Maldives Food and Drug Authority

Ministry of Health

Male', Maldives

Guideline on Good Reliance Practice for Regulation of Medicines

Guideline for Good Reliance Practices for Regulation of Medicines is released under the authority of

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DEFINITIONS

Abridged Regulatory Pathways	Regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. Usually, NRA do the limited independent assessment of specific parts or submission for suitability of use under local conditions and regulatory requirements whilst relying on prior assessment and/or inspection outcomes from reference regulatory authorities or trusted organizations. The review is based on accessible data from reference regulatory authorities including assessment reports, Good Manufacturing Practice (GMP) inspections reports and parts of the common technical document (CTD).
Assessment	Any evaluation of information for conduction of a regulatory function (e.g. evaluation for a clinical trial application, evaluation of an initial authorization for a therapeutic goods or any subsequent post-authorization changes, evaluation of safety and efficacy data, evaluation as part of an inspection, etc.).
Post Registration Variation	A change to any aspect of a registered drug product, including but not limited to a change of formulation, method, site of manufacture, specifications for the finished product and ingredients, container and container labeling, and product information.
Recognition	Mutual recognition is a process which allows conformity assessments (of qualifications, product) carried out in one country to be recognized in another country. Recognition indicates that evidence of conformity with the regulatory requirements is sufficient to meet the national regulatory requirements
Reference Regulatory Authorities (RRA)	A national or regional authority or a trusted institution as adopted by MFDA for the purpose of reliance for medicine regulation along with its scope of reliance.
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.
Risk Management Plan	A plan to identify or characterize the safety profile of the medicinal product(s) concerned, document measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post- authorization obligations that have been imposed as a condition of the marketing authorization

ANSM	***National Agency for the Safety of Medicine and Health Products***
API	*Active Pharmaceutical Ingredient*
BP	*British Pharmacopoeia*
CoA	*Certificate of Analysis*
CoPP	*Certificate of Pharmaceutical Product*
CTD	*Common Technical Document*
DP	*Drug Product*
DS	*Drug Substance*
EMA	*European Medicines Agency*
EP	*European Pharmacopoeia*
USFDA	*US Food and Drug Administration*
FPP	*Finished Pharmaceutical Product*
MFDA	*Maldives Food and Drug Authority*
GMP	*Good Manufacturing Practices*
HPRA	*Health Products Regulatory Authority*
ICH	*International Council For Harmonization*
IP	*International Pharmacopoeia*
JP	*Japanese Pharmacopoeia*
MAH	*Marketing Authorization Holder*
MoPH	*Ministry of Public Health*
MHRA	*Medicines and Healthcare Regulatory Agency*
NPB	*National Pharmaceutical Board*
NMRA	*National Medicine Regulatory Authority*
NRA	*National Regulatory Authority*
PMDA	*Pharmaceuticals and Medical Devices Agency*
RMP	*Risk Management Plan*
RRAs	*Reference Regulatory Authorities*
SMF	*Site Master File*
SRA	*Stringent Regulatory Authority*

TGA	*Therapeutic Goods Administration*
USP	*United States Pharmacopoeia*
WHO	*World Health Organization*

Guideline on Good Reliance Practices for Regulation of Medicines

1 INTRODUCTION

Maldives Food and Drug Authority (MFDA) is a National Regulatory Authority of the Maldives and is responsible agency for performance of all regulatory functions related to medicine regulation. In present day regulatory scenario, reliance is an appropriate way of regulating medicinal products. This approach is not only beneficial for NRAs as it facilitates in prompt decision making but is also beneficial for the industry and patients as facilitates in quick access to quality assured Medicines.

MFDA considers that WHO's guidance regarding reliance is an efficient approach for utilization of resources and expertise of other NRA's having stringent regulatory mechanisms. Keeping in view guidance by WHO, MFDA relies on decisions of other recognized regulatory authorities in regulatory decision makings to further improve and expedite the access to quality- assured, effective and safe Medicines.

MFDA ensures availability of quality assured, safe and effective Medicines either by assessing registration application itself or with relying on decisions / processes of Reference Regulatory Authorities (RRAs), international and regional organizations. However, MFDA still uses its own judgment to consider the benefit-risk balance of each product while taking into account Maldives's domestic circumstances and legislation. The reliance approach helps the MFDA to save resources, improve the quality of its decisions, and make needed therapies available to patients more quickly.

