MiV-N) change but it does not fall under major variation category, then it is considered as MiV-PA change.

b. These changes need prior approval from MFDA before implementation. (e.g. Change in brand/proprietary name, title of firm, etc.).

c. Registration holder / MA holder is required to submit a variation application for the proposed change to relevant section of MFDA along with supporting documents and fulfill the conditions as described in these guidelines.

d. If the application fulfills the prescribed criteria, Medicine Therapeutic Goods Division will process the case for approval of the proposed change by Head of the Division.

2) Major Variations (MaV)

a. These changes may have a significant impact on the quality, safety and/or efficacy of the product e.g. change in manufacturing site, container closure system, etc and it does not fall within the definition of minor variation and new registration.

b. Registration holder needs to seek prior approval for major variations before they are made. Registration holder MA holder is required to submit an application for proposed variation to Medicine Therapeutic Goods Division, MFDA along with supporting documents and fulfill the conditions as described in these guidelines.

c. If the application fulfills the prescribed criteria, Medicine Therapeutic Goods Division will process the case for consideration and decision of the proposed change by National Pharmaceutical Board.

15.3 Exclusion criteria for Post Registration Variations.

15.3.1 The following cases of variations / changes shall not be considered as post-registration variations and require new product registration.

15.3.2 Change of Active Pharmaceutical Ingredient / Drug Substance

a. Change of the API to a different API including change in the salt or isomer form of API.

b. Inclusion or exclusion of an API to a multicomponent product.

c. Change in the strength of one or more APIs.

15.3.3 Change of Pharmaceutical Form /Dosage Form

a. Change in release profile of drug product like change from an immediate-release product to a slow-or delayed release dosage form and vice versa.

b. Change from a liquid to a powder for reconstitution, or vice versa.

15.3.4 Change in the route of administration.

15.3.5 Additional volume of already registered injectable drug products.

15.4 Procedure for submission of Post Registration Variations.

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

15.4.2 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.

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

16 Details of Variations, Applicable conditions and Required Documents.

16.1 Applicable Conditions

16.1.1 For each variation, attempts have been made to identify conditions or circumstance that need to be fulfilled for submitting variation application. For all changes, it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not adversely affect the quality, safety and efficacy of the drug product.

16.2 Required Documents

16.2.1 The list of documents required to be submitted along with application is identified for each variation in this guideline. However, this list is not exhaustive and further documentation if required may be asked from the applicant by MFDA. Regardless of the documents specified, applicants shall ensure provision of all relevant information to support the applied variation. Alternative approaches to the principles and practices described in this document may be acceptable provided that such variations / changes / practices or proposed alternatives are being supported with adequate scientific justification.

16.3 Details of Minor Variation-Notification (MiV-N change)

Minor Variation-Notification (MiV-N)	
MiV-N 1	**Change in the name of Active Pharmaceutical Ingredient / Drug Substance, while the drug substance remains the same molecule(s)**
Conditions	a. No change in Active Pharmaceutical Ingredient/Drug substance (s).
Documents	a. Proof of acceptance by WHO or copy of the latest version of International Non-proprietary Names (INN) list mentioning proposed name of API/DS.
MiV-N 2	**Change of the name and/or address (e.g., street name) of a manufacturer of the drug substance (API)**
Conditions	a. The manufacturing site of the drug substance remains unchanged. b. No other changes, except for the change of the name and/or address of a manufacturer of the drug substance
Documents	a. Updated information of the manufacturer of the drug substance. b. Official document/evidence when required
MiV-N 3	**Change of manufacturing company owner**
Conditions	a. The manufacturing and batch release site of the drug product remains the same. b. No other changes, except for change in the owner of manufacturer
Documents	a. Declaration on the transfer of ownership. b. Official letter about change of old owner to new owner.
MiV-N 4	**Change in any part of the (primary) packaging material not in contact with the finished product formulation such as color of flip-off caps, color code rings on ampoules, change of needle shield (different plastic used).**
Conditions	The change is not related to primary or secondary packaging material and shall not affects the delivery, use, safety or stability of the finished drug product
Documents	a. Reason / justification for proposed change. b. Amendment of the relevant section(s) of the dossier, including revised product labeling as appropriate.
MiV-N 5	**Withdrawal/deletion of the alternative manufacturer(s) for drug substance and/or drug product**
Conditions	An alternative manufacturer is registered
Documents	Reason for withdrawal/deletion
MiV-N 6	**Minor change in the manufacturing process of an immediate release solid oral dosage form, semi solid or oral solutions**

Conditions	a. The change includes following: i. Change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients. ii. Change to alternative equipment of the same design and operating principles of the same or of a different capacity. iii. Process changes including changes such as mixing times and operating speeds within application/validation ranges. b. No change in qualitative and quantitative impurity profile or in physio- chemical properties. c. The manufacturing principle for individual manufacturing steps remain unchanged, e.g., there are no changes in the processing intermediates and manufacturing solvent(s) used in the process. d. The proposed process must be controlled by relevant in-process controls used in the approved process and no changes (widening or deletion of limits) are required for these controls. e. The specifications of the finished product and/or process intermediates remain unchanged. f. The proposed process must lead to an identical product regarding all aspects of quality, safety and efficacy
Documents	a. Amendment of the relevant section(s) of the dossier, as appropriate, including a direct comparison of the approved and proposed processes. b. Copy of approved drug product specifications. c. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the approved and the proposed process. d. A declaration/ undertaking from registration holder that: i. Batch analysis data on the next two full production batches shall be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action). ii. The relevant stability studies of the drug product shall be started and that the relevant stability studies shall be finalized; data shall be provided only if outside specification (with proposed action).
MiV-N 7	**Change of release and shelf-life specifications of the drug product, and/or drug substance, and/or excipient, following the inclusion in the compendium / pharmacopeia**
Conditions	Drug products / Drug substances / excipients which are now included in the compendia / pharmacopeia and applicant intends to adopt these specifications
Documents	a. Tabulation of the current and revised release and shelf-life specifications of the drug product, with changes highlighted. b. Revised release and shelf-life specifications. c. Copy of the relevant monograph from the compendium
MiV-N 8	**Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of ink used for product marking**

Conditions	a. New markings do not cause confusion with other tablets or capsules. b. Any ink proposed for use must be edible. c. Release and shelf-life specifications of the drug product remain unchanged except appearance.
Documents	a. Details and specifications of the proposed new ink (where applicable) b. Detailed drawing or written description of the current and proposed imprint/bossing/markings. c. Revised draft of package inserts and labeling incorporating the proposed variation (where applicable). d. Release and shelf-life specifications of drug product with new product description.
MiV-N 9	**Addition or replacement of measuring device for oral liquid dosage forms etc**
Conditions	a. Size and accuracy of the proposed measuring device must be compatible with the approved posology. b. The new device is compatible with the drug product
Documents	a. Justification for the proposed change. b. Revised draft of the package inserts and labeling incorporating the proposed variations (where applicable). c. Description of the device (where applicable) d. Composition of device material and the material should be of pharmacopeial / pharmaceutical grade. e. Justification that size and accuracy of the device are adequate for the posology as approved in the product labeling.

