GUIDELINES ON
RECALLS AND RAPID ALERTS
OF DEFECTIVE THERAPEUTIC GOODS

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1. HISTORY

This is the first edition of these guidelines.

2. APPLICATION - Guidelines for Industry

This document is applicable to therapeutic goods industry and supply chain, healthcare professionals, patients, sponsors of clinical trials, and regulatory staff for reporting, investigating, and recalling suspected defective therapeutic goods products. These guidelines are expected to be followed by the licensees (manufacturers, importers, distributors, retailers, and sponsors) for voluntary or statutory recall including investigational products during a clinical trial.

3. PURPOSE

These guidelines aim to provide recommendations and explain the procedures adopted by the DRAP for:

i. recall classification;

ii. recall of defective products;

iii. generation of rapid alert for suspected SF therapeutic goods;

iv. information transmission for rapid alert, and

v. stakeholders' communications;

to effectively remove defective products from the market that may cause a health hazard to the consumer and to safeguard public and animal health.

The guidance document is also intended to guide to:

i. notify quality defects / falsification including spurious or counterfeit therapeutic goods or defective investigational medicinal products,

ii. ensure that in the event where a recall is necessary, it shall be carried in an effective and efficient way.

This guidance will also assist therapeutic goods industry in handling of a product recall, understanding what information should be provided to the DRAP and how to inform the consumer about a product recall.

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4. INTRODUCTION

Drug Regulatory Authority of Pakistan (DRAP) is responsible for ensuring that therapeutic goods available in market meet the prescribed standards of quality, safety, and efficacy. When a therapeutic good is suspected of being potentially harmful to consumers due to its defective quality, safety, efficacy, a recall shall be issued, and it must be removed from the market. This guidance document summarizes the series of activities to be undertake in an event of a necessary recall to carry out recall operations in an effective and efficient way.

This document will help both regulators and industry in setting up and maintaining a system that will enable the rapid and, so far as practicable, complete recall of any lot or batch of a defective therapeutic goods or product from sale, when an action is required to protect public or animal health. This guideline demonstrates stepwise procedures to be followed in recall execution and will also help in recall evaluation and achieving compliance within the stipulated time frame at every level. It is the responsibility of marketing authorization (registration/enlistment) holder to ensure that every level of supply chain (manufacturer, importer, distributor, and retail outlets) is well aware of the recall procedures.

This guideline is in line with, and as per the requirement of the PIC/S document "Guide to Good Manufacturing Practice for Medicinal Product Part I" and PIC/S document "Procedure for Handling Rapid Alerts and Recalls arising from Quality Defects".

These guidelines reflect the current thinking perspective of DRAP and could neither be taken as a complete or definite decision of law nor replace or establish formal decisions of the Authority.

5. LEGAL BACKGROUND

Drug Regulatory Authority of Pakistan (DRAP) is performing post marketing surveillance under 4(c) of DRAP Act, 2012 and is responsible for evaluation, coordination and monitoring of safety, efficacy and quality of drugs, drugs recall and withdrawals through Division of Quality assurance and Laboratory Testing. Under section 7 (t) of the DRAP Act, 2012, the Authority develops, adopts, issues and enforce the standards and guidelines to ensure safety, efficacy and quality of therapeutic goods.

Specific legal Provisions regarding recall of Therapeutic Goods under relevant rules are reproduced as under:-

5.1 For Drugs and Biologicals:-

Registration related matters of the Drugs and Biologicals are dealt under the Drugs (Licensing, Registering & Advertising) Rules, 1976. Section 3.7 of Schedule B-II of these rules, describes Product Recalls system and mechanism, which is reproduced as under;

"3.7.1 ***System****.-- There shall be a system to promptly and effectively recall from the market the products known or suspected to be defective.*

3.7.2 ***Authorized person****.-- A person responsible for the execution and coordination of recalls shall be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree, of urgency, this person shall normally be independent of the sales and marketing organization; if this person is different from the authorized person, the latter shall be made aware of any recall operation,*

3.7.3 ***Written procedure****. --There shall be established written procedures, regularly checked and updated for the organization of any recall activity. Recall operations shall be capable of being initiated promptly at least down to the level of the health institutions and all sale channels including wholesale and where possible retail sale and a public notice if required.*

3.7.4 ***Recall with promptness****. -- All competent authorities to whom a given product may have been distributed shall be promptly informed of any intention to recall the product because it is, or was suspected of being defective.*

3.7.5. ***Distribution records.****-- The distribution records shall be readily available to the person(s) responsible for recall, and they shall contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.*

3.7.6. ***Recording of progress****. -- The progress of the recall process shall be recorded and a final report issued, including*

3.7.7 ***Evaluation****.-- The effectiveness of the arrangements for recalls shall be evaluated from time to time.*

3.7.8 ***Storage of recalled drugs.****-- An instruction shall be included to store recalled products in a secure segregated area while their fate is decided.*

3.7.9. ***All concerned to be in informed.****-- The Central Licensing and Registration Boards and other concerned government authorities shall be immediately informed if it is intended to recall product(s) or if a product has been recalled. Effective system shall be maintained to inform the doctors, pharmacists and public of the recalled products."*

5.2 For Medical Devices & Medicated Cosmetics:-

Enlistment and Registration related matters of Medical Devices are dealt under the Medical Devices Rules, 2017. Rule 49(1) of these rules require a recall system to be establish for medical devices, which is reproduced below:

For the purpose of post-marketing surveillance and vigilance of marketed medical devices, a licensee shall establish, maintain and implement an appropriate and effective post-marketing surveillance and vigilance system of medical devices he is dealing with which shall also include the following elements, namely: —

(a) distribution records;

(b) complaint handling system;

(c) mandatory problem reporting, including investigation of problem or incident;

(d) field corrective action; and

(e) recall procedure.

Sub-rule 21 and 22 of Rule 59 of aforesaid rules empowers Medical Device Board (MDB) to order a product recall, which are reproduced as under:-

"(21). The MDB shall issue recall notices for withdrawal of stock from the market, if any medical device is declared by the notified laboratory to be unsafe and of sub-standard. Likewise, the marketing authorization holder shall inform the MDB for the recalls within thirty days after the identification of problem.

(22). The MDB may direct the Inspector for investigation of cases and implementation of recall notices effectively."

5.3. For Nutraceuticals and Alternative Medicines:-

Similarly, enlistment holders of nutraceutical and alternative medicines (Health & OTC products) are also required to withdraw the unsafe therapeutic goods from the market and undergo immediate recall of the defected therapeutic goods, in compliance to the clause (c) and (d) of Form-6 issued under rule 7(16) of the Alternative Medicines and Health Products (Enlistment) Rules, 2014.

These guidelines will further elaborate the general requirements of product recalls to establish an effective recall system by licensee for timely removal of defective product from market or from clinical trial.

