RELIANCE MECHANISM IN REGULATORY PROCESSES
"DRAP APPROACH ON GOOD RELIANCE PRACTICE"

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Drug Regulatory Authority of Pakistan
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Edition History

Change #	Effective date	Revision date	Reason for Revision
Edition 01	30-09-2021	12-12-2022	-
Edition 02	04-01-2023	-	The 1st edition of these guidelines was drafted as per draft Pharmacovigilance Rules. Now the Pharmacovigilance Rules, 2022 are officially notified. Moreover, amendments in the DRAP Act, 2012, Medical Devices Rules, 2017 and Policy for inspection of manufacturers abroad have been notified, therefore, this 2nd edition of guidelines was redrafted in line with newly approved and rules and amended legislations.

1. HISTORY

This is the first edition of this policy document.

2. APPLICATION (For Regulators and Industry)

This document covers the reliance activities in the field of regulatory oversight of therapeutic goods, addressing regulatory functions spanning the full life cycle of a therapeutic product - namely registration and marketing authorization, pharmacovigilance, surveillance, regulatory inspection, laboratory testing, clinical trials oversight, and NRA lot release.

3. PURPOSE

This document is aimed at defining a policy guidance to establish a criteria, procedure, and mechanism for reliance pathway to facilitate regulatory decisions, by giving significant weightage to the assessment performed by other National Regulatory Authorities or trusted institutions as reference for various decision-making processes in regulatory functions performed by DRAP.

The document also serves the purpose of better understanding of reliance approach by the stakeholders, and the mechanism adopted to rely upon the work of regulatory authorities which has been adopted by DRAP with respect to safety, efficacy and quality of various categories of therapeutic goods, in order to effectively and efficiently perform the regulatory functions mandated under the DRAP Act, 2012 i.e to ensure safety, efficacy and quality of therapeutic goods including but not limiting to drugs, biologicals, medical devices, alternative medicines & health products, etc.

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4. INTRODUCTION

Drug Regulatory Authority of Pakistan was established under the Drug Regulatory Authority of Pakistan Act, 2012. The Authority is responsible for ensuring that therapeutic goods approved and available in market meet the prescribed standards of quality, safety and efficacy. DRAP is continually working to enhance performance, quality of its working in addition to facilitation to patients and stakeholders to ensure timely access to safe, effective and quality innovative therapeutic products. The globalization of rapidly evolving health technologies also requires joint efforts by NRAs, to ensure that patients have early access to safe and high-quality medicines. Like many other NRAs, DRAP has adopted reliance approach to improve its working efficiency based on the unilateral mutual recognition pathways leveraging regulatory work of trusted regulatory authorities to reduce its workload with independent decision-making

Establishing and sustaining mature regulatory systems is an enterprise that requires adequate resources including skilled and capable human resources and huge financial investments to run its affairs smoothly and efficiently to ensure availability of safe, effective and quality therapeutic goods. Moreover, the globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and increasing complexity of supply chains have led regulators to recognize the importance of international cooperation in the form of recognition and reliance to ensure the safety, quality and efficacy of locally used products. In view of the extent and complexity of regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative and more effective forms of collaboration in order to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where most needed.

Reliance represents a smarter and more efficient way of regulating medical products in a modern regulatory world. Towards this end, countries are formulating and implementing strategies to strengthen their regulatory systems consistently with Good Regulatory Practices (GRP), including pursuing regulatory cooperation and convergence, as well as reliance. Reliance brings benefit to patients and consumers, the industry, national governments, as well as the donor community, and international

development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.

The recent pandemic has further emphasized the importance of regulatory cooperation and information sharing which are important elements of reliance for streamlining responses during public health emergencies.