16.4 Details of Minor Variation- Prior Approval (MiV-PA change)

MiV-PA 1	**Change of the name/title or address (e.g., street name/number) of the manufacturer of drug product**
Conditions	a. The manufacturing site remains the same. b. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change c. No other changes, except for the change of the name and/or address of a manufacturer of the drug product. d. Ownership of the company is unchanged.
Documents	a. For imported drug products, official letter from related NRA or municipality (for address only) or original legalized CoPP as per WHO format for new manufacturer's name, or original legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin or any legalized document of concerned regulatory authority confirming the change of name of Manufacturer without change in manufacturing site b. For local manufactured drug products, MFDA's approval letter for proposed variation. c. Copy of registration letter and last renewal status d. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV-PA 2	**Change in the name / title and address of Registration Holder or MAH in exporting country (for finished imported products)**
Conditions	a. Registration holder / MAH and manufacturer should be separate entities. b. The change in address refers to only documentary change in address and the manufacturing site remains the same. c. The name change refers to the renaming of a company or organization. d. The change shall not include transfer of marketing authorization to another company. e. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change. f. No other changes, except for the change of the name / Title of Registration Holder or MAH of the drug product.

Documents	a. Original legalized CoPP as per WHO format for new registration holder / MAH and/or address, or free sale certificate from regulatory body of country of origin or any legalized document of concerned regulatory authority confirming the change of name of Marketing Authorization Holder without change in manufacturing site. b. Evidence of the contract between registration / MA holder and manufacturer (with changed / new name), as the manufacturer and product license/registration holder are different entities. c. Copy of registration letter and last renewal status d. Revised notarized sole agency agreement with new registration holder. e. Revised draft of the package inserts and labeling incorporating the proposed variation (where applicable). f. An undertaking that the formulation, API source and Specifications, manufacturing process, release and shelf-life specifications have not changed.
MiV-PA 3	**Change of name and address of importer**
Conditions	a. The manufacturer including batch release site of drug product remains the same.
Documents	a. MFDA's Drug import License with new address. b. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). c. Copy of registration letter and last renewal status d. An undertaking that the firm that no case is pending at any forum / court of law regarding previous name and/or address
MiV-PA 4	**Changes in Summary of Product Characteristics/Labelling/Patient Information Leaflet**
Conditions	a. The changes shall be in accordance of the innovator drug products as approved by any of the Reference Authority
Documents	a. Previously approved product labelling (SmPC, PIL etc) if any. b. Tabulated comparison in existing and proposed SmPC/PIL highlighting the changes made. c. Copy of registration letter and last renewal status d. Copy of approved SmPC/PIL from any of the Reference Authority. e. Latest version of SmPC/PIL of the Innovator product approved from any of the Reference Authority.
MiV-PA 5	**Change of drug product name**

Conditions	a. There shall be no change to the product specifications including formulation, release, and shelf-life specifications, manufacturing process etc except change of product name. b. No litigation shall be pending at any forum / court of law concerning with the proposed change. c. The registration / MA holder will check the suitability of proposed names to ensure that no resemblance or phonetic matching with already registered products as per LASA so that the proposed names should not be liable to cause confusion in print, handwriting or speech with the (Proprietary / brand) name of another registered product. d. The proposed name shall not suggest greater safety or efficacy than supported by clinical data, convey misleading therapeutic use or imply superiority over another similar product or show the presence of substance(s) present or not present in the product.
Documents	a. Justification for the proposed change b. Information regarding previous approvals of change of brand name since registration of drug product. c. Details (batch number, date of manufacture, quantity and stock position) regarding last batch manufactured / imported. d. Copy of registration letter and last renewal status e. An undertaking that the proposed names do not resemble with already registered brands and in case of resemblance /similarity with already registered drug, the applicant will be liable to change immediately. Moreover, no case is pending at any forum / court of law regarding this matter. Line extension f. Legalized CoPP or FSC in case of imported drug products. g. Revised draft package insert and labeling incorporating the proposed variation. h. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable).
MiV-PA 6	**Change of importer/ MA holder in Maldives**
Conditions	a. The manufacturing site remains unchanged. b. No litigation shall be pending at any forum / court of law concerning with the proposed change. c. Present importer has not imported registered drug product for more than 3 years.
Documents	a. Notarized authority letter/sole agent letter (original) from marketing authorization holder/ manufacturer (if both are separate) in name of new importer. b. Copy of registration letter and last renewal status c. Revised drafts of the package insert and labeling incorporating the proposed variation. d. Legalized Certificate of Pharmaceutical Product (CoPP) or other relevant documents as defined by MFDA for new registration

MiV-PA 7	**Change in Market Authorization Holder (MAH) in exporting country**
Conditions	a. The manufacturing site remains unchanged. b. The registration holder in Maldives shall remain the same. c. Undertaking from new MA holder in exporting country that no litigation is pending at any forum / court of law concerning with the proposed change
Documents	a. Notarized authority letter/sole agent letter (original) from new Market Authorization Holder (MAH) abroad. b. Approval of new MAH from regulatory body of exporting country or Legalized Certificate of Pharmaceutical Product (CoPP) mentioning new Market Authorization Holder (MAH). c. Copy of registration letter and last renewal status
MiV-PA 8	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product**
Conditions	a. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product)
Documents	a. Justification for the proposed change. b. For imported products, proof that the proposed site is legally authorized for the packaging activity of the drug product concerned such as CoPP (legalized) which covers GMP certification. c. For locally manufactured drug products, MFDA's regulatory approval for the proposed variation. d. Copy of registration letter and last renewal status. e. Validation scheme and/or report of the manufacturing process to the proposed change of alternative site for primary packaging (where applicable). f. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). g. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). h. A letter of commitment from marketing authorization holder to conduct long term and accelerated stability studies for the first three batches of drug product packed at the proposed site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
MiV-PA 9	**Change of batch size of drug product**
Conditions	a. The change does not affect consistency of production. b. The product formulation remains unchanged. c. Shelf-life specifications of drug product remain unchanged. d. This is applicable to change of batch size up to 10-fold compared to the approved batch size. e. The manufacturing process shall remain unchanged