GLOSSARY

Acronyms

ADR	Adverse Drug Reaction.
API	Active Pharmaceutical ingredient
AE	Adverse Event.
BE&R	Biological Evaluation & Research Division
BMR	Batch Manufacturing Record
BPR	Batch Processing Record
cGMP	Current Good Manufacturing Practice
CSC	Clinical Study Committee
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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MA	Marketing Authorization
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.
RB	Registration Board
RRA	Reference Regulatory Authority
WHO	World Health Organization

Definitions

Authentication	means self-checking of distribution history while accepting a shipment of therapeutic goods by the recipient (e.g., distributor, warehouse, hospital and institution or retailer) as is required to verify the distribution history.
Authorization	means permission granted by the DRAP to any legal person or owner(s) of company or firm to conduct manufacturing, import, export, sale or supply of therapeutic goods under the DRAP Act, 2012, The Drugs Act, 1976 and the rules framed thereunder.
Batch (or Lot)	means a defined quantity of starting material, packaging material, or finish product processed in a single process or series of processes so that it could be expected to be homogeneous in the case of continuous manufacture the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity, and to complete certain stages of manufacture it may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to from a final homogeneous batch;
Batch No. (or Lot number)	means a distinctive combination of numbers and or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, and that permit the production history of the batch to be traced and reviewed.
Batch Records / Batch Manufacturing Record (BMR)/ Batch Processing Record (BPR)	batch records mean all documents associated with the manufacture of a batch of bulk product or finished product showing a history of each batch of product and of all circumstances pertinent to the quality of the final product.
Board	means the concerned Board or any competent forum legally authorized under DRAP Act, 2012, The Drugs Act, 1976 and the rules framed thereunder.

Consignee	Anyone who received, purchased, or possesses the therapeutic goods being recalled.
Consumer / Users	Consumer / user is one who purchases therapeutic goods for its use. Consumer/user may include individual consumer, patients, physicians and hospital etc.
Customer	Any person, firm or party buying/receiving therapeutic goods from the company for storage, distribution and / or sale.
Defective Product	Attributes of therapeutic goods which may affect the quality, safety and/or efficacy of the product.
Distributor / Wholesaler	means a person / entity, buying the products for the purpose of selling again.
Drug	means drug as defined in Schedule-I of the DRAP Act, 2012.
Licensee	means manufacturer, importer, distributor, registration holder or enlistment holder of therapeutic goods.
Manufacture	manufacture means all operations of production, quality control, release, storage and the related controls.
Manufacturer	means a company that carries out at least one step of manufacture.
Marketing Authorization	means a document issued by the DRAP under the DRAP Act, 2012, as a certificate of registration / enlistment of a therapeutic good.

Pharmaceutical Product	means any drug intended for human use or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form.
Quality Control Laboratory (QCL)	means any laboratory notified for the test/analysis of therapeutic goods
Recall	means the removal of specific batch/batches of a therapeutic good/product from the market for reasons relating to the quality, safety or efficacy and/or if they are not in line with the particulars provided in registration / enlistment application of the product
Reference Regulatory Authority	means a regulatory authority as notified by any competent forum, board or committee of DRAP for the purpose of reliance.
Distribution / Wholesale	means sale to a person / entity, buying the products for the purpose of selling again
Retail Sale	means a sale other than distribution / wholesale.
Statutory Recall	A recall directed by the Drug Regulatory Authority of Pakistan (DRAP) / provincial government after notifying that product is considered to be in violation of the laws, the DRAP Act, 2012, The Drugs Act, 1976 and the rules framed thereunder.
Substandard and Falsified (SF) Products	Substandard drug means a drug as defined in Section 3 (zz) of the Drugs Act, 1976. Whereas Falsified products include Spurious, Adulterated, Misbranded and Counterfeit drugs (as defined in Section 3 (zb), 3 (a), 3 (s) and 3 (f) of the Drugs Act 1976 respectively).
Supply chain	means transfer of ownership of API i.e. the upstream supply chain (sources and path of ingredients that go to the manufacturer) and the product i.e. downstream supply chain (path of the finished product after it leaves the manufacturer) for each requirement

	regarding pedigrees / transaction records, authentication / verification.
Therapeutic Goods	includes drugs or alternative medicine or medical devices or biologicals or other related products as may be notified by the Authority under Section 2(xxxvi) of the DRAP Act, 2012. (Therapeutic goods may hereinafter refer as the product.)
Voluntary Recall	A recall initiated by the manufacturer as a result of unusual observation in any product's quality during periodic review (Internal / External) or investigation of a market complaint or any other failure or otherwise, is defective that present a risk of injury to human / animal.

6. RECALLS AND RAPID ALERTS

Recalls and rapid alerts are conducted to protect patients and consumers from the any potential harm that may be caused by use of a defective therapeutic goods. A defective therapeutic good is one that is suspected to be harmful under normal conditions of use or that does not comply with its marketing authorization (its registered) specification or that is lacking in therapeutic efficacy or that has not been manufactured in accordance with accepted standards of Good Manufacturing Practice (GMP).

Recall (voluntary/statutory) is an effective method of removing or correcting therapeutic goods, initiated **either** by the manufacturer as a result of defect (unusual observation) in any product's quality during periodic review (internal / external) or investigation of a market complaint or any other failure or that present a risk of injury or is otherwise defective or directed by the Drug Regulatory Authority of Pakistan (DRAP) or Provincial Health Department/Provincial Government after notifying that the product is considered to be in violation of the laws, the DRAP Act, 2012, the Drugs Act, 1976 and the rules framed thereunder.

The licensee holds the primary responsibility to carry out complete/total recall whether voluntary or statutory. Recall takes place because manufacturers, wholesalers and retailers carry out their legal and moral responsibility to protect the public health from the products that represent a risk of health hazard, injury or are otherwise defective.

7. STAGES OF RECALLING A THERAPEUTIC GOOD

In almost all cases, a product recall is divided into following six stages: -

STAGE **01:**	Receipt of Information of Defective Product (Problem Report)
STAGE **02:**	Submission of Information for Assessment of a Recall
STAGE **03:**	Assessment of Recall
STAGE **04:**	Recall communication to remove defective products from market
STAGE **05:**	Monitoring and Progress of Recall
STAGE **06:**	Evaluation of the Recall

STAGE 01: Receipt of Information of Defective Product (Problem Report)

A recall might be initiated voluntarily by the licensee (i.e. manufacturers or importers having registration / enlistment holder, etc.,) of a product, because of complaints or reports related to the quality, safety, or efficacy of a defective therapeutic good. Alternatively, DRAP/ Provincial Health Departments can also orders a statutory recall of a product to the licensee holder upon receipt of defective product report.

