IPA

Innovation, Quality and Global Reach

IPA Sub-Group 5: Handling of Market Complaints

Best Practice Document

IPA Sub-Group 5: Handling of Market Complaints

Best Practice Document

February 2020

Published by:
Indian Pharmaceutical Alliance
A-205 Sangam
14B S V Road, Santacruz (W)
Mumbai 400 054
India
E-mail: sudarshan.jain@ipa-india.org

February 2020

Contents


AB
ABA
AAB

Preface

In April 2015, The IPA launched its Quality Forum (QF) to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of guidelines for several of these topics. In this document, we focus on best practices for *Handling of market complaints*. We had released a comprehensive set of *Data Reliability Guideline* in February 2017, *Process Validation Guideline* and *Good Documentation Practice Guideline* in February 2018 and *Investigation of non-conformities* in February 2019.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Avinash Joshi (Cadila Healthcare); Shiney Joy (Cipla); Ramakrishna Vempaty (Dr Reddy's); Indrajit Bose (Lupin); Jigar Marfatia (Sun); and Dilkesh Shah (Torrent).
The IPA wishes to acknowledge their concerted effort over the last 24 months. They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and other regulatory bodies such as UKMHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's India Pharmaceutical Forum 2020 in Mumbai, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

Mumbai
February 2020

Introduction

This Best Practice Document (or 'Document' in short) covers drug substances and drug products manufactured and packed in an approved environment which are or may be defective. This contains specific information on handling complaints about the defects reported by the stake holders and proposes options to be considered after a complaint is received. The complaint may be reported by the patient, a regulatory agency, a healthcare professional or any stakeholder observing the defect. The Document is subdivided into a number of sections and each section provides additional best practice on how to perform each activity listed in order to ensure that such complaints are not repeated. Investigations verifying the robustness of procedures and systems followed during the manufacturing, packaging, distribution and handling of drug substance or drug product must be performed and confirmed. Tools may be applied to investigate the cause for defective products. In order to protect public health, a system and appropriate procedure is defined in order to record, assess, investigate and review complaints including potential quality defects and, if necessary, to effectively and promptly recall medicinal products for human use from the distribution network. Quality Risk Management principles must be applied to the investigation and quality defects must be assessed. The assessment may help in decision making with respect to initiating corrective and preventive actions thereby reducing risk in future batches. In extreme cases, the decision might also lead to product recalls.

IPA Sub-Group 5: Handling of Market Complaints

1. Scope

This document is applicable for handling market complaints and initiating proposed actions based on the criticality of complaints for drug product(s) and drug substance(s) manufactured and/or marketed by the company.

2. Purpose

The purpose of this document is to suggests steps for systematic procedure from receiving complaints to closure of complaints for drug substance and drug product from consumers, healthcare professionals, and regulatory agencies, according to procedures along with corrective and preventive actions to be taken.

3. Definitions

- **Critical Complaint:** This is a type of defect which has significant impact on product quality and/or safety affecting the patient.
- **Non-critical Complaint:** This is a type of defect that has no life-threatening effect on the patient but has impact on the quality of the product.
- **Major Complaint:** A defect, other than a critical defect, that has a significant impact on product quality resulting in failure or reduction in the suitability of use of a unit for its intended purpose.
- **Minor Complaint:** A defect that does not have any significant/detectable impact on product quality and/or safety and is mainly related to physical attributes/cosmetic appearance of the product.
- **Patient:** A person receiving or registered to receive medical treatment.
- **Complaint:** Any written, electronic, or oral communication that reports suspected deficiencies related to the identity, quality, safety, effectiveness, or performance of a product/substance after it is released for distribution.
- **Complainant:** Any person or body registering a complaint, or the patient or the customer/healthcare professional who notifies the defect or failure.
- **Drug Product:** A finished dosage form; for example, a tablet, capsule, solution, etc., that contains an active drug ingredient, generally, but not necessarily, in association with inactive ingredients.
- **Drug Substance:** Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
- **Healthcare Professional:** Practitioners including physicians, nurses, pharmacists, dentists, respiratory therapists, physical therapists, technologists, or any other practitioners or allied health professionals.