2 THE CONCEPT OF RELIANCE IN REGULATORY PROCESSES.

The Maldives Food and Drug Authority (MFDA) recognizes the vital need for robust and efficient regulatory decision-making processes in ensuring the safety and quality of medical products and devices available to the population and believe that reliance is a key driver in achieving our public health objectives. For this purpose, the concept of "reliance" is introduced as a guiding principle in existing regulatory framework.

Reliance in regulatory decisions involves the judicious utilization of assessments, regulatory data, and decision conducted by internationally trusted / recognized regulatory authorities, international and regional organizations to take NRA's own regulatory decision. By using the concept of reliance, MFDA aims to further streamline its assessment processes, expedite decision making for quick access to safe and effective medicines, medical devices and alternative medicines for better public health outcomes.

3 OBJECTIVES

The MFDA is committed to enhance trust and cooperation with regulatory partners and stakeholders by relying on the assessment and decisions of Reference Regulatory Authorities (RRAs) as it will facilitate MFDA to make decisions more quickly and efficiently and ultimately ensuring that approved medicinal products are safe and effective for its population. These guidelines have been prepared with the following objectives:

a. To provide guidance to applicants (national and international) regarding MFDA's policy of relying on the assessment reports, information and decisions of Reference Regulatory Authorities during processing of applications for registration of medicines.
b. To explain scenarios where MFDA require additional information or data to adequately assess the safety, efficacy, or quality of a medicine.
c. To clarify that MFDA is the National Regulatory Authority responsible for making all final decisions regarding the approval of marketing authorization / registration or post- approval variations to medicines.

4 MFDA'S APPROACH TOWARDS RELIANCE

For appropriate use of reliance approach in various regulatory functions, MFDA considered possible approaches keeping in view the available legal provisions, need and dynamics of the national health and regulatory system, judicious use of available resources (both human and financial) and it will ultimately lead to more evidence-based and better- quality regulatory decisions, reduce duplication of effort and eventually ensuring timely access to safe, efficacious and quality assured therapeutic goods.

Following are the basic MFDA's approaches for following reliance:

4.1.1 This guideline serves as a comprehensive resource for both applicants and MFDA's regulators by outlining the specific requirements and processes while considering registration of medicine (pharmaceutical and biological drugs) in Maldives. These medicines include new (innovator), generic drug products (pharmaceutical) and biosimilar products (biologicals), which must have already received approval from any Reference Regulatory Authority.

4.1.2 By adopting a reliance approach, MFDA can make the most efficient use of its resources by reducing the burden of duplication of work carried out by RRAs and minimizing redundant efforts for applicants and manufacturers.

4.1.3 This guideline covers the entire spectrum of the approval process i.e. assessment of registration application for safety, efficacy and quality parameters and also post-approval variations, pharmacovigilance and lot release procedure.

5 PRINCIPLES OF RELIANCE

Reliance is guided by the following principles:

5.1.1 Protecting public health remains the foremost priority of MFDA by ensuring the safety and efficacy of drugs/ medicines allowed to be used in Maldives.

5.1.2 Ensuring open communication and sharing of relevant information is a hallmark of MFDA to maintain transparency.

5.1.3 Recognizing the regulatory decisions of Reference Regulatory Authorities provides MFDA with opportunity to timely introduce new medicines in Maldives and make registration process fast, robust and reliable.

5.1.4 MFDA promotes collaboration by working in partnership with Reference Regulatory Authorities to ensure consistency in regulatory standards as per international requirements.

5.1.5 MFDA ensures accountability by upholding the responsibility for the regulatory decisions taken.

6 RELIANCE PATHWAYS

Regulatory reliance can be followed by either of following approaches.

6.1 Verification

6.1.1 Verification is an administrative process for taking a regulatory decision, based on GMP certification / registration or other regulatory functions by any Reference Regulatory Authority. The NRA does not undertake any further assessment activity on its own.

6.1.2 Verification is applied where conformity with requirements of the Reference Regulatory Authority is sufficient to meet the requirements of MFDA.