The reports or complaints may be generated by the following: -

i. Result of testing analysis of products by the national or provincial quality control laboratories;
ii. Healthcare professionals, physicians, pharmacist, dentists, and patients;
iii. Recall of products by principal manufacturer abroad or by the overseas National Regulatory Authorities or from information received directly from other NRAs or WHO;
iv. Hospitals or Research institutes;
v. Manufacturers or distributors or wholesalers or pharmacies or drug sale outlets (retailers).

Upon receipt of information, licensee will analyze the information, assess the validity of the information and potential hazards or danger associated to the consumers and patients, and the action appropriate to the situation.

In case of serious problems which may lead to initiate recall of Class I or Class II (refer to recall classification section), the licensee must inform to the Division of Quality Assurance & Lab Testing, DRAP, within 24 hours after receipt of the complaint or report of a problem.

For less serious problems that may result in a Class III recall, the licensee must inform to the Division of Quality Assurance & Lab Testing, no later than 72 hours after receipt of complaint or report of a problem.

It should be noted that the Licensee have to send information to the DRAP prior to their decision on recall. When the need for recall has been established an appropriate recall strategy may be devised.

6.1. Action Group on Health Hazard Evaluation

The Action Group on Health Hazard Evaluation of defective products report is part of the Division of Quality Assurance and Lab Testing, DRAP.

The role of the Action Group is to minimize the hazard to patients arising from the distribution of defective therapeutic goods by providing an emergency assessment and communication between the licensee, regulatory field force of DRAP and provincial health departments and consumers.

It achieves this aim by:

a. Receiving and assessing reports of suspected defective therapeutic goods.
b. Advising and monitoring necessary actions by the relevant licensee.
c. Communicating the details of actions to be executed by the relevant stakeholders.
d. Recommendations to the relevant Board or Committee on appropriate action.
e. Monitor the determination of recall classification and level of recall.

The Action Group comprises of the officers of Division of Quality Assurance and Lab Testing, DRAP and headed by the Divisional Head, and it can consult with the experts in specialist areas as and when needed.

Action group on Health Hazard Evaluation of defective products can be contacted at Telephone (+92 51 910 73 17) from 09:00 to 17:00, Monday to Friday, except for public holidays, and can also be contacted directly via email at gsms@dra.gov.pk.

STAGE 02: Submission of Information for Assessment of a Recall

When a licensee initiates a recall of a therapeutic product, it is required to notify the DRAP about the recall situations, and provides all relevant information required for the assessment of recall on the Recall Assessment Form (**Annex-I**).

The licensee shall not wait for assembling of all applicable information prior to notify DRAP. This "early" notification to DRAP will be helpful to review and evaluate their call for guidance and assistance in the recall process.

The information required for assessment of a recall is generally include following three categories:-

a) *Details of the Problem*

i. Name and contact of the person reporting problem;
ii. Date of problem reported;
iii. Problem location;
iv. Problem nature or type of defects in product;
v. Any similar problem reports;
vi. Results of quality control tests and other investigations on suspected or other samples.

b) *Details of the Product(s)*

i. Proprietary (brand) name of product, dosage form, strength and active ingredients;
ii. Registration / enlistment number and pack size details;
iii. Batch number(s), quantity, manufacturing and expiry date;
iv. Manufacturer / importer name with contact details and local distribution list;
v. If the product was exported, then also provide detail of importing country(ies);

c) *Risk Assessment and Proposed Action by Licensee*

i. Assessment and evaluation of potential hazard to consumer;
ii. Proposed action ;
iii. Proposed recall classification and level; and
iv. Availability of alternative product.

STAGE 03: Assessment of Recall

Each recall is a unique exercise. There are several factors that require careful consideration in assessment of potential risks associated with the defective product.

The initial assessment should include the following considerations:

i. Risk to health of an individual including risk to vulnerable patients as well as normal individuals;
ii. Risk of not receiving the correct medication;
iii. Long-term risk as well as immediate risk;
iv. Risk to healthcare professionals or the persons administrating a defective product;
v. Risk of cross contamination particularly in case of defective vaccines and assessment of its impact on national vaccination drive, if applicable;
vi. Risk to the consumer of animal food stuff in view of possible residues in the foodstuff.

It is also required to determine the probability that the defect is real and it is linked directly to the product supplied in the market or the defect arises at the time of dispensing.

6.2. Health Hazard Evaluation

The Action Group of Division of Quality Assurance & Lab Testing, DRAP will evaluate the health hazard posed by the defective product being recalled or considered for recall. It will also

evaluate the recall assessment provided by the licensee, perform health hazard evaluation on information provided on **Annex-I** and will consider, but not limited to, the following factors:

i. Whether any disease or injuries have already occurred from the use of the product.

ii. Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard. Any conclusion shall be supported as completely as possible by scientific documentation and/or statements that the conclusion is the opinion of the individual(s) making the health hazard determination.

iii. Assessment of hazard to various segments of the population, e.g., children, surgical patients, pets, livestock, etc., who are expected to be exposed to the product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk.

iv. Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed.

v. Assessment of the likelihood of occurrence of the hazard.

vi. Assessment of the consequences (immediate or long-range) of occurrence of the hazard.

Based on this determination, the action group will ascertain the recall classification i.e., Class I, Class II, or Class III, to indicate the relative degree of health hazard of the product being recalled or considered for recall and propose a recall strategy.

6.3. Recall Classification

Recall classification is a numerical designation, I, II, or III, that is assigned to a particular recall. This classification indicates the relative degree of health hazard presented by the product being recalled and determined by regulatory authority(ies). A guidance on classification of urgency of a recall based on the degree of health hazard imposed by defective product, in line with PIC/S guidance laid down in "Procedure for Handling Rapid Alerts and Recalls arising from Quality Defects" is detailed below;

Class I

Class I Recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative / defective product will cause serious or permanent adverse health consequences or death.

Examples of such situations are:

- Wrong product (label and contents are different products)
- Correct product but wrong strength, with serious medical consequences.
- Microbial contamination/any foreign particle visible with naked eye in a sterile injectable of sterile injectable or ophthalmic product.
- Chemical contamination with serious medical consequences.
- Mix up of products ('rogues') within a pack. For example, two different blister strips within one outer carton, or, two different tablets within the one blister strip.
- Wrong active ingredient in a multi-component product with serious medical consequences.
- Serious adverse reactions which are batch or product related.
- Any other situation as the Competent Authority or the Board may consider.

Class II

Class II Recall is a situation in which use of, or exposure to, a violative / defective product may cause **temporary or medically reversible** adverse health consequences or where the probability of serious adverse health consequences is remote.