- **Regulatory Agency:** Government authority responsible for control and supervision of a particular activity or area of public interest.
- **Adverse Drug Event:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered to be drug-related. An- adverse event associated with the use of a drug in humans, whether or not considered to be drug related, may include the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring form drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.
- **Adverse Drug Reaction (ADR):** A "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function."
- **Lack of Effect:** Failure to produce the expected pharmacological action.
- **Substantiated Complaint:** A complaint which is candid, possessing the claimed or attributed quality of product and matches with product label, artwork number, batch code, colour shades of cartons/labels/blisters/bottles, embossing details, product description and is not the output of pretence, hypocrisy, counterfeiting or tampered drug product.
- **Non-substantiated Complaint:** A complaint which does not arise due to any problem in manufacturing, analysis and packing processes or stability and may be due to mishandling at customer's end, incorrect storage/usage, not following the instructions as per the product literature, and may not necessarily require corrective/preventive action at the manufacturing site.
- **Counterfeit Complaints:** Complaints which are related to falsified medicines containing ingredients of low quality or in the wrong doses. They can also be products deliberately and fraudulently mislabelled with respect to their identity or source and has fake packaging, wrong ingredients, or low levels of the active ingredients.
- **Health Hazard Evaluation (HHE):** A risk assessment to determine the potential impact of a product quality issue to the safety of the patient. It includes a comprehensive medical evaluation of a product quality issue to the patient population that is then used to make an initial informed medical opinion.
- **Primary Packaging:** First level product packaging that comes in direct contact with the product and works as a barrier between the product and environment.
- **Secondary Packaging:** Second level product packaging that does not come into direct contact with the product.
- **Contract Manufacturing Organization (CMO):** Any external entity manufacturing active pharmaceutical ingredient (API), bulk or finished products, responsible for packaging/repackaging/storage of bulk or finished products (e.g., packagers, warehouses, distributors), any contract analysis organization (including laboratory involved in testing of APIs, API starting materials, bulk and finished products, development of analytical testing methods, local retesting and execution of follow-up stability studies).

- **Field Alert Report:** A formal notification to the USFDA for drug products marketed and distributed in USA, for notifying potential issues associated with the drug product that may have impact on the safety, quality, identity, integrity and purity of product, through FDA Form 3331.
- **Recall:** Removal of marketed products for reasons relating to deficiencies in quality, safety, efficacy and labelling.
- **Preliminary Investigation:** This includes evaluation of all first hand available data related to the complaint; e.g., evaluation of control sample, complaint sample photographs, repetitive nature of the complaint/product history, stability data, BMR, BPR, deviation, OOS/OOT observations, etc.
- **Root Cause:** The underlying reason for the non-conformance which is confirmed by evidence of a known sequence of events and observations.
- **Corrective Action:** Action to eliminate the cause of a detected non-conformity or other undesirable situations. Corrective action is taken to prevent recurrence.
- **Preventive Action:** Action to eliminate the cause of a potential non-conformity or other undesirable situations. Preventive action is taken to prevent occurrence.
- **Harm:** Damage to health including damage that can occur from loss of product quality or availability.
- **Hazard:** Potential source of harm.
- **Risk:** The combination of probability of occurrence of harm and severity of harm.
- **Risk Assessment:** A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
- **Risk Evaluation:** A method to compare the estimated risk against the given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.
- **Risk Analysis:** The estimation of the risk associated with the identified hazards.
- **Severity:** A measure of the possible consequences of a hazard.
- **Detectability:** The ability to discover or determine the existence and presence of a hazard.
- **Shelf Life/Expiry Period:** The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.
- **Over-the-Counter Drugs (OTC):** Drug products that are available to consumers without a prescription.
- **Serious ADE:** Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.
- **Unexpected Side Effects or Adverse Events:** Any adverse drug experience that is not listed in the current labelling of the drug product. This includes events that may be symptomatically and

pathophysiologically related to an event listed in the labelling but differs from the experience because of greater severity and specificity.

