PRIORITY REVIEW AND ACCELERATED APPROVAL OF REGISTRATION/ MARKET AUTHORIZATION

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Drug Regulatory Authority of Pakistan
Islamabad-Pakistan

1. HISTORY

This is the first edition of this document.

2. APPLICATION-Guideline for Industry

This document is applicable to manufacturers and importers for guidance on the eligibility criteria and mechanism for registration / market authorization of drugs that address the unmet medical needs in special situation (i.e. Public health emergency), orphan medicinal products or innovative therapies through priority review of submission and accelerated approvals.

3. PURPOSE

This document is meant to provide guidance to industry and health care professionals in elaboration of policy, eligibility criteria and procedure for registration / market authorization of pharmaceutical and biological drugs that address the unmet medical needs in special situation (i.e. Public health emergency), orphan medicinal products and innovative therapies, through priority review of submission and accelerated approvals.

The priority review mechanism provides a specific pathway for faster assessment and availability of vital lifesaving drugs to enhance access. The guidelines are intended to provide technical support for registration requirement and procedure for submission of application for expedited registration of pharmaceutical and biological products (including vaccines) of all types, which fulfill the criteria for priority review and accelerated approvals.

TABLE OF CONTENTS

1. HISTORY 2

2. APPLICATION-Guideline for Industry 2

3. PURPOSE 2

4. INTRODUCTION 4

5. LEGAL PROVISIONS 4

6. GENERAL CONSIDERATIONS 5

7. DEFINATION AND ACRONYMS 5

8. EXPEDITED PATHWAYS FOR REGISTRATION/ MARKET AUTHORIZATION . 6

8.1. General Conditions for Expedited Pathways for Registration/ Market Authorization 6

8.2. Priority Review of Submission 7

8.3. Conditional Marketing Authorization/ Registration 10

8.4. Emergency Use Marketing Authorization / Registration 12

9. REFERENCE: 14

4. INTRODUCTION

Pharmaceutical and Biological Drug Products are required to obtain registration/ market authorization certificate to be put on the market legally in the country. The ultimate purpose of drug registration / market authorization is to ensure that safe, effective and quality drug products can be made available to the citizen.

Registration Board established under Section 7 of the Drug Act, 1976, along with Pharmaceutical Evaluation & Registration (PE&R) Division and Biological Evaluation & Research Division working under Section 4 of DRAP Act, 2012, is responsible for evaluation of application dossiers and granting registration/ market authorization.

Drug Regulatory Authority of Pakistan (DRAP) recognizes that there are circumstances in which standard requirement and procedure for registration / market authorization may be challenging to fulfill and there is an unmet need of such drugs in the country. In such situations, DRAP 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 and / or applicants may be granted a conditional registration / marketing authorization for such drug products where the benefits of immediate availability out weight the risk of less comprehensive data than normally required.

5. LEGAL PROVISIONS

Drug Regulatory Authority of Pakistan (DRAP) under Section 7 (u) of DRAP Act, 2012 perform the functions of registration of drugs. Drug are registered under Section 7 (1) of Drugs Act, 1976as per the procedure for submission of product registration application provided under Rule 26 of Drugs (Licensing, Registering and Advertising) Rules, 1976.

Registration Board has already decided to consider the application dossier for those drugs through priority review process, indicated for treatment of chronic ailments which are short in availability including drugs for treatment of cancer, viral diseases, thalassemia, immunosuppressants, vaccines and sera, new molecules/ formulation (therapies) and blood

factors. These guidelines conform to DRAP Act, 2012 and the Drugs Act 1976 and rules framed there under.

6. GENERAL CONSIDERATIONS

Priority Review and Accelerated approval of Registration / Market Authorization processes are expedited pathways, devised in line with best regulatory practices in the interest of public health. These processed are designed to provide enhance access to vital lifesaving drug product to address an unmet medical needs or address a situation in public health urgency. These processes are appropriate only for those products for which the benefit-risk balance of immediate availability outweighs the risks.

Applicant is responsible for providing all the necessary information in a timely manner. If the applicant cannot meet this requirement, DRAP may convert the submission to the standard registration process.

7. DEFINATION AND ACRONYMS

DS	Drug Substance
DRAP	Drug Regulatory Authority of Pakistan
FDP	Finished Drug Product
MA	Marketing Authorization
MAH	Marketing Authorization Holder
PE&R	Pharmaceutical Evaluation & Registration Division
QSE	Quality, Safety and Efficacy
EUA	Emergency Use Authorization

Life-threatening condition: A condition where the prominent feature (i.e. affecting an important portion of the target population) is serious illness from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of treatment based on mortality and life expectancy data.