6.1.3 MFDA will verify GMP status of abroad manufacturing site as per different options mentioned in Section 8.2 of these guidelines.

6.1.4 MFDA verify that product applied for registration is approved by any Reference Regulatory Authority and is actually available in the market of that Authority.

6.1.5 In the case of imported product registration, MFDA confirm that applied product will be manufactured at same manufacturing site(s) as approved by any Reference Regulatory Authority.

6.2 Abridged/Abbreviated Review

6.2.1 Abridged/abbreviated review is the assessment of suitability of use under local conditions and regulatory requirements, while relying partly or fully on prior assessment / GMP inspection outcomes/ Quality Control (QC) laboratory reports from any reference regulatory authority foe consideration by MFDA and then appropriate decision.

6.2.2 The abridged/abbreviated review may pertain to the full submission or parts thereof, depending on the suitability of use under local conditions and regulatory requirements.

6.2.3 The evaluation of a certain part of the application (e.g. relevant to use under local condition) such as product quality data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition may be necessary

6.3 Reference Regulatory Authorities

6.3.1 Well-resourced National Regulatory Authorities, regional and international bodies having robust regulatory mechanisms are more efficient in performing their regulatory functions and are designated as Reference Regulatory Authorities (RRAs) to meet the challenges of globalization, increasingly complex technologies and growing public expectations of faster access to novel and new therapies. MFDA considers these National Regulatory Authorities, regional and international bodies as Reference Regulatory Authorities (Annexure-I). It is a dynamic list and is subject to change by MFDA as needed like inclusion or exclusion of any NRA in World Listed Authority (WLA) list by WHO.

6.3.2 MFDA relies on decisions of Reference Regulatory Authorities to ensure the safety, efficacy, and quality of medicines for robust and accurate decision-making about their own products, considering that the products registered and sold in the countries of Reference Regulatory Authorities fulfill the harmonized regulatory standards.

7 Regulatory Functions based on Reliance

The concept of reliance plays a pivotal role in various aspects of regulatory decision- making undertaken by Maldives Food and Drug Authority (MFDA). It ensures the efficiency and effectiveness of medicine (pharmaceutical and biological). Following are detailed procedures for each regulatory function in which reliance is applied:

7.1 Registration/ Marketing Authorization (MA) of Medicine.

7.1.1 MFDA is responsible for assessment, evaluation and Registration/ Marketing Authorization (MA) of Medicine, post-registration variations and renewal. Medicine Therapeutic Goods Division, MFDA is responsible for processing and assessment of registration applications, followed by decision (approval or rejection) by National Pharmaceutical Board. The basic principle for registration of medicine is compliance to criteria of quality, safety, and efficacy.

7.1.2 MFDA by using verification pathway rely on the assessment of any Reference Regulatory Authority (RRA) for granting Registration and post registration variation approvals to innovator drug product (pharmaceutical and biological) subject to availability of quality data of applied drug product (pharmaceutical) pertaining to Zone IVA conditions (if required) for pharmaceutical products.

7.1.3 MFDA by using Abridged / Abbreviated pathway rely on the assessment of any Reference Regulatory Authority (RRA) for granting Registration / Marketing Authorization (MA) of Medicine and post approval/registration variation approvals to generic drug product / biosimilar. A due consideration is given to alignment in standards and practices between MFDA and the relying RRA. The procedure involves a comprehensive evaluation of the RRA's assessment of the product including its safety, efficacy, and quality.

7.2 Reliance in Registration/ Marketing Authorization of Medicine

7.2.1 The applicant submits a Registration application to the MFDA including all requisite relevant data and documentation as per the Guideline for Medicine Registration Including Emergency Use Authorization. The MFDA determines whether the applicant has provided sufficient evidence to support the relevant reliance path for the submitted application. If the applicant has provided sufficient evidence, then MFDA will assess the RRA's assessment report to ensure its consistency with the MFDA's regulatory requirements and will rely to grant the Registration or otherwise.