GLOSSARY

Acronyms

ADR	Adverse Drug Reaction.
AE	Adverse Event.
BE&R	Biological Evaluation & Research Division
cGMP	Current Good Manufacturing Practice
CSC	Clinical Studies Committee
CTD	Common Technical Document.
DRAP	Drug Regulatory Authority of Pakistan
DS	Drug Substance
EEC	Enlistment Evaluation Committee
FDP	Finished Drug Product
GRP	Good Regulatory Practices
H&OTC	Health & OTC Division
ICH	International Commission for Harmonization
MDB	Medical Devices Board
MDMC	Medical Devices & Medicated Cosmetics Division
NRA	National Regulatory Authority
PE&R	Pharmaceutical Evaluation & Registration Division
PIC/s	Pharmaceutical Inspection Cooperation Scheme.
PRAEC	Pharmacovigilance Risk Assessment Expert Committee.
RB	Registration Board
RRA	Reference Regulatory Authority
WHO	World Health Organization

Definitions

Abridged regulatory pathways	Abridged regulatory pathways are regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. A 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.).
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)	Reference regulatory authority is a national or regional authority or a trusted institution as adopted by Drug Regulatory Authority of Pakistan for the purpose of reliance on various therapeutic goods along with its scope of reliance.
Reliance:	An act whereby the DRAP takes into account and give significant weight to assessments performed by another NRA or trusted institution or reference regulatory authority, or to any other authoritative information in reaching its own decision. DRAP remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

5. LEGAL PROVISIONS FOR RELIANCE

To ensure early access to quality therapeutic goods and novel therapeutic opportunities, DRAP has adopted reliance mechanisms for various categories of therapeutic goods alongwith its variable scope, for which the safety and efficacy have already been confirmed by the reference regulatory authorities or when the clinical trial has been approved by well-resourced regulatory authorities.

DRAP has been established through DRAP Act, 2012. Several enabling provisions in the DRAP Act, 2012, the Drugs Act, 1976 and rules framed thereunder provides legal framework for reliance and recognition of either regulatory authorities or their particular decisions, these provisions are as below: -

5.1. Functions of Authority under Section 7 (c) (ix) and 7(d) states that:

"7. Powers and functions of the Authority: - The powers and functions of the Authority shall be to, -

...

(c) Issue guidelines and monitor the enforcement of: -

(ix) implementation of internationally recognized standards such as good laboratory practices, current good manufacturing practices, good distribution practices, cold chain management, bioequivalence studies, stability studies, anti-spurious codes, clinical trials, biosimilar evaluations, and endorsement and systematic implementation of World Health Organization, International Conference on Harmonization and Food and Drug Administration guidelines etc.

(d) Coordinate, monitor or engage, in conjunction with other organizations, Provincial Governments and international agencies, in training, study or project related to therapeutic goods. The Authority may engage any individual or counsel to advise or work for managing national and international opportunities for training, education, seminars, conferences etc., with a view to improve capacity building."

5.2. Section 39 of DRAP Act, 2012 states that:

"The Authority may, subject to the prior approval of the Federal Government, co-operate with any foreign authority or international organization in the field of health on the terms and conditions of any program or agreement for co-operation to which such authority or organization is a party, or pursuant to any other international agreement made or after the commencement of this Act."

5.3. Section 43, sub-section (q) of the Drugs Act, 1976:-

prescribe conditions for registration of indentors, importers, wholesalers and distributors within Pakistan and any establishment within any foreign country engaged in the manufacture for export of a drug and prescribe conditions providing effective and adequate means, by arrangement with the Government of such foreign country or otherwise, to enable the licensing authority or the Registration Board to determine from time to time whether drugs manufactured in such establishment, if imported or offered for import into Pakistan, shall be refused admission where the public interest so requires;

Now under Section 7(a) of the DRAP Act, 2912, this power lies with the Authority.

6. PRINCIPLES OF RELIANCE

In developing a strategy on the use of reliance in regulatory functions and activities, DRAP considered possible approaches in the context of the needs and characteristics of the national health and regulatory system together with the current human resource strengthens, capabilities and appropriate use of available financial resources. The decision to practice reliance has been taken keeping into consideration the available legal provisions, existing capacities, regulatory systems' needs, increase the quality of regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, efficacious and quality-assured therapeutic goods.

Reliance is practiced making the best use of the available resources both human and financial. This allows the allocation of resources to other areas of regulatory functions for increasing the effectiveness of the local regulatory oversight. In addition, reliance can lead to more evidence-based and better-quality decisions.