Seriously debilitating condition: A condition that has a prominent feature (i.e. affecting an important portion of the target population) which is morbidity with a well-established, major

impact on the functioning of the person based on objective and quantifiable medical or epidemiologic information. Short-lived and/or self-limiting morbidity is not considered seriously debilitating.

Marketing Authorization (MA): A document issued by the Registration Board setup under the Drugs Act, 1976, as a certificate of drug registration.

Marketing Authorization Holder/ Registration Holder: Any person or legal entity that has received marketing authorization / registration to manufacture and/or distribute a finished drug product in the country. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or registration.

Registration Board (RB): A board set up under Section 7 of the Drugs Act, 1976.

Reference Regulatory Authorities (RRA): As adopted by Registration Board in its 275th meetings.

8. EXPEDITED PATHWAYS FOR REGISTRATION/ MARKET AUTHORIZATION

DRAP has adopted following two pathways for expedited registration / market authorization of drug products which fulfill the criteria provided below under relevant pathway:-

A. Priority Review of Submission
B. Conditional Marketing Authorization / Registration
C. Emergency use Marketing Authorization / Registration

Applicant is invited to submit request about its intention to DRAP for consideration under appropriate expedited pathways for registration / market authorization, if the products fulfill the relevant criteria specified in these guidelines. For this purposes, the applicant shall submit a “Letter of Intent” addressed to Secretary Registration Board prior to submission of application dossier, in order to determine the eligibility of application for relevant expedited pathway.

8.1. General Conditions for Expedited Pathways for Registration/ Market Authorization

Following eligibility criteria for priority determination are designed to ensure that only medicines providing the most beneficial are eligible. The eligibility criteria are:

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

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 Registration Board.

8.2. Priority Review of Submission

Priority review of submission pathways is intended to shorten the assessment timeline. It provides patients and healthcare professional with faster access to new drug products and advanced drugs/therapies. Priority review is based on full dossier along with substantial evidence of quality, safety and efficacy.

The eligibility criteria for priority review of submission pathways are as follows:-

I. Orphan medicines for the treatment of rare diseases
II. New drug molecule / New indication drug
III. Short availability
IV. Serious condition e.g. outbreak of a disease etc.

8.2.1. Applicant's request for priority review of submission

Applicant must first apply for priority determination before lodging a registration application. The application for priority determination should be no more than 10 pages and should address the following:-

a) Justification for addressing the general conditions for expedited pathway for registration / market authorization
b) Fulfilling of eligibility criteria for Priority review
c) Regulatory status in the reference regulatory authorities

In one application, drug products have same pharmaceutical ingredients / Drug substance can be combined. However, for multiple drug products, applicants required to submit separate applications. Priority determination of application will be addressed to the Secretary, Registration Board.

8.2.2. Priority registration process

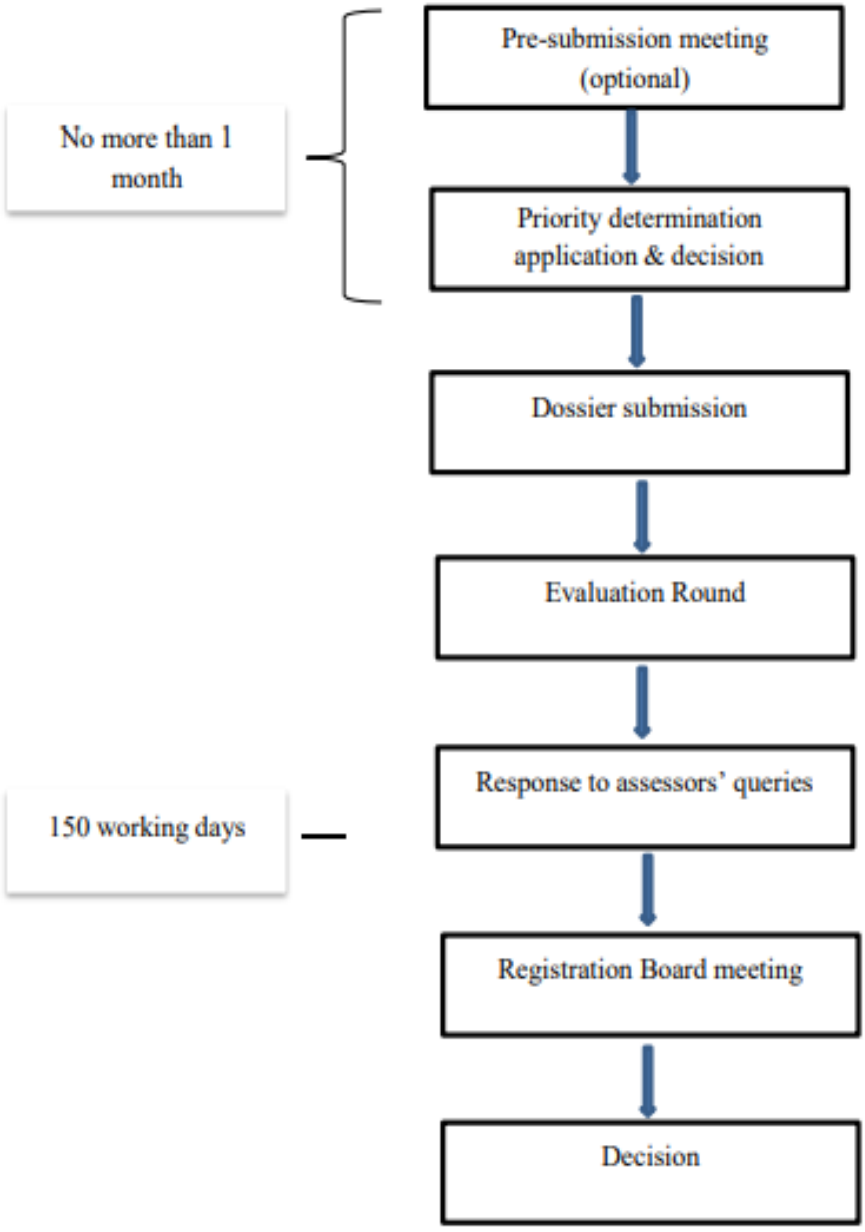
Priority review is based on a full dossier and substantial evidence. A formal Application dossier in the prescribed format (i.e.Form-5F for human products, or Form-5/ 5A for veterinary products, as appropriate) shall be submitted. Priority review registration process is similar to the standard registration process except that the timeline for assessment and evaluation of dossier is aimed to reduce within a target timeframe of 150 working days.