Examples of such situations are:

- Mis-labelling - wrong or missing text or figures.
- Missing or incorrect information - leaflets or inserts.
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences.
- Chemical/physical contamination (significant impurities, cross-contamination, particulates).
- Mix up of products. For example, a case of product A contains one or more packs of product B.
- Non-compliance with specification (e.g. assay, dissolution, stability, content uniformity, fill/weight).
- Insecure closure with serious medical consequences (e.g. cytotoxic, child-resistant containers, potent product).
- Any other situation as the Competent Authority or the Board may consider.

Class III

Class III Recall is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequence.

Examples of such situations are:

- Faulty packaging – for example, wrong or missing batch number or expiry date.
- Faulty closure.
- Any other situation as the Competent Authority or the Board may consider.

6.4. Levels of Recall / Depth of Recall

The level (or depth) of recall of a product/batch shall be determined based on recall classification and level to which distribution has taken place. There are three levels of recall such as consumer/user, retail and wholesale.

6.4.1. Consumer or User Level

which may vary with product, including any intermediate wholesale or retail level. Consumer or user may include individual consumers, patients, physicians and hospitals.

6.4.2. Retail Level

recall to the level immediately preceding consumer or user level. It includes retail groceries, pharmacies, hospital pharmacies, dispensing physician, institutions such as clinics and nursing homes, etc.

6.4.3. Distributor/Wholesale Level

all distribution/wholesale levels between the manufacturer and / or importer and retailer.

6.5. Timelines For Effective Recall System

Based on the category of risks involved, a timeline of within 24 hours up to a maximum of 72 hours of initiation for **Class I** recall. For **Class II** recall up to a maximum of 10 days of initiation and for **Class III** recall up to a maximum of 30 days of initiation is allowed. Sale/supply/distribution of defective product shall immediately be restricted as the **defect is notified**.

This timeline is for initiation of recall procedure to commence from the receipt of information as notified by the Drug Regulatory Authority of Pakistan (DRAP) under statutory recall or voluntary recall by the manufacturer on its own.

For Quality Defects imposing serious health hazards, the recall must be initiated immediately **without waiting for a notification from Authority**. The timeline for stopping sale/distribution of defective product under Class I shall be ensured within 24 hours and the physical recall being completed within 72 hours. The Class II and Class III recalls shall be ensured within 10 and 30 days, respectively.

Class of Recall	Initiation Time	Time to ensure Physical Recall from initiation
I	<24 hours	Max 72 hours
II	< 24 – max 72 hours	Max 10 days
III	< 24 – max 72 hours	Max 30 days

6.6. Recall Strategy

As the information related to the defective therapeutic goods start assembling, licensee will devise an appropriate recall strategy. Various common factors which are required to consider in each recall strategy includes the nature of the defect in the product, incidence of complaints, public safety, distributors networks, etc.

The licensee is also required to discuss the proposed recall strategy and recall classification with the Action Group of DRAP. Any factors which may affect the duration of recall shall also be informed by the licensee. Recall process is required to be completed on the dates as directed by the DRAP.

A recall strategy should also indicate the proposed level in the distribution chain to which the recall is extending. If the recall is limited to distributors / wholesaler level, then substantial justification should be provided for not recalling from retailer or consumer level. Following information should be provided in proposed recall strategy:-

- Indicate the contact number(s) for enquiry and the corresponding operating hours;
- Indicate how the message of recall will be delivered to consumer e.g. press release or recall letters etc.;
- what have the consumers been instructed to do with the recalled product;
- If the recall could create a market shortage, then availability of alternate products in market to minimize the impact on the consumer(s);
- Provide a proposed disposal plan of the recalled products, whether recalled therapeutic goods will be destructed, corrected, etc.

Destruction procedure, along with an appropriate evidence-based record maintenance system of the Licensee is required to be reviewed from the Action Group of DRAP.

STAGE 04: Recall communication to remove defective products from market

The licensee will adopt best approaches for effective communication of recall alert to the targeted audience.

Communication Method	Recall Classification
Recall letters / Notices	Class I, Class II and III
Press Release	Class I or class II where appropriate

6.7. Recall letters

Recall letters are most commonly used tool for effective communication by the licensee with the distribution network, pharmacies / retail outlets and healthcare professionals. A recall letter must be on the licensee's letterhead containing comprehensive information including a factual statement for the reason of recall together with the specific details to allow easy identification of products. Recall letter should also include issuing date and signature along with title and name of signatory. A specimen recall letters is provided at **Annexure-III.**

The recall letter may be sent by email, or other appropriate electronic communication channels, or by post. A recall letter may include

a. Description of the Product; Proprietary (Brand) Name of the product; DRAP Registration / Enlistment Number Name of Registration / Marketing Authorization holder ; name of manufacturer, pack size; dosage form; batch number(s) and expiry date;

b. Reason for Recall; The reason for the recall should be concisely explained. It should be made clear that further distribution or use of the product should cease immediately.

c. Contact Details; The Licensee should clearly identify a hotline for enquiry.

6.8. Press Release

Press releases and rapid alert to public is usually reserved for disseminating information of hazards categorized as Class I, and where appropriate Class II, or under situation where other means for controlling the hazard appear inadequate.

6.9. Stepwise Recall Procedure

- → The licensee/representative of licensee/Quality Assurance of a licensee shall enter the details in the 'Recall Log' and assign a unique recall reference number representing the serial number for a particular year in which the recall has been initiated.
- → The licensee/representative of licensee / Quality Assurance of a licensee shall inform the Distributor/Marketing Company with fastest mode of communication which may include email, telephone, fax, etc. to further stop distribution of the batch(es) in the market and call back the stock available with the distributors, retailers etc, depending on the seriousness of the defect.
- → **"Product/batch Recall Notice"** shall be sent by licensee/representative of licensee/ Quality Assurance of a licensee to Distributor / Marketing Company.
- → Licensee/representative of licensee/ Quality Assurance of a licensee shall also publish a public awareness recall notice in at least two of the daily newspapers having nationwide coverage within 24-72 hours.
- → Distributor / Marketing Company shall immediately check the distribution record to identify the Customers and Warehouse where the subject product / batches have been distributed and forward the copies of the Recall Notice to them for necessary action to immediately hold the available stock and return all unsold stock.
- → The distributor(s) / the Head of warehouse shall send the Return feedback report along with goods / products (if any) to the licensee/representative of licensee /QA head of a licensee of the stock available with them. The licensee/representative of licensee /QA head of a licensee shall reconcile the stocks of the recalled materials against the total quantity of distributed material and fill the "Recall Reconciliation Report" separately for each Batch of Product. The copy shall be forwarded to Drug Regulatory Authority of Pakistan and shall be presented to the Drugs Inspector when inquired for review and necessary action.
- → The recall of the product/batch shall be completed depending on the class of recall as proposed by the Licensee and agreed to by the Action Group on Health Hazard Evaluation of Defective Products, within the defined time.