Basic principle of reliance implies that regulatory work is shared by any means by reference regulatory authorities through dossier assessment reports, GMP inspection reports, quality control reports, safety signals, etc., while DRAP considers the data of reference regulatory authorities while rendering its regulatory responsibilities according to its own scientific knowledge and regulatory procedures. The reliance can be unilateral, mutual or multilateral, and provides basis to arrive at a regulatory decision while considering local regulatory responsibilities and procedures.

The basic aim is to gear up the evaluation process for enlistment/ registration / market authorization and surveillance of therapeutic goods. The key principles for reliance on information or decisions of reference regulatory authorities are as follows: -

6.1. Risk-Based Approach

It is regulatory best practice to implement quality risk management. For example, a product which is prequalified by WHO or approved by other reference regulatory authorities has low risk with respect to quality, safety and efficacy compared to a product with no such prior reviews and/or approvals.

6.2. Optimum Use of Available Resources

DRAP allocate resources and a level of effort that is proportionate with the level of risk. DRAP believes on reliance and optimal use of available resources. This approach is undertaken to ensure that patients are provided with the safe, efficacious and quality assured therapeutic goods. This includes removing duplication and identifying elements in the benefit-risk assessment that are critical in the domestic situation. For innovative products, this may mean bridging the benefit-risk assessment done by reference regulatory authorities to ensure the early availability of innovative treatment to the local population, suitability of its use with the local climatic conditions.

6.3. Ensuring the "Sameness "of Products

One of the principles for reliance is to ensure identical products with reference regulatory authorities or where differences exist, these are clearly stated and defined.

6.4. Compliance with Nationally Regulatory Requirements

Reliance on reference regulatory authorities do not substitute compliance with applicable national requirements. Submissions and documentary evidence should be consistent and comply with local regulatory and legal requirements.

6.5. Flexibility to Adapt National / Domestic Situations

DRAP may devise / adapt/revise its own national strategies or procedures that may suit national or domestic circumstances in the best public interest to ensure availability of safe, efficacious and quality therapeutic goods.

7. REFERENCE REGULATORY AUTHORITIES

Well-resourced National Regulatory Authorities having robust drug regulatory mechanisms are more efficient in performing their regulatory functions and may be designated as reference regulatory authorities (RRA) to meet the challenges of globalization, increasingly complex technologies and growing public expectations of faster access to novel therapies. DRAP relies on decisions of reference regulatory authorities to ensure the safety, efficacy, and quality of therapeutic goods 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 standards. However, scope and extend of this reliance and recognition is different for different categories of therapeutic goods.

This reliance also enables the DRAP for better post marketing surveillance particularly related to safety and efficacy issues. Reference regulatory authorities have stronger reporting and information sharing system, which may be used by DRAP as a useful tool for effective surveillance and new indications or contra-indications.

8. AREAS FOR RELIANCE IN REGULATORY PROCESS AND DECISION-MAKING

Divisions of DRAP are practicing reliance or recognition mechanism for regulating therapeutic goods falls under their mandate. The areas of reliance for different types for regulatory process of therapeutic goods are as under:

8.1. Marketing Authorization of Pharmaceutical Drugs and Biological Products:

PE&R and BE&R Divisions of DRAP are responsible for assessment, evaluation and registration for pharmaceutical drug products and biological drugs, respectively. Registration of pharmaceuticals and biological drug products are performed by the Registration Board (RB), constituted under Section 7, Sub-Section (u) of the DRAP Act, 2012. RB works under the Drugs (Licensing, Registering & Advertising) Rules, 1976, which provides basic principle for drug registration in accordance with the criteria of quality, safety, and efficacy. RB is empowered in light of following provisions for reliance and recognition for registration / market authorization of pharmaceutical and biological drugs: -

1. Rule 29(6) of Drugs (Licensing, Registering & Advertising) Rules, 1976, states as follows:

   "The Registration Board shall, before registering a new drug for which the research work has been conducted in other countries and its efficacy, safety and quality has been established therein, require the investigation on such pharmaceutical, pharmacological and other aspects, to be conducted and clinical trials to be made as are necessary to establish its quality and, where applicable, the biological, availability, and its safety and efficacy to be established under the local conditions."