The timeframe is calculated after priority determination process, from acceptance of application dossier for evaluation through to the decision of Registration Board.

Applicant is responsible for providing DRAP with all necessary information in a timely manner. If applicant cannot meet this requirement, application will be considered pending on the part of applicant.

8.2.3. Requirements

Since priority review of registration applications does not provide any exception to the required data and relevant documents and such applications will be dealt as per the approved SOPs. Therefore, the applicant has to provide all the required data and other relevant documents as mentioned in Form 5F (for human) and Form5 / Form 5A (for veterinary).



A mutual stop-clock will be applied during evaluations/ assessment rounds and the applicant is expected to submit responses within a time frame of 14 working days. Firm may receive questions throughout the evaluation period as soon as the evaluators have questions arising from their assessments. Given the nature of the evaluation process, it is not possible to predict in advance when questions will be asked during the period of the assessment.

8.3. Conditional Marketing Authorization/ Registration

For products intended for use in emergency situations, such as outbreak of a disease, less comprehensive pharmaceutical and non-clinical data may also be accepted in special situation of public health urgency. For example legalized copy of administrative documents (e.g. CoPP, etc.) may be accepted later. Drug products / formulation which are not yet registered can only be applied for conditional marketing authorization while fulfilling the following criteria.

I. Drug Product is aimed at treating, preventing or diagnosing, seriously debilitating or life-threatening disease and not registered previously in Pakistan.
II. Drug product required in public health emergency and not registered previously in Pakistan.

8.3.1. Applicant's request for conditional marketing authorization/ registration

Applicant must first apply for determination of suitability for conditional marketing authorization/ registration before lodging an application dossier. The application for determination of suitability should be no more than 10 pages and should address the following:-

a) Justification for addressing the general conditions for expedited pathway for registration / market authorization;
b) Justification for addressing eligibility criteria for conditional marketing authorization/ registration;
c) Regulatory status in reference regulatory authorities.

In one application, drug products have same pharmaceutical ingredients / Drug substance can be combined. However, for multiple drug products, applicant is required to submit separate applications. Priority determination application will be addressed to the Secretary, Registration Board.

8.3.2. Conditional marketing authorization/ registration application process

Applicants for a conditional marketing authorization are advised to engage in early dialogue with DRAP to discuss their product development plan well in advance of the submission of a registration/ marketing-authorization application.

For products deemed suitable for a conditional marketing authorization, applicants are also encouraged to consider requesting for priority review of submission.

8.3.3. Requirements

A formal Application dossier should be submitted on prescribed format (i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate) with supporting documents to request for a conditional marketing authorization / registration. The application dossier will be evaluated by the assessors of DRAP in the light of approved SOPs or as guided by the Board. The evaluation report will be presented before the Registration Board.