8 DOCUMENTATION REQUIREMENT FOR RELIANCE MECHANISMS

8.1.1 Request must be submitted on Application form for Registration of a Product and the form must be filled on Dhirithi portal in accordance with the relevant guidelines. An applicant may inform MFDA about the assessment by using reliance pathway i.e. verification or Abridged/ abbreviated review. For applying in any of the aforementioned mechanisms, the applicant/ manufacturer must ensure that the applied product meets the criteria mentioned in the Guideline for Medicine Registration Including Emergency Use Authorization

9 ASSESSMENT USING RELIANCE PATHWAYS

9.1 Administrative Information

All administrative information as outlined in the application of product shall be provided.

a. Quality information (Stability data)

- Quality documentation should include all the data as submitted to the Reference Regulatory Authority (RRA), unless indicated otherwise according to the requirements of the MFDA. Stability study for active pharmaceutical ingredient/Drug substance and drug product as per Zone IVA (for pharmaceutical) and relevant conditions for biological and other thermos labile drug products. In case of non-availability of this data, the commitment and protocol should be provided for stability studies under the appropriate climatic conditions for MFDA and then the stability data will be assessed by the MFDA and will be decided accordingly by National Pharmaceutical Board using Abridged/Abbreviated Review.

b. Safety and Efficacy Information

- For the registration / enlistment 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 and will be decided using verification pathway of reliance.

c. Additional Data in both Mechanisms

- MFDA may require following additional data as and when required:

1. A cover letter from the applicant explaining the rationale for reliance on the Reference Regulatory Authority (RRA).
2. A copy of the registration granted by the RRA or confirmation by MFDA from official website of RRA.
3. A copy of the product information leaflet (PIL) approved by the RRA.
4. A copy of the risk management plan (RMP) approved by the RRA.
5. Proposed label as per legislation / requirement of MFDA.
6. A statement from the applicant confirming that the approved medicinal product shall be manufactured and marketed in accordance with the approved registration and PIL.

d. Post Registration Variations

- Application for consideration of any post registration variation will be submitted as per Guidelines for Registration of Medicine and EUA. Assessment shall be done as per details recorded in above sections for depending on application part i.e. pertaining to quality or safety and efficacy information.

10 REGULATORY INSPECTIONS (GMP)

10.1.1 Compliances to Good Manufacturing Practices is a mandatory consideration for registration of a medicinal product (pharmaceutical and biological). MFDA has adopted reliance approach for verification of GMP of foreign manufacturing site by applying risk-based exemption approach. Importers applying for registration of imported drug products are exempted for inspection of manufacturing unit abroad, if the applied product qualifies any of the following criteria:

a. Registered / enlisted in any of Reference Regulatory Authority (Annexure-I).
b. Registered / enlisted in minimum three of the drug regulatory authorities of former Eastern Europe.
c. Manufacturer GMP certificate (for applied dosage form facility) is available on EUDRA-GMDP website
d. (http://eudragmdp.ema.europa,eu/inspections/gmpc/searchGMPCompliance.do)

e. WHO Pre-qualified product and manufacturing facility (section) thereof.

f. Any product approved by Pharmaceutical Inspection Co-operation Scheme (PIC/S) Participating Authority and manufacturing facility (section) of such product or manufacturing site/facilities conformed to the regulatory inspection by any of the PIC/S Participating Authority (https://picscheme.org/en/members)

g. Inspection exemption on risk assessment criteria based on inspection of manufacturing facility by any other NRA (other than NRA of country of origin) in the past 3 years. MFDA will review another NRA's inspection report to determine whether it is consistent with the MFDA's inspection requirements or otherwise. If the MFDA is satisfied with the NRA's inspection report, it will accept the report as evidence of GMP compliance, otherwise it may conduct own inspection of the applicant site. In aforementioned case, such inspection reports will be shared by NRA via their official web addresses to confirm their genuineness / authenticity.

h. In case of suspension or cancellation of registration of the product by exporting country or delisting of WHO-PQ status or suspension / cancellation by PIC/S Participating Authority, the registration holders shall be bound to inform MFDA about such suspension or cancellation within fifteen days. In case of non-compliance, the Registration Board may take action as per law against the importer, which may also lead to suspension/cancellation of registration of such product.

i. MFDA may conduct risk based GMP inspection of the manufacturing facility any time (before or after grant of approval) due to any reason as it deems fit like repeated GMP violations, supply of substandard products, Adverse Drug Reaction due to manufacturing problem etc.