6.9.1. Responsibilities in Recall Procedure

6.9.1.1. Director or Management of the Marketing Authorization Holder

- ↳ To monitor and ensure effective recall.

6.9.1.2. Quality Control / QA Head of the Manufacturer

- Informing the management in writing about any product defect which may require recall.
- Informing the regulatory authorities immediately after recall decision is made.
- Issuance of recall notice to all distributor/ marketing company.
- Overseeing the system for receiving, verification, quarantining, segregation and securing of recalled stock.
- Labelling of the recalled stock.
- Investigating the incident which resulted in a product recall.
- Making decision on destruction / disposition of recalled stock as per SOP of the firm.

6.9.1.3. Warehouse Head

- Receipt, verification, quarantine/ segregation and secured storage of recalled stock under lock & key.
- Informing QC/QA about the recalled goods.
- Providing support during recall investigation.

6.9.1.4. Distributor/ Marketer

- Ensure the removal of defective batch of product from the market in a stipulated time as per class of the recall.
- Co-ordinate with Wholesalers / retailers for the recall of batch(es) in the market.

6.9.1.5. Wholesalers / Retailers

- To hold the defective batch(es) of product immediately after the receipt of the recall information.
- Co-ordinate with consumers for the recall of batch(es) in the market.

STAGE 05: Progress Monitoring of Recall and Implementation Feedback

Licensee has the prime responsibility for implementing recall action, and for ensuring compliance with the recall procedure at its various stages. The licensee is responsible to develop an effective recall system and maintain all records which will assist in recalling a product from the market.

Following are general requirements for record maintenance by the licensee for effective recalls:

a. A system for maintenance of all manufacturing records for capturing complete history of all batches from starting materials to the finished products i.e. batch manufacturing record, batch processing records, etc.
b. A database for maintaining all distribution records including physician samples and export quantities, should be retained accessible to permit rapid recall of any batch.

Generally, the complete records pertaining to manufacturing and distribution should be retained for two years after the date of transaction or one year after the expiry date of the batch whichever is longer.

Licensee is also required to retain records of complaint received about each product. Complaints should be examined appropriately by the technical personnel and any subsequent action taken should also be documented and shown in the records.

6.10. Recall Reconciliation Report

After the completion of timeframe of recalling product, or at other agreed intervals in accordance to the direction of the Action Group, Division of Quality Assurance & Lab Testing, DRAP, the licensee shall submit interim and final report to monitor the progress of recall implementation.

6.10.1. Interim Report

The interim report should be submitted to Action Group, Division of Quality Assurance & Lab Testing, DRAP, generally at every 7 days of commencement of recall. Following are the contents of the interim report: -

i. When the recall notification was issued, and which communication channels were utilized.

ii. Number of distributors/firms/institutions etc., whom the defective product(s) was supplied;
iii. Number of responses received from them;
iv. Names of entities which did not responded to licensee for recall notification;
v. Quantity of stock returned till report date;
vi. Estimated time frame for the completion of the recall.

6.10.2. Final Report

A final report should be submitted to Action Group, Division of Quality Assurance & Lab Testing, DRAP, within one month of recall commencement and following information should be provided in the final report: -

i. Reason for recall
ii. Details of Actions taken by the Licensee;
iii. Extent of distribution of the relevant batch across the country and export
iv. Quantity of stock returned, corrected, outstanding;
v. Quantity of stock consumed;
vi. Quantity of stock not located;
vii. Date of recall completion;

The Action Group, Division of Quality Assurance & Lab Testing, DRAP, will establish the effectiveness of recall implementation and unless satisfactory reports are received, licensee may be asked to undertake further action.

STAGE 06: Evaluation of the Recall

The purpose of evaluation is to check effectiveness and verify that all consignees at the recall depth specified by the strategy have received notification about the recall and have taken appropriate action. The recalling firm will ordinarily be responsible for conducting effectiveness checks.

In addition to the effectiveness checks conducted by recalling firm, DRAP itself or through its field offices, may also contact or inquire firm's customers as a means of assuring that the

recalling firm and its consignees are performing their recall responsibilities. If DRAP determines the recall to be ineffective, the recalling firm will be asked to take appropriate actions, including re-issuing recall notifications.

6.11. Follow-Up Actions

The follow-up action consists of a check on the effectiveness of a recall, an investigation of the reason for the recall, root cause analysis and remedial action taken to prevent recurrence of the defect.

The licensee/representative of licensee/QA Head of licensee shall monitor the recall process of product/batch to determine whether the recall is progressing satisfactorily.

The stocks of recalled goods shall be placed under "Quarantine" and stored separately under lock and key in a secure area until final decision.

Wherever required, QA Head of the manufacturing site shall perform the physical inspection of recalled goods and collect sample from recalled goods for investigation to establish the root cause of the product quality defect.

The investigation of the recalled batch(es) shall be conducted as per the SOP of the licensee, on "Investigation of Non-conformities" to identify the root cause of the failure and initiate corrective and preventive actions (CAPA).

Impact assessment shall be conducted on other batches of the concerned product and further extended to batch(es) of other product(s), wherever applicable.

If the cause of recall is established to be quality issue associated with any of the raw material used, then the traceability of that material shall be established in all the product(s)/batches.

Based on conclusion of the investigation findings, the QA Head of licensee / representative of licensee shall forward investigation report along with corrective and preventive action and appropriate disposition plan of the batch(es) of recalled goods as per destruction/disposition SOP of licensee to the Directorate of QA&LT, DRAP. Disposition/destruction shall be done in the presence of Drugs Inspector or a team specified for the purpose by DRAP.

7. TERMINATION OF A RECALL

A recall will be terminated when QA&LT Division of Drug Regulator Authority of Pakistan determines that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy, and when it is reasonable to assume that the product subject to the recall has been removed and proper disposition or correction has been made according to the degree of hazard of the recalled product. Written notification that a recall is terminated will be issued by QA&LT Division of Drug Regulatory Authority of Pakistan to the recalling firm. A recalling firm may request termination of its recall by submitting a written request to QA&LT Division stating that the recall is effective in accordance with the criteria set forth, and by accompanying the request with the most current recall status report and a description of the disposition of the recalled product.

8. MOCK RECALL

Mock recall shall be carried out for at least one batch of any product, dispatched for sale where maximum distributors are involved, to test the effectiveness of the arrangements of recall. Effectiveness of recall procedure can also be checked by 'evaluation of a real recall'.

During mock recall traceability shall be performed for at least, one of the raw materials used in the batches identified for mock recall.

Mock Recall shall be performed at least for the longest distribution chain and whenever there is a change in distributor/marketing company.

Records of such mock recall should be maintained by the QA Head of the company and presented to Drugs Inspector when required/inquired.