The Registration Board will consider the application dossier with evaluation report and decide whether the data submitted fulfill the requirements to justify that the benefit to public health of the drug product's immediate availability on the market outweighs the risk. The Registration Board may consider granting conditional marketing authorization / registration and may specify certain obligations regarding the product with its decision.

The applicant will be required to complete specific obligations (e.g. ongoing or new studies, and in some cases additional activities) with a view to providing comprehensive data confirming that the benefit-risk balance is positive.

If a conditional marketing authorization is granted, the specific obligations and deadlines for their completion will be specified in the marketing authorization. DRAP may also make these conditions publicly available for information of health care professional.

Registration Board, on recommendations from DRAP, may consider granting a registration / marketing authorization in absence of comprehensive data under exceptional circumstances or public health emergency.

8.4. Emergency Use Marketing Authorization / Registration

Drug Regulatory Authority of Pakistan would provide the recommendations to Registration Board to authorize the use of a medical product for an emergency use for a certain period of time. During a declared emergency involving a heightened risk of public health, the Board may consider following for emergency use authorization / registration;

- An unapproved medical product or
- An unapproved use of an approved medical product,

As the case may be, during a declared emergency involving a heightened risk of public health, the Board may allow the counter measures to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by such agents, when there are no adequate, approved and available alternatives.

8.4.1. Applicant's request for Emergency Use Marketing Authorization / Registration

Applicant must first apply for determination of suitability for emergency use marketing authorization/ registration before lodging an application dossier. The application for determination of suitability should be no more than10 pages and should address the following:-

d) Justification for addressing the general conditions for expedited pathway for registration/ market authorization in case of emergency;
e) Justification for addressing eligibility criteria for Emergency Use Marketing Authorization/ Registration;
f) Regulatory status in reference regulatory authorities (if available).

In one application, drug products have same pharmaceutical ingredients / Drug substance can be combined. However, for multiple drug products, applicant is required to submit separate applications. Priority determination application will be addressed to the Secretary, Registration Board.

8.4.2. Emergency use marketing authorization/ registration application process

Applicants for an emergency use Marketing authorization are advised to engage in early dialogue with DRAP to discuss their product development plan well in advance of the

submission of a registration/ marketing-authorization application. After submission, the application would be evaluated and evaluation report will be presented before Registration Board. The Board will decide the fate of application considering the risk-benefit ratio and the type of emergency situation.

8.4.3. Requirements

The exact type and amount of data needed to support an EUA may vary depending on the nature of the declared emergency and the nature of the candidate product or Registration Board may issue guidelines regarding the required data for emergency use marketing authorization / registration. The requirement of data will be decided by the board considering following conditions;

- The seriousness of the clinical condition;
- The incidence of the clinical condition;
- The likelihood that the product may be effective in treating the condition;
- The effect use of the product may have in ensuring national security;
- Whether the product could be used by a large population or is limited to subpopulation(s)
- The extent to which the product would serve a significant unmet medical need in a special population;
- The availability and, where known, safety and effectiveness of other countermeasures;
- The urgency of the treatment needed (i.e., the window of opportunity for treatment can vary between different medical conditions);
- The adequacy of the supporting nonclinical and clinical information;
- The quantity of product required
- Availability of other alternative brands of the same formulation

While DRAP authority will decide the type of application form (Form 5F, Form 5, Form 5A) to be submitted for emergency use marketing authorization / registration.

8.4.4. Termination of Emergency Use Marketing Authorization / Registration

Upon termination of emergency, unapproved product or labeling and product information for an unapproved use must be disposed of and the registration holder must intimate to the relevant division of DRAP in written. A manufacturer / Importer may choose to have unapproved product returned after termination. Notwithstanding any such termination, an authorization shall continue to be effective to provide for continued use in any patient who began treatment before termination (to the extent found necessary by the patient's attending physician).

8.4.5. Revocation of Emergency Use Marketing Authorization / Registration

Registration Board will periodically review the circumstances and appropriateness of an EUA, including circumstances that might warrant revocation of the EUA. Such circumstances may include significant adverse inspectional findings (e.g., where an inspection of the manufacturing site and processes have raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/ benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that undermine the Agency's conclusion that the product "may be effective" against a particular agent); and availability of a preferred product.

9. REFERENCE:

1. The DRAP Act, 2012.
2. The Drugs Act 1976.
3. The Drugs (Licensing, Registering and Advertising) Rules, 1976.
4. WHO Emergency Use Assessment and Listing Procedure (EUAL) for candidate medicines for use in the context of public health emergency.
5. EU Guideline on the conditional marketing authorization for medicinal products for human use.

DRUG REGULATORY AUTHORITY OF PAKISTAN
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