GUIDE TO
REPORTING AND INVESTIGATION OF QUALITY DEFECTS IN THERAPEUTIC GOODS

Document History: **1st Edition**
Effective Date:

Drug Regulatory Authority of Pakistan
GOVERNEMNT OF PAKISTAN
Telecom Foundation Complex, Sector G-9/4, Islamabad.

HISTORY

This is the first edition of these guidelines.

APPLICATION ----- (Guideline for Industry)

This is a guide for the Manufacturers, Importers, Wholesalers, Distributors and retailers. This guide covers the reporting of potential quality defects to Drug Regulatory Authority of Pakistan involving the following categories of medicinal products for human and veterinary use:

- Therapeutic goods which are the subject to a registration/enlistment from DRAP.
- Active substances used in the manufacture of therapeutic goods, in the event of a serious or potentially life-threatening situation.

Note: where the defective active substance has been used in the manufacture of finished product batches, already released to market, this guidance document applies, in the usual way, for the finished product manufacturer.

PURPOSE:

The purpose of the guidance is to ensure that stakeholders are better equipped to report and investigate quality defects arising from current Good Manufacturing Practices issues. The overall aims are:

(i) To ensure that potential quality defects are properly investigated and reported appropriately in the requisite timeframes.
(ii) To ensure that the requisite oversight is applied to defect issues, corresponding with the level of risk posed to end user.

DRAP verifies monitoring of investigations into quality defects, to assess the level of risk and agree which market actions, if any, are required to mitigate against that risk and to oversee corrective and preventative actions.

1. QUALITY DEFECTS

A quality defect in a medicinal product may be defined as an attribute of a medicinal product or component which may affect the quality, safety and/or efficacy of the product.

2. CLASSIFICATION OF QUALITY DEFECTS

Suspected or confirmed quality defects may be classified into three categories, according to the risk posed to patient or animal health.

Critical quality defects are potentially life threatening or could pose a serious risk to patient or animal health.

Major quality defects are those which could cause illness or mistreatment but are not critical.

Minor quality defects are those which are unlikely to pose a risk to patient or animal health.

As a general rule, only minor and some major defects may be considered non-reportable.

3. INITIAL INVESTIGATION PHASE / INFORMATION GATHERING

In many cases, the classification, required action(s) and reporting requirements associated with a quality defect will be easy to determine immediately, for example an obvious quality defect, known to affect multiple units or batches. In some cases, these aspects will not be clear, usually where single or sporadic reports are observed or received from the market. It can be unclear if such cases represent a true defect issue or not. Either way, enough information should be gathered, to confirm:

a. If there is a potential defect (i.e. that the complaint/report is justified)
b. If there is a risk to patient or animal health
c. When and if the issue needs to be reported to DRAP
d. If any market action is required

There are two phases in assigning the above criteria of (b) to (d) to a defect:

(i) Gathering information on the defect and
(ii) Assessing its potential effects.

3.1. Information Gathering

Before assessing the risk associated with a potential quality defect, a greater understanding of the defect should be gained. Information gathering can include such elements as:

- Full description of the defect and an examination of samples, if possible
- Correspondence with the individual(s) who reported the defect, if applicable
- Review of batch records and any change controls or deviations associated with the batch(es)
- Review of previous complaints for the product/batch(es)

Review of previous complaints for the product/batch(es) shall reveal the following;

(i) The defect is isolated in nature and, therefore, may not need to be reported if the level of risk does not warrant it, or

(ii) The defect is more widespread throughout a batch/batches and/or has the potential to lead to a shortage or recall; in such cases it should be reported. Full knowledge of the extent of a defect upon reporting is helpful and can greatly speed up the investigative process.

3.2. Risk Assessment

The ICH Q9 Guideline on Quality Risk Management (QRM) may usefully be applied for risk assessment and to determine whether a suspected defect should be reported.

Subsequent to or in parallel with initial investigation methods, the actual risk associated with the defect itself should be considered. Good information gathering can make risk assessment easier and less time-consuming.