Documents	a. Justification for the proposed change b. Comparative tabulated format of approved and proposed batch size and batch manufacturing formula. c. Validation scheme and/or report of the manufacturing process of the proposed batch size. d. Copy of registration letter and last renewal status. e. Specifications of the drug product f. Revised section of registration application form (where applicable). g. Release and shelf-life specifications of the drug product. h. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to approved and proposed batch sizes. i. For oral solid dosage forms, comparative dissolution profile for at least one production batch (where applicable). j. Appropriate real time and accelerated stability data to support proposed variation.
MiV-PA 10	**Quantitative change in coating of tablets and/or size of capsule shell**
Conditions	a. The dissolution profile of the proposed product is comparable to that of the approved product. b. Specifications of the drug product remain unchanged except for the weight and/or size (where applicable).
Documents	a. Justification for the proposed change. b. Comparative tabulated format of approved and proposed product and batch manufacturing formula. c. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms. d. Revised draft of product label incorporating the proposed change (where applicable). e. For modified release oral products, stability data of the drug product and to report if any results fall outside shelf-life specifications (with proposed action) f. Copy of registration letter and last renewal status. g. Specifications of drug product. h. A declaration/ undertaking that: i. The change does not interfere with the drug product specifications test method. ii. The relevant stability studies of the drug product have been started and shall be reported if any results fall outside specifications (with proposed action).
MiV-PA 11	**Change of dimensions and/or shape of tablets, capsules, suppositories or Pessaries**
Conditions	There will be no qualitative or quantitative change in API.

Documents	a. Justification for the proposed change. b. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). c. Copy of registration letter and last renewal status. d. Detailed drawing or written description of the approved and proposed appearance. e. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed dimensions/shape for oral solid dosage forms. f. For scored tablets, data on test of uniformity of the subdivided parts of tablets at release as conformed to compendia requirement. g. Specifications of the drug product with proposed dimension and/or shape.
MiV-PA 12	**Change of secondary packaging materials**
Conditions	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties
Documents	a. Justification for the proposed change. b. Tabulated differences between existing and proposed information. c. Copy of registration letter and last renewal status d. An undertaking that: i. The proposed color scheme / label has no resemble with already registered Products. In case of resemblance, new label will be changed immediately. ii. Proposed change has not impact on the shelf life of the product. iii. No case is pending at any forum / court of law regarding this matter.
MiV-PA 13	**Change in the design or color scheme of packaging material**
Conditions	a. The proposed packaging design/color scheme must not resemble to already registered product. b. Packaging material shall remain same
Documents	a. Justification for the proposed change. b. Tabulated comparison of differences between existing and proposed design. c. Regulatory approval of change from country of export in case of imported drug. d. Copy of registration letter and last renewal status e. An undertaking/ declaration that: i. No case is pending at any forum / court of law regarding this matter. ii. All information related to the product like dosage, administration, indication and direction for use etc. on the label are in line with the registration / marketing authorization. iii. The proposed label complies all provisions of relevant rules and regulations.
MiV-PA 14	**Change of the coloring agent /capsule shell color of the product**

Conditions	a. Same functional characteristics / specifications including no change in dissolution profile for solid oral dosage forms. b. The proposed coloring agents /capsule shell are of pharmaceutical grade. c. The specifications of the drug product remain unchanged, except for the update of product description with respect to appearance/odor/taste as a consequence of the change (where applicable).
Documents	a. Justification for the proposed change. b. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). c. Revised product formulation and batch manufacturing formula. d. Copy of registration letter and last renewal status. e. Tabulated comparison of qualitative and quantitative information of the approved and proposed coloring agent /capsule shell color. f. For proposed excipients made of ruminant's source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). g. Revised specifications of the drug product. h. Certificate of Analysis of proposed coloring agent /capsule shell (where applicable). i. A declaration/ undertaking that: i. The proposed coloring agent/capsule shell color does not interfere with the drug product specifications test method. ii. A letter of commitment from marketing authorization holder to inform users of the relevant change (where applicable). iii. Stability study has been started and report if any results fall outside drug product specifications (with proposed action).
MiV-PA 15	**Addition/ change of flavoring agent of the product e.g oral liquid/ dry powder suspension/sachet**
Conditions	a. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. b. The proposed flavoring agents must be of pharmaceutical use. c. The specifications of the drug product remain unchanged, except for the update of product description with respect to flavor/taste as a consequence of the change (where applicable).

Documents	a. Justification for the proposed change. b. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). c. Revised product formulation and batch manufacturing formula. d. Tabulated comparison of qualitative and quantitative information of the approved and proposed flavoring agent. e. Copy of registration letter and last renewal status f. For proposed excipients made of ruminant's source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). g. Revised specifications of the drug product. h. Certificate of Analysis of proposed flavoring agent (where applicable). i. A declaration/ undertaking that: i. The proposed flavoring agent does not interfere with the drug product specifications test method. ii. A letter of commitment from marketing authorization holder to inform users of the relevant change (where applicable). iii. Stability study has been started and report if any results fall outside drug product specifications (with proposed action).
MiV-PA 16	**Change of shape or dimension of container closure system**
Conditions	a. The change only concerns the same packaging type and material. b. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. c. Change in the dimension of the primary packaging (where applicable). d. Specifications of the drug product remain unchanged.