9. ROLE OF DRUG REGULATORY AUTHORITY OF PAKISTAN

For effective implementation, it will be the responsibility of DRAP to;

i. Oversight of recall implementation
ii. Determine that strategy is devised for recall and recall is properly classified.
iii. Notification and Public Announcement
iv. Monitoring and Assessing the effective implementation of Recall and,
v. Termination of a Recall
vi. Maintenance of database of recalled products

DRAP authorizes the recall action by determining that the action meets the definition of a recall or the applicable definitions for recalls conducted under different regulatory or statutory authorities.

DRAP reviews the information, recall strategy provided by the firm, suggests changes including the issuance of a public announcement, assesses the health hazard presented by the recalled product and monitor the classification of the recall, and if required may re-assign the classification.

DRAP may issue its own public announcement on a firm's recall and also posts information about recalls on DRAP's official website: www.dra.gov.pk. DRAP may also provide recall information to provincial government and to Foreign Governments/Authorities if and when required.

When a firm refuse to recall after being requested or ordered to do so by the Authority or the Authority has reason to believe that the firm's recall strategy is not effective, or is not being implemented effectively, Regulatory actions will be taken as recommended by Director QA&LT or the Action Group for Health Hazard Evaluation and Monitoring, for such specific recall or by the relevant Board for the purpose.

The role of the QA&LT Division and Inspectors in a recall is to assess the adequacy of the Licensee's decision on the recall of the product and to monitor the progress and effectiveness of the recall till appropriate disposal of recalled product.

It is also role of DRAP to ensure that product recall is not used as promotional means by any manufacturer/importer and such action shall be deemed as contravention of conditions of advertisement.

10. ESTABLISHMENT INSPECTION AND OFFICIAL SAMPLING

During the investigating of problem or root cause analysis, Action Group on Health Hazard Evaluation and Monitoring or the concerned Board, may recommend an Establishment Inspection by Federal Inspector of Drugs or Federal Inspector of Drugs along with panel of experts which may be followed by sampling of product being recalled if and when required to further identify the root cause and its impacts.

For all recall inspections, in addition to verify the identification of the root cause, following factors shall also be taken into consideration:

i. Issue a Notice of Inspection
ii. Discuss the suspected problem with management and review the firm's complaint file;
iii. Investigate all areas, control points and/or circumstances which may have a bearing on the product's deficiency;
iv. Review batch records, processing logs and/or other types of records for defective lots and associated lots;
v. Review and obtain copies of the firm's quality control/analytical data of defective product;
vi. Determine actions the firm has taken, is taking, or has planned to take to prevent similar occurrences. If corrective action is not underway, determine the firm's timetable for achieving correction; and
vii. Determine what action the firm has taken or plans to take, and the time frames involved, regarding remaining defective / suspected product(s) in market.

11. RAPID ALERT SYSTEM

Rapid Alert System is intended to transmit information when an urgent action is required to protect the public health, relating to the recall of a therapeutic goods which have quality defect, or for SF therapeutic goods. Rapid alert will enable prompt information exchange between regulatory field force of DRAP and provincial health departments, and also to WHO portal on substandard and falsified medical products and other counterpart regulatory authorities. It can also be used for transmission of other high impact information such as product withdrawals, notifying quality defects, counterfeit or fraud in drug substance (API), or investigational medicinal products when deemed relevant for the safety and efficacy reasons. The Licensee or representative of licensee or Quality Assurance in-charge of a licensee shall maintain an updated Rapid Alert Contact List of all his distributors/marketing company for prompt communication and respond of recall in compliance with timelines as defined in recall classification.

As soon as the product/batch(es) to be recalled is/are identified, licensee shall review the information related to the defective product/batch(es) and decide about recall classification as per the guidance provided in this document in case of voluntary recall or as notified by Authority in case of statutory recall.

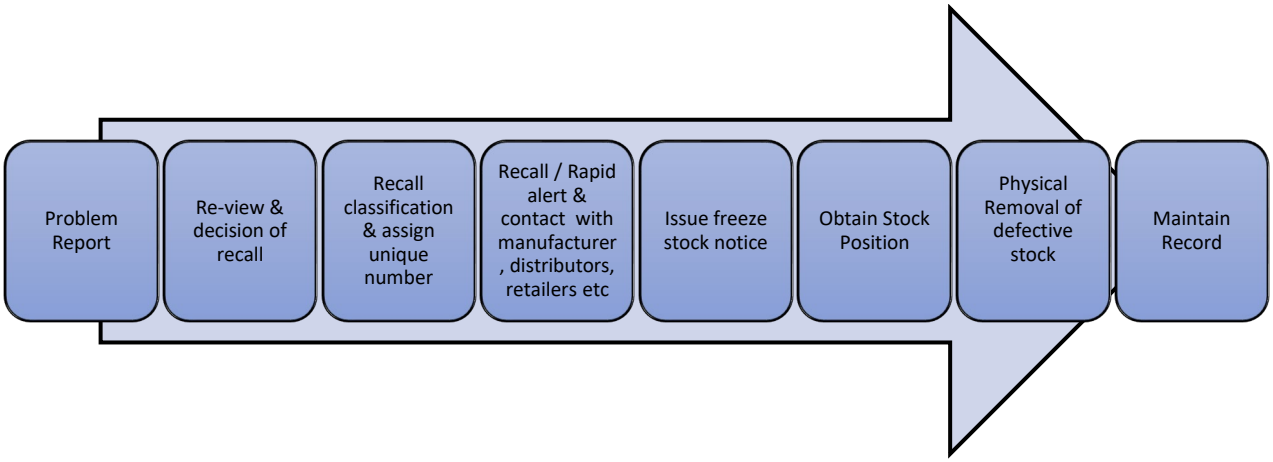
Within 24 Hours of the decision taken or receipt of notification for the recall of the product/batch(es) the communication shall be sent to immediately restrict the distribution/sale of defective product, stating the severity of the defect, using the fastest mode of communication which may include email, telephone, fax, SMS etc to the entire supply chain.

The licensee/representative of licensee shall inform the Drug Regulatory Authority of Pakistan where the product batch(es) in question was distributed immediately after the decision of recall has been taken. Recall assessment shall be made on **Recall assessment form (Annexure I)** and forwarded to Directorate of Quality Assurance & Laboratory Testing, Drug Regulatory Authority of Pakistan.

It shall be the responsibility of the manufacturer and marketing company to inform up to retail level on the reason of recall in his freeze stock notice / sale restrict notice.

It shall be the responsibility of distributor/marketing company / retailer to inform the stock position of product being recalled to his immediate supplier or manufacturer, to Drug Authority of Pakistan and also his area Federal Inspector of Drugs as and when required.