There are four distinct parts to quality risk management: risk assessment, risk control, risk communication and risk review. Determining whether a defect should be reported should involve risk assessment and risk communication activities. Risk control and risk review will follow, but only as remedial measures, where necessary after the decision has been made on the reporting of the defect.

Factors to consider while assessing the risks associated with a potential quality defect include:

a. Potential consequences of the defect on patients or animals

b. Nature of the product involved (e.g. its route and method of administration, its therapeutic class, etc.)

c. Nature of the patient population (or the most vulnerable of the patient populations e.g. neonates, infants, children, elderly, pregnant women etc) using the product.

d. Risk posed by the patient not taking the product as a result of the defect (risk vs benefit ratio).

4. DECISION ON REPORTING AND TIMELINES

Once initial investigations, as required, have described the defect, established its extent and classified the risk, it should be possible to determine when, and if, it should be reported to DRAP, using the following guidance and approximate timelines:

Critical or major defect issues which may lead to a recall, should be reported immediately (as soon as reasonably possible). So that agreement can be reached on quarantine actions, recall level and availability of replacement stock, to minimize the exposure of the defective batch. Before reporting, stock can be quarantined at the primary wholesale or distributor level, to minimise additional exposure.

Minor or major issues where there is no proposed market action, but which are deemed reportable, should be reported in a timely manner. It is permissible to allow time for information gathering, but the amount of time spent doing so should be commensurate with the perceived risk. This could be a few days for potentially higher risk defects, to a maximum of around two weeks where the risk is lower. It is generally not considered acceptable to wait more than two or three weeks, or necessary to complete an investigation before reporting.

4.1. What to report:

Manufacturers shall report any defect that may result in a recall of stock or restrict supply. Examples include but need not be limited to;

- Non-conformance with any of the details of the registration/enlistment (labeling, packaging, components, method manufacture, raw material suppliers).
- Risk to Sterility Assurance for example a probable media failure or environmental monitoring indicating gross contamination, specified pathogens, unusual microorganisms or any other unexpected results.
- Risk of product mix-up– any situation where a patient may inadvertently take one product in place of another. This includes mis-labelling and rogues.
- Cross contamination either by other pharmaceutical materials, or by substances that could be harmful (residual solvents, non-pharmaceutical substances such as pesticides, industrial chemicals).
- Where the product may cause physical injury, for example presence of broken glass or plastic particles in an eye preparation or an oral liquid.
- Stability out of specification (OOS), or out of trend with implications for batches in the market (remember other production batches may also be implicated).

Reportable quality defects should be notified by manufacturers, wholesalers and distributors using the **quality defect report form (Appendix 1)**. The **information to be provided** when reporting a potential quality defect is detailed in the **(Appendix 2)**. While details of the investigation performed to date should be included in the initial quality defect report, submission of the quality defect report should not be delayed, pending completion of the root cause investigation.

A separate quality defect investigation report should be prepared upon completion of the company investigation to establish the root cause of the quality defect which includes the steps taken to investigate, correct and to prevent the source of the quality defect.

Once a batch of product has been made available for sale at a wholesaler and, once that batch is retrieved due to a potential quality issue, this is considered a recall and procedure for recall (Rapid Alerts and Recalls Arising from Quality Defects Guidelines) should be followed accordingly.

4.2. Assessing A Quality Defect As Not Reportable:

Certain criteria should be used in order to determine whether a quality defect should be reported to DRAP or not. **The defect should meet <u>all</u> the below criteria in order to be considered as non-reportable:**

(i) The defect is isolated in occurrence. A quality defect should only be considered non-reportable if it is determined that it is a defect which is not widespread throughout a batch or batches of a product, or in multiple products.

(ii) No market action is considered necessary by the company for the affected batch(es). It is important to note that some minor defects do result in market action, such as the quarantine or recall of a batch or a number of batches and should be reported. For example, minor packaging and/or labelling defects may in some cases be corrected by recalling and repackaging the affected units to bring those units into compliance with their marketing authorisation.