Documents	a. Justification for the proposed changes in container closure system. b. Information on the proposed container-closure system (e.g. description, materials of construction, and specifications). c. Copy of registration letter and last renewal status. d. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). e. Re-validation studies for manufacturing process and sterilization process performed in case of sterile products which are terminally sterilized. f. Revised Sections of registration applications (where applicable). g. A declaration/undertaking that the relevant stability studies of the drug product have been started and that the relevant stability studies shall be finalized; data shall be provided only if outside specification (with proposed action). h. The proposed label complies all provisions of relevant rules and regulations. i. An undertaking that: i. Other specifications of the product would remain the same. ii. There is no change in the qualitative & quantitative composition of the product and manufacturer will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug. iii. In the case of changes to the thickness of a packaging component or for sterile FPPs: stability data (as per conditions of zone IV-A), where applicable, results of photo-stability studies will be conducted on 03 lab scale batches or developmental scale batches. iv. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies to ensure appropriate delivery. v. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to MFDA and all the stock will be recalled from the market immediately.
MiV-PA 17	**Replacement of the company or party responsible for batch release**
Conditions	a. Only applicable for batch release. b. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed. c. The manufacturer of the drug product remains the same

Documents	a. Justification for the proposed change. b. Official letter from manufacturing company that the batch release responsible is changed. c. Proof that the proposed site is appropriately authorized (accredited by the NRA) to be responsible for batch release, such as a valid GMP certificate or CoPP which covers the GMP certification for imported products and MFDA approval for locally manufactured products. d. Copy of registration letter and last renewal status. e. Document for method transfer to the proposed site along with validation of method and mock testing on already manufactured batches, f. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV-PA 18	**Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in- process test)**
Conditions	a. Release and shelf-life specifications of drug product remain unchanged. b.The change does not result from unexpected events arising during manufacture (e.g., new unqualified impurity, change in total impurity limit)
Documents	a. Justification for the proposed change. b. Copy of registration letter and last renewal status. c. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). d. Revised in-process specifications together with justification and relevant process validation data. e. Comparative tabulated format change of the in-process controls. f. Certificate of analysis and comparative batch analysis data of drug product of at least two production/pilot batches
MiV-PA 19	**Change in the test procedure of the drug product (including replacement or addition of a test procedure)**
Conditions	a. Drug product specifications are not adversely affected unless the specifications are tightened. b. Results of method verification/validation show new test procedure to be at least equivalent to the former procedure. c. The change should not be the result of unexpected events arising during manufacture or because of stability concerns
Documents	a. Justification for the proposed change. b. Copy of registration letter and last renewal status. c. Description of the analytical methodology. d. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test. e. Comparative tabulated format of the currently approved and proposed release and shelf-life specifications of the drug product. f. Certificate of analysis and batch analysis data of the finished product of two production batches when made available

MiV-PA 20	**Change of release and shelf-life specifications of the drug product** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
Conditions	a. Applicable to non-compendial / non-pharmacopeial methods. b. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. c. The test methods remain the same or changes in the test methods are minor. d. If there are changes to the test procedure, then relevant conditions and documents will be required.
Documents	a. **Specification limits are tightened** i. Tabulated comparison of the current and revised release and shelf-life specifications of the drug product with changes highlighted. ii. Certificate of analysis and comparative batch analysis data of the drug product for all tests in the new specification of at least two batches. b. **Addition of new test parameter and limits** i. Justification for the proposed change ii. Description of new test parameter and limits along with validated method and summary of analytical validation data for non-compendial method. iii. Stability data and report if any results fall outside shelf-life specifications (with proposed action) (where applicable).
MiV-PA 21	**Standardization of formulation in accordance with the Innovator's Drug Product/ Reference Authorities and Pharmacopeias**
Conditions	Existing formulation shall remain the same
Documents	a. Justification for the proposed change. b. Copy of registration letter and last renewal status. c. Document in support of proposed correction/evidence of approval status by Reference Authorities/ innovator drug product and/ or Pharmacopeias. d. Undertaking that the provided information/ documents is true/ correct.
MiV-PA 22	**Reduction or removal of overage**
Conditions	a. Change of previously approved manufacturing overages of drug substance only. b. Release and shelf-life specification of drug product remain unchanged.
Documents	a. Justification for the proposed change. b. Tabulated comparison of currently approved and proposed batch manufacturing formula. c. Certificate of analysis of 2 batches of finished drug product. d. Stability data and report, if any result fall outside shelf-life specification.
MiV-PA 23	**Change in source of empty hard capsule**
Conditions	a. No change in formulation and manufacturing process of drug product. b. No applicable to change from hard capsule to soft gel. c. Formulation including excipients will remain unchanged d. Release and shelf-life specification of drug product remain unchanged.

Documents	a. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product using hard capsule between two sources (where applicable). b. Certificate of analysis of empty hard capsule of the proposed source. c. Specification and composition of empty hard capsule of new source (including origin i.e. synthetic, vegetable or animal source). d. Stability data and report, if any result fall outside shelf-life specification.
MiV-PA 24	**Addition or removal of score / break line on tablet**
Conditions	a. Innovator drug product has same score / break line on tablet. b. Release and shelf-life specifications of the drug product remain unchanged except appearance.
Documents	a. Justification of the proposed change (including change in dosage regimen) b. Details and specifications of the proposed change. c. Detailed drawing or written description of the current and proposed score / break line on tablet. d. Revised draft of package inserts and labeling incorporating the proposed variation (where applicable). e. Release and shelf-life specifications of drug product with new product description. f. Certificate of analysis of two production /pilot scale batches.

16.5 Details of Major Variation (Ma V)

Major Variation (MaV)	
Ma V 1	**Change or addition in the source of Active Pharmaceutical Ingredient / Drug Substance or Half-Finished Products i.e. Pellets / Granules / Ready to Fill Bulk etc.**
Conditions	Specifications of drug substances remain unchanged.
Documents	a. Real time and accelerated stability studies of DS / Half finished products (pellets / granules / ready to fill bulk) conducted by manufacturer of DS / half finished product as per conditions of zone IV-A or zone IV-B on 3 commercial scale batches. b. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable). c. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. d. Documents confirming that the proposed source has valid permission for manufacturing of DS / pellets / granules / ready to fill bulk by the regulatory authority of country of origin. e. Copy of registration letter and last renewal status. f. A letter of commitment from marketing authorization/ registration holder to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
Ma V 2	**Change of the manufacturing site of drug product**
Conditions	a. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change. b. The registration holder/importer shall remain the same. c. Market Authorization Holder abroad shall remain the same. d. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place
Documents	a. Document from NRA for confirmation of approval status of proposed site like valid good manufacturing practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CoPP) which covers GMP certification. b. Official letter authorizing the proposed site to manufacture the product. c. Copy of registration letter and last renewal status. d. Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batches) from the proposed site, and the last three batches from the current site. Batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action). e. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the previous approved and proposed manufacturing site for oral solid dosage forms. f. Product development data including real time and accelerated stability data