2. Rule 30(10) of Drugs (Licensing, Registering & Advertising) Rules, 1976 states as follows:

   "If a drug or any of its ingredients, which is imported or manufactured by a company in Pakistan is also approved for registration and free sale by

its subsidiary, sister concern, associate or parent company in the country where it was originally developed or in any of the countries namely, USA, European Union Countries, Canada, Japan, Australia, and—

(a) if that drug at any time, for safety reasons is withdrawn or banned or certain restrictions are imposed in any of the said countries, then it shall be the responsibility of the manufacturer in Pakistan or as the case may be, the indenter, to immediately withdraw the drug from the market in Pakistan or, as the case may be to impose similar restriction and to inform the registration Board within fourteen days of such an information having come to his knowledge and having taken the necessary action. The Registration Board after getting the said intimation shall take similar action for the same drug available from other sources within the shortest possible time;

(b) if a clinical information for a drug is approved by the Drug Regulatory Authority in any of the said countries, the same clinical information shall be considered as approved for drug registration in Pakistan unless modified by the Registration Board on the basis of scientific data available to it, and such clinical information may include indication, contra-indications, side effects, precautions, dosage, etc.;

(c) if any adverse drug reaction not otherwise included in the application for registration, is registration, is registered in any of the said countries, it shall be the responsibility of the concerned manufacturer or in case of imported drugs the indenter or manufacturer's agent in Pakistan, to be aware of such adverse action and to report to the Registration Board within thirty days of becoming so aware.

3. Section 1 (2) of the Schedule-I of the DRAP Act, 2012, defines biological drugs as:-

(2) "Biological Drugs (Finished form)", are Biological Drugs that are defined in sub-section (I) above and are manufactured, packed by the manufacturer under his responsibility of quality assurance and is further released by the National Control Authority or the National Control

Laboratory of the country of origin under the World Health Organization's Lot Release system of evaluation.

Under these provisions, RB with the approval of DRAP has adopted reference regulatory authority, which are placed at **Appendix-I**, for reliance on their regulatory information in consideration of application through abridged pathway for initial approvals as well as the post-approval changes and renewals to facilitate the supply of the medicine and timely safety information for patients.

Currently, the Authority applies reliance procedure for granting registration / Market Authorization in the following circumstance: -

a) Finished products of biologicals and pharmaceuticals drugs which are approved by the reference regulatory authorities are considered as safe, effective and of quality while considering for registration in Pakistan.

b) For drugs substance, which are already registered by the reference regulatory authorities in a particular strength and dosage form are considered as safe and efficacious, while considering registration of new drugs in local perspective.

c) DRAP has also signed a MoU with World Health Organization regarding collaborative registration process to enable early excess of those drugs and biologicals, Products which have been evaluated and listed as pre-qualified by WHO.

The mechanism adopted for relying on information encompasses following:

i. Review of public assessment reports, summary of product characteristics and labelling information.
ii. Recognition of reported safety and efficacy concerns of already registered medicines.
iii. Review of Certificate of Pharmaceutical Products (CoPP).
iv. Certificate of suitability issued by European Directorate for the Quality of Medicines (EDQM)
v. 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.

vi. Regulatory status or any other regulatory information available in the public domain through their website.

8.2. Regulatory Inspections (GMP):

Compliances to Good Manufacturing Practices is mandatory consideration for registration of a pharmaceutical and biological drugs. DRAP has adopted reliance approach for verification of GMP of foreign manufacturing by applying risk-based exemption approach. Importers applying for registration of imported drugs and biologicals are exempted for inspection of manufacturing unit abroad, if criteria as defined in the "Import Policy for Inspection of Manufacturers Aboard", is fulfilled and the aforesaid policy is placed at **Appendix-II.**

The reliance for exemption from GMP Inspections of manufacturers abroad is practiced if the applied pharmaceutical or biological product: -

a) is registered or granted marketing authorization in any of reference regulatory authority as adopted by Authority and Registration Board or
b) is registered or having marketing authorization in minimum three of the drug regulatory authorities of former Eastern Europe, or
c) manufacturer GMP certificate (for applied dosage form facility) is available on EUDRA-GMDP website, or
d) is WHO Pre-qualified and manufacturing facility (section) of that product. , or
e) is approved by any PIC/s participating authority, and manufacturing facility (section) of that product.
f) Manufacturing site / facility conforms to the regulatory inspection by any of the PIC/s participating authority

Reliance is also extended in the form of exemption from foreign inspections for medical devices. Establishments applying for enlistment/registration of imported medical devices are

exempted for inspection of manufacturing unit abroad, if product is coming from regulatory authorities as specified in Rules 67(1) (a) and /or is WHO pre-qualified as per Rule 71(3) of Medical Devices Rules, 2017.