- **Product Quality Problems:** Issues that can occur if a product is not working properly or if it has a defect.
- **Potentially Preventable Mistakes:** Problems that may be caused by various issues, including choosing the wrong product because of labels or packaging that look very similar, for instance, confusing two products that have similar brand or generic names. Mistakes may also be the result of using a device with hard-to-read controls or displays, which may cause the user to record a test result that is not correct.
- **Therapeutic Failures:** Problems that can include a situation when a medicinal product does not seem to work as well when the patient switches from one generic to another.
- **Working Day:** Any period from a Monday through a Sunday, taking into account the normal daytime business hours, excluding holidays and weekly off-days, at the manufacturing site. Scheduled weekly off-days are to be excluded from the calculation of a Working Day. If the site is located in India reference of overseas working calendar is not applicable.
- **Dosage Units:** The total number of individual dosage units, distributed or shipped under the approved application or product family (for non-application products) to customers, including distributors.
- **Total Number of Complaints:** All complaints received by the site in the reporting period- related to the quality of products manufactured in the site (i.e., complaints involving any possible, including actual, failure of a drug product to meet any of its specifications designed to ensure that any drug product conforms to appropriate standards of identity, strength, quality, and purity) regardless of whether this is subsequently confirmed or not.
- **Total Number of Packs:** Total number of packs (the final product form that leaves the plant, one level lower than tertiary packs, and most frequently the secondary packaging unit, e.g., pack of blisters or bottle in carton pack) released in the reporting period.
- **Total Number of Attempted Lots Released:** The number of lots attempted per the above definition, which are released for distribution or for the next stage of manufacturing of the product.
- **Number of Critical Complaints:** Complaints received by the site which may indicate a potential failure to meet product specifications, and may impact product safety and could lead to regulatory actions, up to and including product recalls. Critical complaints include those that potentially could lead to FDA notification (e.g., Field Alert Reports, Biological Product Deviation Reports, etc.).

4. Responsibilities

Site Quality Assurance

- To receive and log the complaints.
- To obtain information from the complainant about the defective product.
- To initially categorize complaints received.
- To investigate, review, document and respond to the complaints.
- To implement and monitor CAPA.

- To perform risk assessment for system failure.
- To assess substantiated and non–substantiated complaints.
- To ensure completion of investigation within defined timeline.
- To handle complaint sample.
- To investigate complaint based on additional information received after closure of complaint and to close the complaint.
- To share investigation report with PV for LOE, ADE/ADR complaints.
- To share the investigation report with the complainant.
- To maintain complaint records.
- To perform trend analysis of complaints.
- To inform management and Head, Corporate Quality about the decision to recall.

Site Production/PDL/Packaging Development

- To assist in investigating the complaints received with site QA.
- To review trend analysis of complaints.

Site Quality Assurance Head

- To acknowledge the complaint received with the complainant.
- To authorize the initial categorization of complaints and to categorize complaint post investigation.
- To file FAR/AN and notify Corporate Quality Head and management.
- To ensure destruction of complaint sample.
- To ensure implementation of CAPA for complaints and trends.
- To initiate recall, if necessary, and notify Corporate Quality Head and management.

Pharmacovigilance (PV)

- To handle ADR/ADE related complaints.

5. Introduction to Complaints

Complaints are indications of dissatisfaction with quality, performance or a defect after a drug product/substance has been released for distribution. It is, therefore, an excellent post-market surveillance indicator. A complaint could lead to rectifying/changing the manufacturer's systems. Complaints do not only refer to the drug product/substance, but also to its labelling and packaging.