	from the proposed site and report if any results fall outside shelf-life specifications (with proposed action). g. Comparative manufacturing process at the two sites. h. Validation data or validation protocol to be submitted and where relevant, batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated. i. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). j. Product formula. k. Release and shelf-life specifications of drug product. l. Batch numbering system (where applicable). m. Specification of drug substance.
Ma V 3	**Qualitative or quantitative change of excipients**
Conditions	a. There will be no qualitative or quantities change in API/DS. b. Specifications of drug product remain unchanged, excluding product description except for update of product description with respect to appearance/odor/taste as a consequence of the change (where applicable). c. Replacement of an excipient with a comparable excipient of the same functional characteristics. d. The dissolution profile of the proposed product is comparable to that of the approved product. e. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed product formula. f. Change of colours and flavors will not be in this variation as MiV-PA
Documents	a. Justification for the proposed change supported by product development data (including stability aspects and antimicrobial preservation where applicable). b. Copy of registration letter and last renewal status. c. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). d. A declaration that the proposed excipient does not interfere with the drug product specifications and test method (where applicable). e. Comparative tabulated format of the approved and proposed product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight (where applicable). f. Comparative dissolution profile data of at least one batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms. g. Revised batch manufacturing formula. h. Validation scheme and/or report of the manufacturing process appropriate to the proposed change in product formula should be provided upon submission. i. Revised Sections of drug product registration application as per Medicines Registration Guide (where applicable).

	j. Specifications of the proposed excipient. k. For proposed excipients made of ruminant's source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). l. Drug product specifications. m. Confirmation that proposed excipients are of pharmacopeial grade. If not present in any pharmacopeia, then pharmaceutical grade excipients will be used. n. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on at least two production batches according to approved and proposed product formula. o. Stability data of at least six months and to report if any results fall outside shelf-life specifications (with proposed action). p. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).
Ma V 4	**Change in shelf life of drug product (extension or reduction)**
Conditions	a. No change to the composition, primary packaging type in direct contact with the FPP and to the recommended conditions of storage. b. Stability data were generated in accordance with the currently accepted stability protocol. c. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
Documents	a. Copy of the currently accepted shelf-life specifications. b. Copy of registration letter and last renewal status. c. Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol, test results with relevant for a minimum of two production-scale batches for a period sufficient to support the proposed shelf-life. d. Updated post-acceptance stability protocol and stability commitment. e. Approval of regulatory body of country of origin (in case of imported products). f. If the reduction in shelf life is necessitated because of stability concerns, declaration of reason for reduction in shelf life g. An undertaking that in case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to MFDA all the stock will be recalled from the market immediately.
Ma V 5	**Change of storage conditions of the drug product**
Conditions	a. The studies must show conformance to the approved shelf-life specification. b. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.
Documents	a. Justification for the proposed change. b. Proposed change is supported by documentary evidence from reference regulatory authorities and/ or innovator product. c. Copy of registration letter and last renewal status. d. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of the product and in the

	authorized packaging material and results of microbiological testing should be included (where appropriate). e. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). f. If the change is necessitated because of stability concerns, declaration of relevant reason for change in storage condition. g. An undertaking that in case of any quality complaint/ OOS result observed by the marketing authorization holder, the same will be reported to Registration Board and all the stock will be recalled from the market immediately
Ma V 6	**Change in primary packaging material of drug product**
Conditions	a. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. b. Specifications of drug product remain unchanged
Documents	a. Justification for the proposed change b. Revised drafts of the package insert incorporating the proposed variation (where applicable). c. Copy of registration letter and last renewal status. d. Accelerated and real time stability studies on the proposed packaging. e. For semi-solid, liquid oral and injectable dosage forms, data must be provided that no interaction between the content and the packaging material occurs (e.g. no extraction/leaching of components of the proposed material into the content and no loss of components of the product into the pack), permeation testing (light transmission, moisture permeation, O_2, CO2 etc) and demonstrating equivalent or superior protection compared to the existing packaging system. f. Comparative table of the current and proposed immediate packaging specifications and appropriate Information on the proposed container closure / primary packaging type such as description, material of construction of primary packaging, specifications etc, for changes to functional packaging related to container closure (e.g. MDIs etc), data to demonstrate the functioning of the new packaging. g. Container-Content compatibility studies. h. Validation scheme and/or report of the manufacturing and sterilization process for sterile products i. Tabulated comparison of the approved and proposed specifications of the primary packaging material (where applicable). j. Revised sections of registration applications (where applicable). k. Six months stability data and with undertaking to report if any results fall outside specifications (with proposed action) up to the proposed shelf life. l. Approval of regulatory authority for proposed change in case of imported drug product.
Ma V 7	**Change in Prescribing Information (PI) and labelling related to changes in Indications, Contraindications, dosage etc.**
Conditions	These changes have already been approved by any reference authority and implemented by innovator drug product

Documents	a. Justification of proposed changes and difference between existing and proposed information in tabulated form. b. Reference of prescribing information approved by Reference Regulatory Authorities and innovator product. c. Copy of registration letter and last renewal status. d. Copy of approval from regulatory agency / authority from country of origin for innovator's drug product. e. Copy of label outer pack in case of changes in indication/ dose/ administration etc.
Ma V 8	**Change of specifications or method of analysis of finished drug product**
Conditions	a. Proposed specifications or method of analysis are not included in any pharmacopeia except in cases where proposed manufacturer specifications are more stringent than pharmacopeial specifications. b. For change in specifications, method of analysis will remain same or with minor change. c. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns. d. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change
Documents	a. Justification for the proposed change, b. Comparative table of current and proposed specifications or method of analysis. c. Validated method of analysis in case of change of method of analysis. d. Copy of registration letter and last renewal status. e. Certificate of analysis of at least one batch and comparative summary of results, in tabular format, for one batch using current and proposed procedures. f. Undertaking that : i. No case is pending at any forum / court of law regarding this product. ii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to MFDA and all the stock will be recalled from the market immediately.
Ma V 9	**Inclusion or replacement of the solvent/diluent for the drug product**
Conditions	a. The proposed change will not result in any change in the dosage form, regimen, indication, method of administration of the product. b. The diluent/ solvent is added/ replaced in line with the innovator drug product as approved by any reference authority.
Documents	a. Justification for the proposed change. b. Revised drafts of the package insert and labeling incorporating the proposed variation. c. Copy of registration letter and last renewal status. d. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). e. A declaration/ undertaking from the marketing authorization holder that