The recall notice received, the stock at that time, the procedure for freezing the stock and record of returned/recalled stocks shall be maintained by the distributor/retailer and shall be made available for verification by area Federal Inspector of Drugs as and when inquired who may verify and report on its timely freezing and return.



11.1. Rapid Alerts to be Issued For Public

The purpose of these alerts is to ensure a timely, proportionate, accurate and consistent response to possible health events arising from Substandard or Falsified products which represent a significant threat to public health. In addition to general public, the target audience of these alerts will also include Physicians, Pharmacists and Nurses working at all levels of healthcare facilities and pharmacies, etc. These alerts will be issued in case of statutory recall or evidence of availability of a Substandard or Falsified product in the market or in response to product alerts issued by WHO or other regulatory bodies. These alerts will be issued in a uniform format approved by the Drug Regulatory Authority of Pakistan and will be uploaded on designated page on Authority's website for access of the target audience.

QA&LT division of Drug Regulatory Authority of Pakistan may also take the following criteria into account before issuing a medical product (Therapeutic good) Alert for information of general public:

i. Has the report been validated (e.g. through Quality Control Laboratory reports etc.)?

ii. Does a genuine and significant threat to public health exist?
iii. Have adequate steps been taken to remove the product from the supply chain? (Has recall been initiated as per procedure explained in Section 4 of this document?)
iv. Is the report recent or is it likely that the SF product remains in circulation?

11.2. Report Validation

Validation can take a number of forms but the most reliable is the test/analysis report of Central Drugs Laboratory or any Provincial Drug Testing Laboratory. Other forms include the root cause analysis submitted by the firm in case of a voluntary recall arising from a quality defect, patient complaints regarding a suspected SF product or in some cases visual inspection. The individual facts of a case can also demonstrate the SF nature of a product, this may include products which have been mis-labelled, concealed or smuggled. Drug Regulatory Authority of Pakistan will make all efforts to establish the veracity of reports received.

11.3. Contents of Rapid Alert / Recall Alert to be issued by DRAP

The purpose of a Rapid Alert and Recall alert is to warn the target audience regarding the existence of a dangerous SF Therapeutic good and its reporting to Drug Regulatory Authority of Pakistan.

The content of the alert will be accurate, specific and precise based on the most recent information available with the Authority, whilst providing advice and where possible reassurance. It will include the following information, if available:

i. Name of product
ii. Name of active pharmaceutical ingredient(s)
iii. Batch / lot number
iv. Date of manufacture
v. Date of expiry
vi. Strength and dosage form
vii. Main intended use
viii. Photographs (If available)
ix. Date of discovery
x. Place of discovery

xi. Result of any laboratory testing carried out

xii. Request for increased vigilance

xiii. Any other relevant information

xiv. DRAP's Medical product Alert e mail address (gsms@dra.gov.pk)

QA&LT Division will issue a medical product alert as soon as the incident has been validated and the risk to public health identified. The Medical product Alert will be identifiable with a specific assigned number in the following format i.e. "Medical product Alert Nº Class of recall. Type of recall (Statutory or voluntary) – Month. Year. Number of recall".

It is recognized that a careful balance needs to be struck between issuing an alert and causing an unnecessary alarm.

11.4. Publication of Alerts

Rapid Alert and Recall Alerts for therapeutic goods will be published in a uniform format on the designated page of DRAP's website (www.dra.gov.pk) as well as on Provincial Government's website, and will remain on the website for a period of 5 years before archiving. A press release may also be issued on official social media handles of Drug Regulatory Authority of Pakistan.

12. FORMS AND FORMATS

a.	Annex-I	Recall Assessment Form
b.	Annex-II	Recall log
c.	Annex-III	Recall letters / Notice to distributors / marketing company / retailers
d.	Annexure-IV	Product Alert to be issued by DRAP

13. REFERENCES

In developing these guidelines, guidance documents referred are;

i. Schedule B-II of the Drugs (Licensing Registering and Advertising) Rules, 1976
ii. PIC/S Guide to Good Manufacturing Practice for Medicinal Product Part I
iii. PIC/S Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects
iv. WHO Recall Guidelines
v. FDA Voluntary Recalls - 21 CFR 7

ANNEXURE-I
RECALL ASSESSMENT FORM

(To be filled by licensee / representative of licensee)

To, Recall Ref No: ……..

……

……. Date: ……..

…….

Recall information	**Information by the Holder of Certificate of registration/Distributor/wholesaler**	**Comments from DRAP (expert committee, concerned Board / competent forum) (For DRAP use only)**
Origin of report		
1. Name of person/organization reporting the problem (State whether it is a complaint, quality defect, lab report, voluntary or statutory)		
2. Date of report		
3. Name of recalling firm (Registration/Enlistment holder/manufacturer) (Specify separately for finish import / contract manufacturing as the case may be.)		
4. Physical address of recalling firm		
5. Telephone number of recalling firm		
6. Alternate number of recalling firm		
7. E-mail address of recalling firm		
8. Name of Quality head/QA Incharge recalling firm		
Product(medicine) details		
1. Name of product affected		
2. Registration number		
3. Dosage form		
4. Strength		

<table>
<tr><td>5. Pack size/type</td><td colspan="2"></td><td></td></tr>
<tr><td>6. Batch number and expiry date</td><td colspan="2"></td><td></td></tr>
<tr><td>7. Date manufactured</td><td colspan="2"></td><td></td></tr>
<tr><td>8. Date released</td><td colspan="2"></td><td></td></tr>
<tr><td>9. Total quantity prior to distribution</td><td colspan="2"></td><td></td></tr>
<tr><td>10. Quantity released for distribution prior to the recall</td><td colspan="2"></td><td></td></tr>
<tr><td>11. Date of distribution (s)</td><td colspan="2"><table><tr><th>Sr. No.</th><th>Distribution Name</th><th>Date</th></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td>12. Local distribution (give full details and quantity)</td><td colspan="2"></td><td></td></tr>
<tr><td>13. Overseas distribution (give full details and quantity)</td><td colspan="2"></td><td></td></tr>
<tr><td>Nature of defect</td><td colspan="2"></td><td></td></tr>
<tr><td>1. Source of problem (e.g. SS/OOS test report, patient/ hospital/pharmacy/ manufacturer, etc</td><td colspan="2"></td><td></td></tr>
<tr><td>2. Details of problem</td><td colspan="2"></td><td></td></tr>
<tr><td>3. Number of complaints received if any</td><td colspan="2"></td><td></td></tr>
<tr><td>4. Action taken so far (if any)/ Proposed action and its urgency</td><td colspan="2"></td><td></td></tr>
<tr><td>5. Type of hazard/health risk and assessment of risk to the user</td><td colspan="2"></td><td></td></tr>
<tr><td>6. Proposed recall classification and level of recall</td><td colspan="2"></td><td></td></tr>
<tr><td>7. Other relevant information</td><td colspan="2"></td><td></td></tr>
</table>

The form should be signed and dated appropriately.