Exemption from foreign inspections, if medical device is approved for marketing in reference regulatory authorities or if it is WHO pre-qualified.

Reliance is also extended for import of starting materials (e.g. Active Pharmaceutical Ingredients), for which issuance of Good Manufacturing Practices certificate of national regulatory authority of exporting country is considered as a bench mark while granting permission for import of Active Pharmaceutical Ingredients in Pakistan.

8.3. Clinical Trials Approval:

Clinical trials are governed under the Bio-study Rules, 2017, wherein Clinical Study Committee (CSC) is mandated to grant approval of clinical trials of therapeutic goods in Pakistan. Relevant enabling provision for reliance are reproduced as below: -

1. Sub-rule 08 of the Rule 13 of the Bio-study Rules, 2017 states as follow;

   "The CSC shall also consider relevant clinical trial decisions, reports or other information from stringent regulatory authorities and regional or international bodies like WHO, ICH and others. Any application for approval or registration of clinical trial will not undergo in the assessment process, if the same at any stage, has already been rejected, suspended or put on hold due to any reason, in ICH member countries or stringent regulatory authorities and shall be rejected during the process of screening."

2. Rule 12(1) of the Bio-study Rules, 2017 also binds the sponsor as follow:

   "The sponsor shall promptly review and report to the CSC, all information relevant to risk-benefit assessment and the safety of the investigational product, obtained during the investigation or otherwise received from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific

literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the DRAP."

Under these relevant provision, reference regulatory authorities are same as has been adopted by the RB, which are placed at **Appendix-I**. No clinical trial is considered for assessment, if same at any stage, has already been rejected, suspended or put on hold due to any reason, in ICH member countries or stringent regulatory authorities and shall be rejected during the process of screening.

The mechanism adopted for reliance encompasses following:

i. Review of approval or rejection of clinical trials in reference regulatory authorities.

ii. 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.

iii. Regulatory status or any other regulatory information available in the public domain through their website.

iv. Reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities.

8.4. Pharmacovigilance Activities:

Pharmacovigilance activities are regulated under the Pharmacovigilance Rules, 2022under which Pharmacovigilance Risk Assessment Expert Committee (PRAEC) is mandated to monitor AE and ADR and its reporting mechanism, assessment and evaluation of pharmacovigilance data, followed by recommendation of regulatory actions. In these rules provision for reliance is reproduced as under:-

1. Sub-rule 1 (h) of Rule 10 of Pharmacovigilance Rules, 2022 is as follows:

Pharmacovigilance Risk Assessment Expert Committee (PRAEC) shall consider or recognize and if deemed appropriate shall implement within Pakistan, the pharmacovigilance relevant decisions of other countries and of regional and international bodies of the following nature, namely:

i. *modification or removal of an approved indication of therapeutic good due to safety concern;*
ii. *addition of contraindications;*
iii. *imposition of post-authorization safety or efficacy studies due to safety reasons;*
iv. *major changes in the statements of warning, precaution or adverse reactions in the product information;*
v. *withdrawal or suspension of therapeutic good in other countries due to safety reasons; and*
vi. *any other safety information or decision which it considers appropriate, for ensuring safety of the public.*

National Pharmacovigilance Center (NPC), DRAP is responsible to ensure the safety of marketed products through signal detection and initiation of necessary risk minimization measures. NPC actively coordinates with Uppsala Monitoring Center for sharing pharmacovigilance data.

It also relies on regulatory decisions arising due to pharmacovigilance activities of reference regulatory authorities, regional and international bodies, having local importance and which might impact the health of patients.