	shelf-life specifications of drug product are not affected. f. Revised sections of drug product registration application as per Medicines Registration Guide (where applicable).
Ma V 10	**Major change in the manufacturing process of the finished drug product**
Conditions	a. The proposed process shall lead to an identical product regarding all aspects of quality, safety and efficacy. b. The manufacturing site remains unchanged. c. Product specification remains unchanged.
Documents	a. Justification for the proposed change. b. Description of the proposed manufacturing process and product development data thereof. c. Copy of registration letter and last renewal status. d. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms e. Validation scheme and/or report of the proposed manufacturing process. f. Copy of approved specifications with copy of proposed specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy needs trials. g. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product for a minimum of one production batch manufactured according to approved and proposed processes. h. Real time and accelerated stability data of at least six months and to report if any results fall outside shelf-life specifications (with proposed action) i. Evidence of approval of proposed change by regulatory authority of country of origin.

16.6 General consideration for variations.

a. 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".

b. 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.

c. 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 Special Permissions and Exemptions

17.1.1 MFDA grants special permission for import of unregistered drugs to hospital to ensure access of drugs for the treatment of patients. These exemptions are granted in the form of Preauthorization in reference to the Guideline for Pre-Authorization Approval of Medicines (MTG-RE-PA/GLN-TE 010) and are exclusively granted to hospitals for use of medicines in their own facilities only.

17.1.2 These permissions are subjected to following points: -

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.

18 Clinician's Request for Approval of New Medicine

18.1.1 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.

18.2 Required Documents

a. A completed "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

18.3 Process of clinician form

18.3.1 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.

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

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

18.4 Rejection of Form

18.4.1 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.

19 Post Marketing Surveillance

19.1.1 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 with the applied documents for registration.

19.1.2 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.

15 References

1. WHO Global Benchmarking Tool (GBT) for Evaluation of National Regulatory Systems of Medical Products, Revision VI. Geneva: World Health Organization; 2021.

2. World Health Organization, WHO Technical Report Series, No. 863, 1996.

3. WHO Technical Report Series No. 970, 2012

4. ICH Quality guidelines Q1A – Q1F Stability.

5. World Health Organization. *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.

6. 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

7. 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

8. World Health Organization. (2013). (Technical Report Series). *WHO guidelines on variations to a prequalified product (Annex 3)*. (Forty seventh, Ser. no. 981, pp. 1–62) Retrieved from https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/prequalification/trs981-annex3-who-variations-prequalified-product.pdf?sfvrsn=809e81b_2.

9. 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.

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10. 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

11. 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

12. 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

Annexure-I

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:

Annexure-II

Regulatory Authorities for reliance

	Country	Authority
	Australia	Therapeutic Goods Administration
2	Austria	Austrian Agency for Health and Food Safety (AGES)
3	Belgium	Federal Agency for Medicines and Health Products (FAMHP)
4	Bulgaria	Bulgarian Drug Agency
5	Canada	Health Canada
6	Croatia	Agency for Medicinal Products and Medical Devices of Croatia (HALMED)
7	Cyprus	Ministry of Health — Pharmaceutical Services

	Country	Authority
8	Czech Republic	State Institute for Drug Control (SUKL)
9	Denmark	Danish Medicines Agency
10	Estonia	State Agency of Medicines (Ravimiamet)
11	Finland	Finnish Medicines Agency (Fimea)
12	France	National Agency for the Safety of Medicine and Health Products (ANSM)
13	Germany	Federal Institute for Drugs and Medical Devices
14	Greece	National Organization for Medicines
15	Hungary	National Institute of Pharmacy and Nutrition (OGYEI)
16	Iceland	Icelandic Medicines Agency

	Country	Authority
17	Ireland	Health Products Regulatory Authority
18	Italy	Italian Medicines Agency (AIFA)
19	Japan	Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency
20	Latvia	State Agency of Medicines
21	Liechtenstein	Office of Health / Department of Pharmaceuticals
22	Lithuania	State Medicines Control Agency (VVKT)
23	Luxembourg	Ministry of Health
24	Malta	Medicines Authority
25	Netherlands	Health and Youth Care Inspectorate (IGZ)

	Country	Authority
26	Norway	Norwegian Medicines Agency
27	Poland	Chief Pharmaceutical Inspectorate
28	Portugal	National Authority of Medicines and Health Products (Infarmed)
29	Romania	National Agency for Medicines and Medical Devices
30	Slovakia	State Institute for Drug Control (SIDC)
31	Slovenia	Agency for Medicinal Products and Medical Devices (JAZMP)
32	Spain	Spanish Agency of Medicines and Medical Devices (AEMPS)
33	Sweden	Medical Products Agency
34	Switzerland	Swiss Agency for Therapeutic Products (Swissmedic)

	Country	Authority
35	United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)
36	United States of America	Food and Drug Administration
37	Republic of Korea	Ministry of Food and Drug Safety (MFDS) intlpharm@korea.kr
38	Singapore	Health Sciences Authority (HSA) hsa_intl_office@hsa.gov.sg
39	Argentina	ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica the Borrower's or National Food, Drug, and Medical Technology Administration)
40	Brazil	ANVISA (Agência Nacional de Vigilância Sanitária or National Health Surveillance Agency)
41	Chile	ISP (Public Health Institute of Chile)
42	Indonesia	BADAN POM (*Agency for Drug and Food Control*, or **Indonesian FDA)**

	Country	Authority
43	Mexico	COFEPRIS
44	Cuba	CECMED
45	Malaysia	National Pharmaceutical Regulatory Agency (NPRA)

Annexure-III

APPLICATION CHECKLIST for full dossier

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 Pathway the product is applying under.
3. All documents required shall be submitted in colored 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.
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 check list shall be filled and uploaded in excel format to Dhirithi Portal with relevant documents based on the registration pathway .****(This form can be retrieved in Dhirithi Portal under publication).*

6. If any section within the criteria of the form left unfilled, or/ and a mandatory document and the required information is not submitted, MFDA will reject the dossier.
7. **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 Select application type:**