Complaints may or may not have significant impact on the health of the patient.

Complaints help in identifying product defects and possibly quality system problems, which might have not been adequately implemented in the company.

Complaints may be received from various sources either verbally, in written form, or by electronic means, along with samples, photographs and/or other evidence depicting the defect. The source of complaints may be the patient, healthcare professionals, regulatory agencies, qualified pharmacists, trade sources, distribution chain personnel or any other source.

Complaints are classified by the person handling complaints at the company after logging to prioritize the investigation. Complaints can be classified into one of the follows:

- Critical
- Major
- Minor

Critical Complaints are those complaints about defects which impact the quality of the product and affect the patient. Examples of defects leading to critical complaints for drug products/drug substances can be listed as follows: product mix up, product not meeting regulatory specifications, contamination and microbial growth, presence of insect, mix up of printed packaging material, use of wrong printed packaging material, wrong labelling, serious adverse reactions leading to death, regulatory notices advising recall, failure to meet statutory labelling conditions, gross physical change in product (e.g., precipitation), wrong expiry date mentioned, missing dose of a critical therapeutic or life-saving drug, integrity breach, presence of metallic or glass contamination, etc.

Major Complaints are about defects that reduce the suitability of use of a dosage form for its intended purpose. Examples of complaints categorized as major complaints include oral dosage forms not meeting disintegration/dissolution norms, gross damage to packaging, serious ADE (expected), texture change, grittiness, contamination and microbial growth due to defective supply chain, etc.

Minor Complaints do not affect product quality. Such complaints relate mainly to defects that are cosmetic in nature. Some examples of such complaints are smudging of printed matter, shortage of tablets in a strip, broken tablets, missing blisters in cartons, missing leaflets or multiple copies of the same leaflet, etc.

Complaints can be further subdivided into substantiated and non-substantiated after the preliminary investigation is completed within three (03) days of logging the complaint.

Substantiated Complaints are those that are due to defects in process or systems employed by the manufacturing company. These complaints have sufficient evidence to support the suspicion of such defects.

Non-substantiated Complaints are those complaints which do not have sufficient evidence to support the suspicion of defect. These may not have occurred at all, or there is lack of evidence to prove the defect. These may occur due to improper handling of the drug product/substance. Use of the drug product in ways other than prescribed could also lead to misunderstanding by the patient resulting in such complaints.

There are other types of complaints also which could originate from therapeutic activity. They can be due to insufficient pharmacological activity, such as:

- **Lack of Effect** where the drug product is not able to effect sufficient pharmacological activity and reduce the discomfort of the patient. In many cases, such complaints could be the result of improper administration of the drug product by the patient.

- **Adverse Drug Reaction/Effect** are events leading to unexpected reactions after administering a drug product, for example, the development of rashes, nausea, etc. Such events can take place in cases where combinations of two or more drugs are administered. Adverse drug reactions may occur for drug products administered for prolonged periods of time or even after a single administration.

Apart from all the above listed complaints, sometimes complaints lead to unexpected revelations. The defects reported may also result in identifying counterfeit samples.

Counterfeit Complaints are those in which it has been proven that the defective product is a copy of the original product and does not belong to the manufacturing site printed on the label. This can be proved only when the manufacturer receives samples of defective drug products from the complainant, and on matching these against the retained samples, differences are noticed.

Regulatory agencies take complaints about drug products/substances very seriously and expect the manufacturer to respond in the shortest possible time. There are several instances where the regulatory agencies follow up with the manufacturer and trigger unannounced inspections of facilities manufacturing products that are under the scanner. Systems, procedures and personnel involved in the process of manufacturing drug products/substances are required to follow robust practices where defects can be identified before the product/substance reaches the market.