8.5. Marketing Authorization (Enlistment / registration) of Medical Devices:

Enlistment/ registration of medical devices is governed under the Medical Devices Rules, 2017. Under these rules, Medical Devices Board (MDB) is empowered to grant establishment license and enlistment/registration of medical devices for marketing in Pakistan. Relevant enabling provision for reliance are reproduced as below:-

1. Rule 15(2) of Medical Devices Rules, 2017 provides reference regulatory authorities for enlistment / registration of medical devices, which is reproduced as under:

MDB may grant certificate of enlistment or registration of medical devices if authorized by the stringent regulatory authorities as specified by the MDB for life-saving medical devices and registration by the MDB shall be based on registration of the medical devices registered by the regulatory authorities of USA, Japan, Australia, Canada, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and United Kingdom or pre-qualified by World Health Organization or CE marked by conformity assessment bodies (CABs) notified in NANDO database under the relevant European directive for medical devices subject to evidence and supporting documents.

2. Rule 67(1)(a) of Medical Devices Rules, 2017 provides enabling provision for outsourcing of medical devices:

Out sourcing of manufacturing of medical devices may be allowed subject to fulfillment of the following conditions, namely: —

(a) the establishment for manufacturing medical device being contract giver, intending to outsource, has been licensed and its medical device enlisted or registered by the MDB or approved by any regulatory authority of USA, Japan, Australia, Canada, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and United Kingdom or pre-qualified by World Health Organization or CE marked by manufacturer whose conformity assessment is performed by conformity assessment bodies notified in NANDO database under the relevant European directive for medical devices subject to evidence and supporting document;

3. Section 71(2) and (3) of Medical Devices Rules, 2017 provides exemption from inspection of manufacturers abroad:

(2) A medical device shall be exempt from inspection under sub-rule (1) where the medical device is approved by regulatory authorities of the countries specified in rule 67 irrespective of the fact that the manufacturing unit is not located in these countries.

(3) The medical devices pre-qualified by the World Health Organization or CE marked by conformity assessment bodies (CABs) notified in NANDO database under the relevant European directive for medical devices subject to evidence and supporting documents shall be exempt from inspection of manufacturing units abroad under sub-rule (1).

Under these legal provisions, the Authority applies the reliance procedure in following circumstances: -

a) Enlistment/registration of life-saving medical devices is granted based on reliance i.e. approval by the Reference Regulatory Authorities. For the purpose of reliance, reference regulatory authorities are specified in the rules 15(2), of Medical Devices Rules, 2017.

b) Reliance is also extended to facilitate outsourcing as per provision of Rule 67 of Medical Devices Rules, 2017. Enlistment/ registration of medical devices may be subject to inspection of manufacturing facilities as determined by the MDB, however, reliance is also extended in the form of exemption from foreign inspections for countries specified in the Rule 67(1)(a) and pre-qualified by WHO under Rule 71(3) of Medical Devices Rules, 2017.

The mechanism adopted for reliance on regulatory information encompasses the following:

i. Review of public assessment reports, summary of product characteristics and labelling information.
ii. Recognition of reported safety and efficacy concerns of already registered medical device.
iii. 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.
iv. Regulatory status or any other regulatory information available in the public domain through their website.

Due to newly regulated field of medical devices exemption period has been notified for various classes of medical devices vide SRO 526(I)/2021 dated 30th April, 2021 in which reliance has also been extended on import of various classes of medical devices during exemption period as specified in Rule 52.Relevant rule for reliance i.e 52 (1) (i) & (ii) is reproduced below:

a) For clearance of class A medical device from Pakistan Customs, it is mandatory for importer to submit notarized ISO 13485 and notarized letter for authorization from manufacturer abroad along with any of the following documents, namely; -
   a. Notarized free sale certificate from country of origin; or
   b. Notarized declaration of conformity from manufacturer abroad; or
   c. Notarized production or full quality assurance certificate (CE-marking certificate) from conformity assessment body CAB);

b) For clearance of class B, C or D medical device from Pakistan Customs, it is mandatory for importer to submit notarized ISO 134851 and notarized letter of authorization from manufacturer abroad alongwith any of the following documents, namely:-
   a. Notarized free sale certificate from country of origin along with declaration of conformity, full quality assurance certificate (CE-marking certificate) from CAB. However, for class D medical device, design examination certificate shall be mandatory; or
   b. Notarized free sale certificate from any of the reference countries i.e., USA, Japan, Australia, Canada, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom; or
   c. Notarized free sale certificate from country of origin along with WHO prequalification status;