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

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

1. Registration Pathways **(Applicant shall color the chosen pathway)**

Reliance Option 1.1.1 Verification. Reliance on MA (approved by reference NRAs)	**5 years**	
Reliance Option1.2.1 GMP verification (manufacturing site certified by PIC/S member NRA) Abridge	**5 years**	
Reliance Option 1.2.2 WHO prequalified products/manufacturers	**5 years**	
Reliance Option 1.3.1 Collaborative registration procedure (CRP-PQ)	**3 years**	
Reliance Option 1.3.2 Collaborative registration procedure (CRP-SRA)	**3 years**	

Full procedure 1.1 Full dossier	**5 years**	☐
Full procedure 1.2 Full dossier (CTD Format)	**5 years**	☐
Notification: for low-risk medicines like vitamins and vitamin preparation that are categorized as medicines.	**5 years**	☐

2. Registration type

A) New Registration	☐	**(Color the registration type as shown)**
B) Re-registration	☐	

3. Product Evaluation Summary

(If any mentioned document is not requirement for the chosen pathway mention NOT APPLICABLE FOR THIS PATHWAY for that specific column)

	Client submitted information (Fill this column as shown below)	Evaluation Remarks	Check and verified
A) Legal status	-		

Letter of appointment as the local agent if the applicant is local	***Statement by Applicant (local) Submitted (mention the uploaded slot numbe**r)*		
Letter from manufacturer to MFDA	***Submitted (mention the uploaded slot numbe**r)*		
B) General Product Information			
a) API information under any of the mentioned criteria	***Submitted (mention the uploaded slot number)***		
b) Product name	***Product Name including strength (eg: Gepride 2mg)***		
c) International Nonproprietary Name (INN) or the Active Pharmaceutical Ingredient (API) or Generic name including e. Pharmacopeia standard / Formulation of the product	***The name and amount of active pharmaceutical ingredient(s) / Drug substance(s) present in the formulation and in the form of salts or chelates shall be clearly stated. Example: 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 IP + Docosahexaenoic Acid 150mg BP +vitamin D3 200IU***		

d) Non-active ingredient or Excipient including e. Pharmacopeia standard / Formulation of the product	***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. Formulation eg: BP, IP,USP etc.***		
iii. 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).	***Example: CoA for all raw materials submitted (mention uploaded slot number)***		
iv. 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	***Example :Submitted (mention uploaded the slot number)***		
v. The test mentioned above shall be as per the official monogram for purity.	***Example: submited a declaration letter for aasuarence. Mention slot Number***		
vi. Registration holder will ensure that the manufacturer will perform impurity testing as identified by the manufacturer of innovator drug product like N-Nitroso dimethylamine (NDMA), N-Nitroso diethylamine (NDEA) in valsartan, metformin etc.			

e. ii) ii. If there is no pharmacopeial formulation as mentioned in point c and d 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 as nominated by the Authority.	***Example: Submitted (slot Number Else not required as this is not an inhouse formulation)***		
f) Dosage form of the product	*i. Dosage form shall be as specific as possible with respect to the product's actual dosage form. Example: Film-coated Tablet , sustained release tablets.* *ii. 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(s) of the product	*Strength is defined as the amount of active pharmaceutical ingredient(s) / Drug substance(s) in the dosage form. Strength shall be provided for all APIs/DS including if the product is a combination drug. Each strength shall be separated with a "+" Example.: 500mg + 250mg*		
h) Volume of the preparation	*10 X 10's*		
i. Product description, Container type and Pack sizes	*i. Description of primary packaging shall be defined with the pack size. Example blister pack of 12 tablets* *ii. 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* *iii. Length, width, height of primary and secondary packaging shall be provided in detail.*		
j. Route(s) of Administration	*Route of administration proposed for the product shall be included as mentioned in the product label and specified accordingly.*		

k. Indication or Use of the product	*The intended uses or the indication of the product shall be clearly specified.* *Example: Used for upper respiratory infections* ***Give reference by providing a link or any other valid source.***		
l. Therapeutic Class	*i. The WHO ATC code* *ii. WHO ATC classification* ***Give referenceby providing a link or any other valid source***		
m. Storage conditions	*i. The condition in which the drug product shall be stored and kept shall be clearly specified. Example temperature, humidity etc. Of the product storage as mentioned in product label shall be specified* *ii. Non-numeral statements such as "Store in a cool dry place" is not encouraged.*		
n. Shelf life of the product	*Product Shelf life shall be specified in months.*		
o. Dispensing Category	*Dispensing Category in country of origin shall be specified. 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 dosage form	*Example :ABZ PHARMACEUTICALS LTD, Lane No. 11, Phase-9, SIDCO Industrial Complex, Bari Brahmana, Jammu-181 2948. India* ***(must be same as the product label)***		
C3) Manufacturer responsible for packaging of the finished product, if different	***Fill only if different from manufacturer, else N/A since it's not different***		

C4) Manufacturing License number	***Example:*** *JK/01/05-06/75 on Form 25 & JK/01/05-06/76 on Form 28 & Valid up to 08.05.2025*		
Sample /artwork, Full package picture	*Example: submitted, Mention uploaded slot number*		
Documents as per registration pathways			
1.1.1 Reliance on MA (approved by reference NRAs) Verification	***Example: Mention the evidence provided as per the guideline. and uploaded slot number***		
1.2.1 GMP verification (manufacturing site certified by PIC/S member NRA) Abridge	***Example: Mention the evidence provided as per the guideline. and slot number***		
Evidence of approval by the NRA of the country where the finished dosage form is manufactured and batch release takes place	***Example : Mention the evidence provided as per the guideline. and slot number***		
Verifiable declaration of approval by at least 3 other NRAs	***Example: Mention the evidence provided as per the guideline and slot number***		
1.2.2 Evidence of WHO prequalification of the product and site	***Example : Submitted slot Number Else not required under this pathway***		
1.3.1 Letter of manufacturer showing interest in going for this pathway. (CRP-PQ)	***Example :Submitted slot Number Else not required under this pathway***		
1.3.2 Letter of manufacturer showing interest in going for this pathway. (CRP-SRA)	***Example : Submitted slot Number Else not required under this pathway***		
Marketing Authorization certificate from the country of manufacture	***Example : Submitted slot Number Else not required under this pathway***		