Handling complaints is one of the most important functions of the manufacturing facility. Written procedures describing the handling of all complaints received through any mode regarding a drug product must be established and followed. Such procedures could include provisions for review, by the site QA, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a decision as to the need for an investigation in accordance with 21 CFR 211.192. Such procedures may include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA in accordance with 21 CFR 310.305 and 514.80. A written record of each complaint must be maintained in a file designated for drug product complaints. The file regarding such drug product complaints can be maintained at the establishment where the drug product involved was manufactured, processed, or packed; such a file may be maintained at another facility if the written records in such files are readily available for inspection at the facility from where the drug product in question originated. Written records involving a drug product to be maintained for until at least one (01) year after the expiration date of the drug product, or for one (01) year after the date that the complaint was received, whichever is later. In the case of certain OTC drug products that do not need to provide for expiration dating because these meet the criteria for exemption under 21 CFR 211.137, such written records must be maintained for three (03) years after distribution of the drug product.

The written record may include information such as name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.

If an investigation is conducted under 21 CFR 211.192, the written record can include the findings of the investigation and follow-up. The record or copy of the record of the investigation must be maintained at the establishment where the investigation occurred in accordance with 21 CFR 211.180(c). If the investigation is not conducted under 21 CFR 211.192, the written record can include the reason that such an investigation was found not to be necessary together with the reason/s and the name of the responsible person making such a decision.

There are several instances of USFDA issuing 483's because of improper complaint handling. According to USFDA's 2016 enforcement statistics, product complaint handling system (21 CFR 211.198: Complaint Files) is the second most cited 483 with 326 EIR observations which was 3 % of overall EIR observations.

Review of past 483's from USFDA reveal lack of inadequate procedures, failure to follow established procedures and lack of documented evidence (Good Documentation and Data Integrity) as primary causes of warning letters.

(Source: https://www.fda.gov/ICECI/EnforcementActions/ucm531890.htm)

6. Handling of Complaints

This is the beginning of the investigation determining the authenticity of the complaint. This activity focuses on the detection of potentially defective drug products/substances. The QS/GMP regulation expects a set mechanism of review, evaluation and reporting once a complaint is received. Trained professionals with authority to decide the outcome are expected to handle complaints.

Handling complaints is one of the most important activities indicating willingness to resolve the dissatisfaction about the drug product/substance. Set procedures with timelines to address various stages involved in addressing complaints are expected by the regulatory agencies and are verified during their audits.

Complaints trigger investigation to confirm the product's integrity and to prove the robustness of the manufacturing activity of the company. Companies must have written procedures in place for processing complaints.

Deficiencies in complaint handling procedures lead to losing valuable data which might help in identifying defective products and quality systems.

Review mechanisms help- in identifying existing and/or potential causes of nonconforming product or other quality problems.

All competent authorities, concerned in the matter, including the complainant, must be informed in a timely manner in case the investigation leads to recall or abnormal restriction in the supply of the product if there is a confirmed quality defect like faulty manufacture, product deterioration, detection of falsification, non–compliance with marketing authorization, etc.

Stages of handling complaints are as follows

- Receipt of complaint
- Categorization of complaint
- Notification to regulatory agency
- Initiating investigation
- Receipt and handling of samples
- Risk Assessment and CAPA
- Closure of the complaint
- Trending
- Historical review

Receipt of complaint

- Site QA must receive the complaint.
- Site QA must log the complaint within one (01) working day.
- Complaint can be shared with PV if the nature includes ADR/ADE or a combination of these with product quality.
- Complaint number must be assigned by site QA. If the number of complaints is more than one (01) from the same complainant and for different products, different numbers shall be assigned for each complaint.
- Site QA must acknowledge the receipt of complaint with the complainant within three (03) working days through the company's procedure.
- Additional information, if required, with photographs and sample can be obtained from the complainant. Annexure ("Information from complainant") can be obtained from the complainant.

Categorization of the complaints

- Site QA must categorize the complaint initially as critical or non- critical based on the nature of the complaint.
- Site QA Head must confirm the categorization of the complaint.