ANNEXURE - II

RECALL LOG

(Reconciliation Form)

(to be filled in by licensee / representative of licensee)

Recall ref. no. (Firm)	Time & Date of recall Initiation	Product name	Batch ./ Lot No	Mfg Date	Exp Date	Reason for recall	Classification [Class I,II,III]	Quantity Produced / B. Size (A)	Unsold or Undistributed quantity in possession (B)	Quantity Distributed (C)	Quantity Returned / Recalled	Closure Date & Sign.	Remarks (%age of recall)

ANNEXURE – III

RECALL LETTERS / NOTICE TO DISTRIBUTORS / MARKETING COMPANY / STOCKISTS / RETAILERS

(To be filled by licensee / representative of licensee)

To;	……. …….. ……	Recall Ref No. …….. Date: …….

Please stop further distribution/sale of below mentioned product/batches with immediate effect. Kindly recall the stocks of these batch/es from the market.

Product details (Name, Strength, Dosage, Pack and Reg / enlistment Number)	**Batch/ Lot No.**	**Mfg. Date**	**Exp. Date**	**Batch Size**	**Quantity released for sale**

Tick the appropriate.

Type of Recall	Voluntary / Statutory
Recall Classification	Class I Class II Class III
Extent of Recall	Wholesaler Distributor Retailer Hospitals/Healthcare Professionals/Consumers Authorized Exporters/Agents in Importing country

Reason for recall:

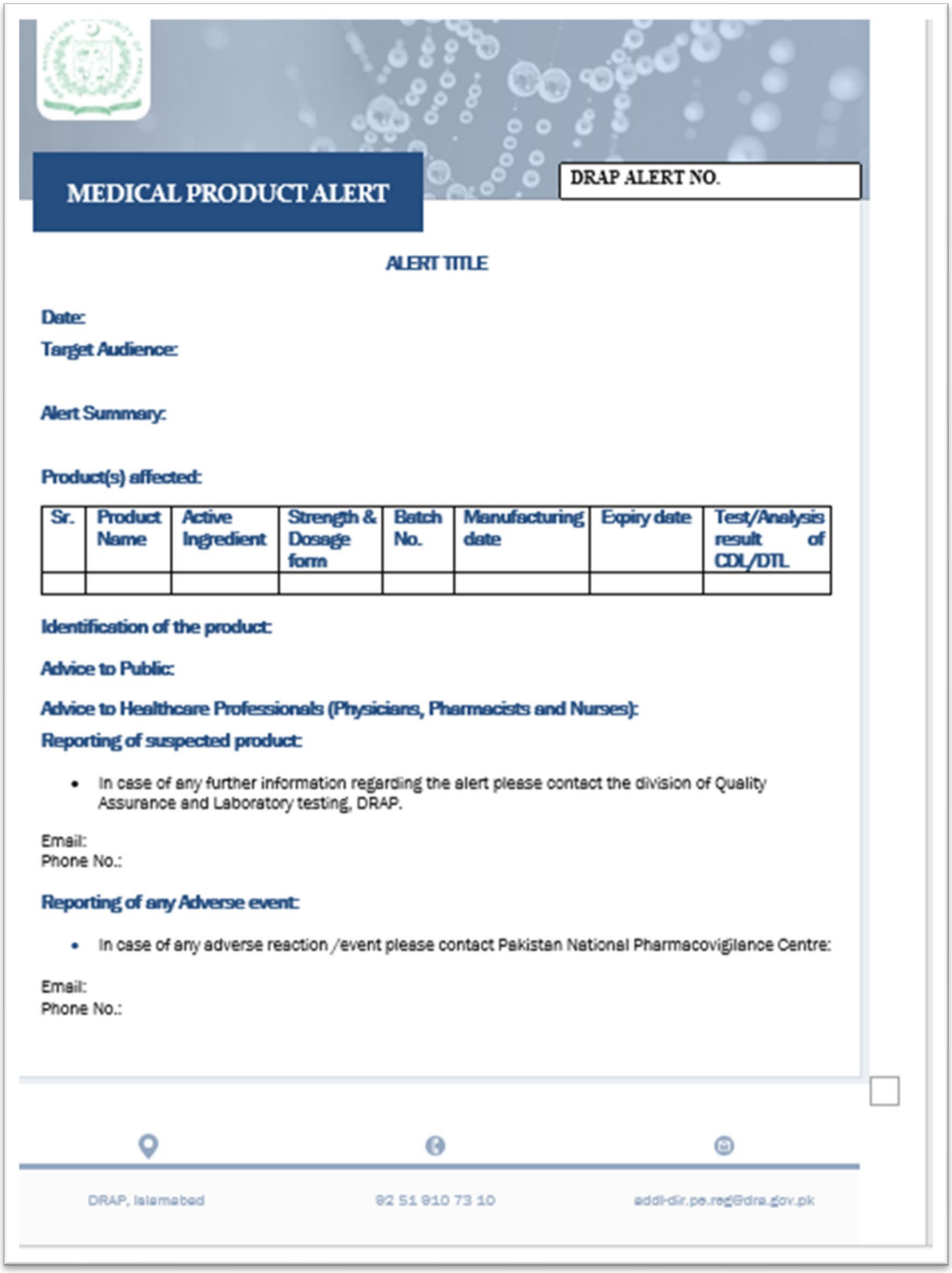
Licensee / representative of licensee

(Name, Sign, Stamp & Date)

Manufacturing site: ……. Mfg.Lic.No.: ……...

ANNEXURE – IV

RECALL / PRODUCT ALERT TO BE ISSUED BY DRAP



MEDICAL PRODUCT ALERT

DRAP ALERT NO.

ALERT TITLE

Date:

Target Audience:

Alert Summary:

Product(s) affected:

Sr.	Product Name	Active Ingredient	Strength & Dosage form	Batch No.	Manufacturing date	Expiry date	Test/Analysis result of CDL/DTL

Identification of the product:

Advice to Public:

Advice to Healthcare Professionals (Physicians, Pharmacists and Nurses):

Reporting of suspected product:

- In case of any further information regarding the alert please contact the division of Quality Assurance and Laboratory testing, DRAP.

Email:
Phone No.:

Reporting of any Adverse event:

- In case of any adverse reaction /event please contact Pakistan National Pharmacovigilance Centre:

Email:
Phone No.:

DRAP, Islamabad 92 51 910 73 10 addl-dir.pe.reg@dra.gov.pk

DRUG REGULATORY AUTHORITY OF PAKISTAN
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Email: addl-dir.qa@dra.gov.pk Phone:92-51-9262142
www.dra.gov.pk