	Marketing authorization certificate from 2 or more reference NRAs	***Example : Submitted slot Number Else not required under this pathway***		
	4. Is the formulation acceptable?			
	Is the pharmacokinetic profile acceptable, suiting to patient compliance and nature of disease	*N/A*		
	Is the dosage form easy to administer and acceptable to patients.	*N/A*		
	If the medicine is not a single active ingredient formulation but a combinations is it acceptable according to the criteria B49:E50B49:D50	*N/A*		
	If the product is modified release is it acceptable in terms of the therapeutic objective	*N/A*		
	Is the packaging acceptable? primary container , and packaging material label, box, blister/ strip foil	*N/A*		
	Product information Literature/ Product package insert acceptable?	*N/A*		
	5. Is quality acceptable?			
	API Validation report	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
	If applicable bioavailability studies against a benchmark product.	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
	Proof of Validation of the manufacturing method	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		

Standard batch size quantity with label claim, Batch size, quantity of all active ingredients and excipients	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Technical specifications and sources of all raw material(s) with pharmacopeia specification	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Brief profile of manufacturer with products manufactured	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Company profile (for newly registering manufacturers)	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Manufacturing plant layout and machinery involved	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Manufacturing and packaging process	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
List of personnel, their responsibilities, and qualifications (Name, qualification and experience (in years) of the authorized key personnel)	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Regulatory decisions taken on this finished product from any regulatory authorities (A formal, signed statement from the manufacturer and/or MAH)	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
Copy of the finished product specification(based on a referance to an official monogram and if an in-house method is used, it shall be endorsed by a third party)	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		

Shelf life validated by stability studies for climatic zone IV	***A) Real-Time stability data of shelf life:*** *Example: Long term stability data submitted for 36 months with Temperature at 30 ± 2°C / Humidity at 75 ± 5 %RH* ***(mention the uploaded slot number)***		
	B) Accelerated stability data: Example: *Accelerated stability data submitted for 6 months with Temperature at 40 ± 2°C / Humidity at 75% ± 5 % RH* ***(mention the uploaded slot number)***		
Stability report statement	***Example:*** *Provided (mention the uploaded slot number)*		
7. ***Documents for Quality verification***			
Certificate of Analysis for batch release, Certificate of Analysis of Finished product (CoA)	***Example:*** *Provided (mention the uploaded slot number)*		
Certificate of a Pharmaceutical product (CoPP)	***Example*** *:Certificate number: WHO/GMP/2023-2026/75/04 issued by Drugs Licensing Authority, Jammu, (J & K), India (mention the uploaded slot number)*		
Registration status of Finished product in countries other than country of origin and country of origin	***Example :*** *Registered in India or any other country and mention the registration number JK/01/05-06/75 on Form no 25 Date of issue. 23.04.2011* ***Give referenceby providing a link or any other valid source***		

Valid GMP certificate attesting to the status of the manufacturer as to competency, of personnel, equipment and facilities.	***Example :*** *Certificate number: DFO/D-538/3677 issued by Office of the State Drugs Controller, Drugs & Food Control Organization, Patoli Mangotrian, PO: Janipur, Jammu - 180007 (J & K) India (**mention the uploaded slot number)***		
If GMP certificate not available is a copy of most recent GMP inspection report conducted attached?	***Only if it is a requirement as per registration pathway*** *If submitted mention provided and slot number*		
8. Other factors considered			
For cough/cold, paracetamol preparations: -Tests for DEG/EG submitted for all excipients and source validation of excipients submitted	***Only if it is a requirement as per registration category*** *(If submitted mention provided and slot number Else N/A under the submmitted category)*		
Has local health problems which influence selection morbidity, mortality, need analysis considered?	*N/A*		
Can the medicine be used with the facilities and professional expertise available	*N/A*		
If the product sample is testable at NHL, does the product pass?	*N/A*		
Is the medicine a WHO pre-qualified product?	*If it is a WHO pre qualified product mention as such*		
Proof that the product is WHO pre-qualified	*Give reference by providing a link or any other valid source*		
Is the medicine available in ADL	*If availabele* ***Example:*** *(Yes this medicine is available in ADL and mention P code)* ***OR*** *this specific brand not available , though other generics available.* ***OR*** *This medicine is not available in ADL, This application is for new registration.* ***(Fill accordingly)***		

Price of the product in USD	***A) Cost price in USD: Example :*** *0.05 USD per Tablet*		
	B) Retail price in USD: Example : *0.11 USD per Tablet*		

Annexure-IV

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.
- **Sterility-**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.

Annexure-V

CERTIFICATES OF SUITABILITY (CEP)

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

The CEP is a document that is 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 a 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.

Annexure-VI

TECHNICAL INFORMATION ON THE ACTIVE PHARMACEUTICAL INGREDIENT

The documentation shall also contain the following information:

1. General information:

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

2. **API manufacturing process:**
    a) Manufacturer(s): name, full address, company responsible for each manufacturing process step and quality
    b) control (including contracted companies, third-parties).
    c) Description of the production process, including materials, equipment and operating conditions (for example,
    d) temperature, pressure, pH, time ranges, stirring speed, etc.); and of the in-process controls.
    e) Identification of the critical steps including the respective tests and acceptance criteria
    f) Production process flowchart indicating the formation of intermediates and possible impurities, including the
    g) clarification of the respective chemical structures.
    h) Indication of the raw materials, solvents, catalysts, etc…
    i) Indicate the production scale and yield.
    j) Specifications of the raw materials and packaging materials.
3. **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.
4. **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,
    c) intermediate products, degradation products, reagents and catalysts.
    d) Inorganic Impurities: reagents and catalysts, heavy metals, inorganic salts.
    e) Residual solvents.
5. **Quality Control of the API:**
    a) Appearance
    b) Identification
    c) Assay
    d) Impurities (organic, inorganic and residual solvents)
    e) Physicochemical properties (pH, melting point, etc.).
    f) Particle size distribution.

g) Polymorphism, including the adopted analytical methodology and results of the tests intended to determine the probable polymorphs of the ingredient.
h) For chiral ingredients, data on the stereoisomer content.
i) Water determination
j) Microbiological limits: sterility, endotoxins (if applicable).
k) Specific optical rotation (if applicable

6. Description of the analytical methodology:

a) 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.
b) In case of pharmacopeial methodology, the company shall submit the method co-validation.

7. Packaging Material:

a) Description and specification of the primary packaging
b) Stability and Photostability Report
c) photostability studies shall be conducted in compliance with the specific technical regulation /standard