Preliminary investigation

- Preliminary investigation can be performed for critical complaints within three (03) working days from complaint awareness date.

Regulatory notification

- Alert Notification/FAR can be filed by site QA with respective regulatory agency within three (03) working days from the complaint awareness date. The AN/FAR must include the preliminary investigation report.
- Corporate Quality Head can be notified of the AN/FAR.
- All the batches/lots/markets likely to be impacted must be mentioned in the AN/FAR.
- Follow-up reports and final AN/FAR can be filed along with the interim and final investigation reports respectively as per the commitment given in the initial AN/FAR.
- Site QA Head must also report in a timely manner to the marketing authorization holder/sponsor and all Competent Authorities concerned in the matter about the detection of counterfeit, recall of the product or an abnormal restriction in the supply of the product.

Investigation

- Complaints involving product quality can be investigated with cross-functional teams, wherever applicable, as per the investigation procedure of the company.
- If the complaint is critical in nature, preliminary investigation must be completed within three (03) working days.
- Investigation can be performed as per the investigation procedure of the company.

- Investigation can be performed by adopting suitable tools like fishbone analysis/Ishikawa, 5-Whys analysis, brainstorming, etc.
- Retention samples, complaint samples, input materials and any other samples as applicable will be subjected to investigation.
- Batch records, in- process records, analytical records, stability data as applicable and all allied records must be reviewed as part of the investigation.
- Historical review of product complaints/deviation/incident/investigations can be carried out to establish potential impact of market complaint on the concerned batch/other batches of same product/substance and/or other manufactured products.
- Historical review of complaints from the previous two years (from the date of receipt of complaint) can be performed.
- Additional experiments, if required, may be carried out with the help of relevant cross functional departments to establish the root cause of the defect as per approved study protocol.
- Investigation of batches of the drug product/drug substance manufactured using the same raw material/key starting material/packing material of the complaint batch must be performed and if it leads to a possibly faulty equipment, the equipment may be subjected for investigation. Annexures for individual dosage forms/drug substance are given as attachments.
- If preliminary investigation points to raw material(s), key starting material(s) and/or packing material(s) as likely cause of complaint, the balance stock material of the respective QC reference number used in the complaint batch can be quarantined till the completion of investigation. Quarantine may be effective until clearance to use given by Site QA.
- Investigation can be extended to all batches of the same or other drug product/substance manufactured during the period in which the complaint batch was manufactured and impact assessment must be performed irrespective of whether the other batches were distributed or not.
- Health Hazard Evaluation can be performed for the complaints covering the following, wherever applicable, but not limited to, product/strength mix-up, drug not available to the patient due to dissolution failure, degradation of product, etc.
- Alert Notification/FAR can be communicated to the Regulatory Agencies within three (03) working days of detecting the defect irrespective of the stage of investigation.
- All customers must be notified about the defect within three (03) working days in case of drug substance.
- The complaint/s due to counterfeiting can be assessed and if the sample is found to be counterfeit in nature, Marketing, QA/RA, and Regulatory Agencies in countries where the product is distributed must be informed for appropriate action.
- Risk assessment can be carried out taking into account system failure during investigation. It could be performed as per QRM procedure.
- Risk Assessment for market complaints can be based on severity and occurrence.
- The evaluation of risk to the quality of the drug product/substance can be assessed based on scientific knowledge and ultimately linking it to the patient's safety.
- Immediate actions may be taken to rectify the problem wherever applicable.

- Appropriate CAPAs can be initiated based on the findings of the investigation and risk assessment.
- Site QA must implement the CAPA and monitor its effectiveness.
- Site Quality Assurance can assess whether the complaint is substantiated or non-substantiated and its impact on the marketed product.
- Substantiated complaints can be categorised as Critical/Major/Minor based on the investigation findings by site Quality Assurance Head/Designate.
- Investigation must be completed in thirty (30) calendar days from complaint awareness date.
- If investigation is incomplete within thirty (30) calendar days, an interim report must be prepared within the original due date and extension can be taken with justification.
- After completion of investigation, final investigation report must be prepared and shared with complainant.
- Site Quality Assurance can initiate product recall, if applicable, based on the decision of recall committee as per recall procedure.
- Site Quality Assurance Head must notify Corporate Quality Head, all stake holders and management about the recall.