4.3. What not to report:

- Non-conformances for batches <u>not yet released</u> (unless the root cause also links released stock) – these should be managed through industry's Pharmaceutical Quality/Quality Assurance System. Manufacturer should assess the risk to quality safety and efficacy, identify the root cause, assess whether other batches/products/processes may be similarly affected, identify what remedial action is required to mitigate the non-conformance, identify actions to prevent recurrence. But you do need to report defects for <u>released</u> batches, even if stock hasn't yet been distributed to market.
- Customer complaints for isolated issues – manage through your Pharmaceutical Quality System/Quality Assurance. For example, a customer may complain that the

batch variable data (batch number, expiry date) on a secondary carton pack is missing, smudged or not readable. If it is only one occurrence, it can be managed through your PQS as above. However if it is a widespread or repeated occurrence, then there may be a need to take market action, for example recall of affected stock or issue a Caution in Use.

- Manufacturer shall keep a complete record of all non-reportable quality defects, perform investigations and take corrective and preventive action and such record shall be verified by Inspectors during regulatory inspections.

5. CONTACT DETAILS AND HOW TO REPORT

By e-mail (preferred method of reporting). Please complete the quality defect report form (Appendix 1) and e-mail to qualitydefects@dra.gov.pk

Through Post to

The Director, QA&LT, DRAP,
Division of Quality Assurance & Lab Testing,
Drug Regulatory Authority of Pakistan,
3rd Floor, T.F Complex,
6 – Mauve Area, Sector G-9/4, Islamabad

ANNEXURE-I
QUALITY DEFECT REPORT FORM

(To be filled by licensee / representative of licensee)

To,
……
……
……

Ref No: ……..

Date: ……..

Defect information	**Information by the Holder of Certificate of registration/Distributor/wholesaler**	**Comments from DRAP (expert committee, concerned Board / competent forum)**
Origin of report		
1. Name of person/organization reporting the problem (State whether it is a complaint, quality defect, lab report)		
2. Date of report		
3. Name of firm (Registration/Enlistment holder/manufacturer) (Specify separately for finish import / contract manufacturing as the case may be.)		
4. Physical address of firm		
5. Telephone number of firm		
6. Alternate number of firm		
7. E-mail address of firm		
8. Name of Quality head/QA Incharge		
Product(medicine) details		
1. Name of product affected		
2. Registration number		
3. Dosage form		
4. Strength		
5. Pack size/type		
6. Batch number and expiry date		
Nature of defect **(For Manufacturers Only)**		
1. Source of problem (e.g. SS/OOS test report, patient/ hospital/pharmacy/ manufacturer, etc		
2. Details of problem		
3. Number of complaints received if any		

4. Action taken so far (if any)/ Proposed action and its urgency		
5. Type of hazard/health risk and assessment of risk to the user		
6. Proposed recall classification and level of recall if applicable		
7. Investigation (May also be provided in attachments)		
8. Corrective and Preventive Action (May also be provided in attachments)		
9. Any other relevant information (May also be provided in attachments)		

List of attachments to this report

Place and date: _____

Signature and typed name: _____

To be submitted via: _____

6. APPENDIX INFORMATION TO BE PROVIDED TO THE DRAP WHEN REPORTING A POTENTIAL QUALITY DEFECT

Product and batch details

- Product name, dosage, form, strength
- Active substance(s)
- Manufacturer(s)

- Pack size(s)
- Batch number(s) and expiry date(s)
- Number of units in the batch(es)

- Dates of distribution of the batch(es), i.e. first/last dates of distribution to/from the primary wholesaler
- Markets to which the batch(es) were distributed and quantities that went to each

Description of the defect

- As full a description of the defect as possible (best obtained by inspection of defect samples, but can also include correspondence with the reporter, photographs)
- Outcome of examination and/or testing of retained sample, where appropriate
- Number of similar complaints/issues identified for the batch or product (all markets)

- Confirmation of review of batch records, historical data and any relevant findings identified
- Review of previous complaints, investigations, if applicable
- Date when defect was first identified
- Summary of the main findings to date of the investigation performed.