8.6. Enlistment / Registration of Alternative Medicines / Health Products:

Enlistment/Registration of Alternative Medicines and Health & OTC products is governed under Alternative Medicines & Health Products (Enlistment) Rules,

2014. Although in these rules, no specific provision is available for reliance. However, the DRAP has approved reliance mechanism for this category, which is reproduced as below:-

"The combinations having evidence of Free Sale in the country of origin [Certificate of Pharmaceutical Product (CPP on WHO Format) shall be considered as replacement for Free Sale and GMP] along with proof of marketing in any of reference regulatory authorities as adopted by the Registration Board shall be considered for enlistment under the Alternative Medicines & Health & OTC Rules."

The reference regulatory authorities for enlistment under Alternative Medicines & Health Products (Enlistment) Rules, 2014 are same as defined by the DRB and are placed at **Appendix-I** of this document.

The mechanism adopted for reliance of regulatory information encompasses the following:

i. Review of public assessment reports, summary of product characteristics and labelling information.
ii. Recognition of reported safety and efficacy concerns of already registered/enlisted alternative medicines and health product.
iii. 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.
iv. Regulatory status or any other regulatory information available in the public domain through their website.

8.7. Lot release of biologicals:

No human vaccines, blood products (plasma derivatives medicinal products) and anti-sera (antivenoms and anti-rabies) shall be sold and used until a "Lot Release Certificate" from the Federal Government Analyst of the National Control Laboratory for Biologicals, Islamabad has been obtained. This is the legal requirement under the Section 1(7) of Schedule-I of the DRAP Act, 2012.

Currently, lot release certificate for imported consignment is based on reliance in the form of summary protocol review alongwith lot release certificate of national regulatory authority of exporting country.

9. RELIANCE PROCEDURE

Regulatory processes can be optimized, and duplication of efforts can be minimized through reliance. In addition, scientific expertise can be leveraged, leading to more fruitful and robust decision making, and enhancing the capacity of regulators. Consequently, reliance can also allow efficient utilization of resources by NRAs for other areas and improve access to quality assured medicines. DRAP is implementing reliance approach for qualifying products applications while following these steps:-

9.1. Verification and review of reliance information:

Divisions of DRAP will verify that the documents and related information for the applied product for enlistment/registration / marketing authorization of any therapeutic goods or the Clinical trial in Pakistan has been authorized by reference regulatory authorities.

For registration, the product characteristics (use, dosage, precautions) should conform to that agreed in the authorization by the RRA and for drugs substance, which are already registered by the reference regulatory authorities in a particular strength and dosage form are considered as safe and efficacious, while considering registration applicants of new drugs in local perspective.

9.2. Additional Documentations:

During the review process, DRAP may ask the applicant to submit additional information to be included in the dossier or specific statistical / analytical requirements or sometime full application data to ensure the quality, safety and efficacy. Similarly, there could be circumstances when local clinical trial data is necessitated.

In addition to the full assessment report from the RRA, the applicant shall be required to submit a full Clinical Trial application, full Application for Marketing Authorization, full application for GMP inspection as required by the Authority’s guidelines before authorization of the application through the reliance pathway.

9.3. Assessment based on reliance procedure:

The information to be used for reliance shall be evaluated according to the prescribed assessment procedure to ensure that submitted documents fulfill the absolute required information for the purpose of the respective assessment.