11 CLINICAL TRIALS

11.1.1 MFDA's reliance clinical trials involves accepting data from RRA approved clinical trials. To ensure the reliability of this data, MFDA carefully evaluates the processes, methodologies, and ethical considerations of the relevant RRA in line with international standards such as ICH- GCP. This approach expedites the approval of clinical trials while upholding the highest standards of ethical conduct, patient safety, and data integrity. The mechanism adopted for reliance encompasses following:

a. Review of approval or rejection of clinical trials in any Reference Regulatory Authorities.
b. In case information is not available on the official website, the Reference Regulatory Authority is contacted directly via electronic mail for a query or clarification on a particular issue under consideration.
c. Regulatory status or any other regulatory information available in the public domain through their website.
d. Reports from reference regulatory authorities.

12 PHARMACOVIGILANCE

12.1.1 Reference Regulatory Authorities have better reporting and information sharing system and thus MFDA prioritizes pharmacovigilance data information sharing with RRAs and the utilization of their assessments for regulatory decisions. This process includes the establishment of efficient communication channels for the exchange of safety-related data. MFDA may rely on the RRA's assessments of the safety of a product. This collaboration accelerates the response to emerging safety concerns and facilitates the protection of public health.

12.1.2 The MFDA collects safety information about products that it regulates, including adverse event reports, product recalls, and safety warnings and will share safety information with RRAs on a regular basis.

12.1.3 The MFDA considers the assessments of RRAs when making regulatory decisions about products. For example, if an RRA issues a safety warning about a product, the MFDA may also issue a safety warning or take other regulatory action.

12.1.4 Better post marketing surveillance particularly related to safety and efficacy issues, which is an effective tool for surveillance and new indications or contra-indications

13 LABORATORY TESTING

13.1.1 To ensure the accuracy and consistency of laboratory testing data, MFDA accepts testing results from RRA approved and WHO pre-qualified laboratories in line with recognized standards or any other laboratory as identified by MFDA. This reliance reduces the burden on regulatory authority in general and testing laboratory in specific and promotes efficiency in the testing process while maintaining the quality and safety of products.

13.1.2 The applicant submits laboratory testing data to the MFDA in support of a MA application, a clinical trial application, or a vigilance report.

13.1.3 The MFDA may review the laboratory testing data to ensure that it was generated by an RRA approved or WHO pre-qualified laboratory or laboratory as identified by MFDA.

13.1.4 MFDA may perform risk-based testing of drug products from its own or any other laboratory any time (before or after grant of approval) due to any reason as it deems fit like repeated GMP violations, supply of substandard products, Adverse Drug Reaction due to manufacturing problem etc.

14 LOT RELEASE

14.1.1 MFDA also practices reliance in the context of lot release testing. When a RRA conducts lot release testing, MFDA may accept the results with mutual agreement. This agreement involves the establishment of harmonized standards and methodologies to ensure the accuracy and consistency of testing. By relying on the RRA's lot release testing, MFDA expedites the availability of products in the market while safeguarding public health through a joint commitment to quality control and may follow document-based lot release procedure.

15 REFERENCES

a. Health Services Act, 29/2015

b. Medicine Regulation 2014/R-46

c. Regulations on National Pharmaceutical Board 2019/R-135

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

e. WHO, Good Reliance Practices (GReP), Annex 11, 55th report of the World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), WHO Technical Report Series No. 1033, 2021.

f. WHO, Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities, Annex5.World Health Organization, WHO Technical Report Series No. 986, 2014.

g. WHO, Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products, Annex 6. World Health Organization, WHO Technical Report Series No. 1019, 2019.

1 Annexure-I: List of Reference Regulatory Authorities for Reliance

Following are Reference Authorities for matters related to registration of medicine (pharmaceutical and biological drugs) and approval of clinical trials.

#	Country	Authority
1	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
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
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)
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)
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)**
43	Mexico	COFEPRIS
44	Cuba	CECMED
45	Malaysia	National Pharmaceutical Regulatory Agency (NPRA)