10. REFERENCES

1. The DRAP Act, 2012.
2. The Drugs Act 1976
3. The Drugs (Licensing, Registering and Advertising) Rules, 1976
4. The Medical Device Rules, 2017
5. The Alternative Medicines & Health Products (Enlistment) Rules, 2014
6. Pan American Health Organization. Regulatory Reliance Principles: Concept note and recommendations. 9th Conference of the Pan American Network for Drug Regulatory Harmonization.
7. WHO. (2020). Good reliance practices in regulatory decision-making: High-level principles and recommendations. WHO Drug Information, 34(2), 201–230.
8. Bio Study Rules, 2017
9. Pharmacovigilance Rules, 2022

APPENDIX-I

LIST OF REFERENCE REGULATORY AUTHORITIES

Following are reference regulatory authorities for matters related to registration of pharmaceutical & biological drugs, enlistment of alternative medicines & health products and for approval of Clinical trials:

Sr #	Country	Regulatory authority	Pharmaceutical & Biological Products	Alternative Medicines & Health Products	Clinical Trials
i.	USA	Food & Drug Administration (FDA)	✓	✓	✓
ii.	Canada	Health Canada	✓	✓	✓
iii.	Australia	Therapeutic Goods Administration (TGA)	✓	✓	✓
iv.	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	✓	✓	✓
v.	UK	Medicines and Healthcare Regulatory Agency (MHRA)	✓	✓	✓
vi.	France	National Agency for the Safety of Medicine and Health Products (ANSM)	✓	✓	✓
vii.	Germany	Federal Institute for Drugs and Medical Devices	✓	✓	✓
viii.	Netherland	Medicines Evaluation Board	✓	✓	✓
ix.	Switzerland	Swissmedic	✓	✓	✓
x.	Austria	Austrian Agency for Health and Food Safety	✓	✓	✓
xi.	Denmark	Danish Medicines Agency	✓	✓	✓
xii.	Sweden	Medical Products Agency	✓	✓	✓

xiii.	Norway	Norwegian Medicines Agency	✓	✓	✓
xiv.	Belgium	Federal Agency for Medicines and Health Products	✓	✓	✓
xv.	Finland	Finnish Medicine Agency	✓	✓	✓
xvi.	Italy	Italian Medicine Agency (AIFA)	✓	✓	✓
xvii.	Ireland	Health Products Regulatory Authority (HPRA)	✓	✓	✓
xviii.	Iceland	Icelandic Medicine Agency	✓	✓	✓
xix.	Spain	Spanish Agency for Medicines and Health Products	✓	✓	✓
xx.	Europe	European Medicines Agency (EMA)	✓	✓	✓
xxi.	WHO	World Health Organization	✓	✓	✓

APPENDIX-II

POLICY FOR INSPECTION OF MANUFACTURER ABROAD FOR REGISTRATION OF FINISHED DRUGS

1. Dosage form specific inspection of manufacturer abroad shall be carried out before grant and renewal of registration. However, products fulfilling below mentioned criteria are exempted from dosage form specific inspection of manufacturer abroad:

- Any product approved by drug regulatory authorities of United States of America, Japan, Australia, Canada, UK, Germany, France, Switzerland, Netherlands, Austria, Belgium, Denmark, Finland, Sweden, Italy, Ireland, Luxemburg, Norway, Scotland, Spain and European Medicines Agency.
- Any product having approval of minimum three drug regulatory authorities of former Eastern Europe.
- Any product's manufacturer having GMP certificate (for applied dosage form facility) available on EUDRA-GMDP website. (http://eudragmdp.ema.europa,eu/inspections/gmpc/searchGMPCompliance.do)
- Any WHO prequalified product and manufacturing facility (section) of such product.
- Any product approved by Pharmaceutical Inspection Co-operation Scheme (PIC/S) Participating Authority and manufacturing facility (section) of such product. (https://picscheme.org/en/members).
- Manufacturing site/facilities conformed to the regulatory inspection by any of the PIC/S Participating Authority.

2. For cases not fulfilling the abovementioned exemption criteria, following mechanisms for inspection shall be adopted by DRAP in order of priority:

- Third party audit / inspection on the expense of the applicants and/or
- Virtual/Onsite inspection of the manufacturers abroad by DRAP.

3. ln 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 the Registration Board 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.

DRUG REGULATORY AUTHORITY OF PAKISTAN
Telecom Foundation Complex, G-9/4, Islamabad, Pakistan
Email: info@dra.gov.pk Phone:92-51-9107313
www.dra.gov.pk