Receipt and handling of samples

- Complaint samples must be photographed for depicting the nature of the complaint and labelled as "Complaint Sample" by site QA. The photographs must be attached along with the market complaint documents for future reference.
- Three attempts can be made by site QA to collect the complaint sample and additional information for investigation if not received.
- Investigation must be initiated based on available information. If the complaint sample is not available or submitted post follow-up within the timeline, the complaint can be closed. However, if the complaint sample is received after closure of the complaint, the same must be re-opened. The procedure of investigation and sharing information with stakeholders can be as per the procedure mentioned earlier.
- All complaints received must be stored as per the prescribed conditions in designated area till closure of market complaints. Complaint samples may be retained for training purpose.
- Site Quality Assurance Head/Designate can ensure the destruction of complaint sample after closure of the complaint.

Closure of complaint

- Complaint must be closed by site QA in sixty (60) calendar days from complaint awareness date which includes the time period of thirty (30) calendar days for investigation.
- In case where the investigation is extended beyond thirty (30) calendar days, the complaint can be closed after thirty (30) calendar days from the date of completion of investigation.
- Site QA must ensure the initiation of action items for CAPA before the closure of the complaint.
- Site QA can maintain the complaint records along with investigation records.

Trending of complaints

- Trend analysis must be performed by Site Quality Assurance as per following steps:
  - Identification of trending need
  - Trending frequency
  - Data collection and presentation
  - Data verification
  - Data Analysis
  - Data evaluation and interpretation
- Trend analysis for product complaints must be based on product, dosage form, market, nature of complaint, categorization of complaint (initial and final category), substantiated/non-substantiated complaint, status of complaint (open/close), root cause, etc.
- Trend analysis for ADE complaints must be based on product, dosage form, market and category (seriousness and expectedness criteria).
- Frequency for trend analysis can be quarterly and annual.
- Trend analysis can be completed within one month of completion of quarter/year. Rolling data must be considered for trending.
- Trending data can be collected as per applicable QMS.
- Collected data must be compiled and presented by site Quality Assurance.
- Data can be verified by cross functional team.
- The collected data must be analyzed by statistical/logical methods using appropriate tools like pie charts, bar charts, Pareto analysis, etc.
- Trending can identify KPIs which help in reduction or elimination of specific and repetitive defects.
- Trending can identify areas of improvement where there is any recurrence of problems. Appropriate CAPAs can be initiated accordingly. Impact of trend analysis must be considered for impact assessment on other products/batches.
- Summary report for trend analysis can be prepared by site QA and reviewed by the cross-functional teams and approved by site Quality Assurance Head.

Management Reviews

Site Quality Assurance must communicate the summary of market complaint information to management for review. Frequency of communication can be as per company policy.

Record Keeping

Market Complaint Record must be maintained for a period of ten (10) calendar years for manual records; for electronic records, the normal retention period adopted by the company can be followed.

Quality Metrics Data

FDA Safety and Innovation Act (FDASIA),2012, authorized collection of manufacturing quality data from pharmaceutical companies and also obtaining certain records from drug manufacturers in lieu

of, or in advance of, an inspection. FDA is considering utilization of quality metrics as an input to its inspection models as well as to predict possible drug shortages, to determine inspection schedules for a manufacturer, to assess post market change reporting, and to restructure the format of inspection.

Some off the metrics on which FDA can be considered:

Product Quality Complaint Rate (PQCR): These are complaints involving any possible, including actual, failure of a drug to meet any of its specifications designed to ensure that any drug conforms to appropriate standards of identity strength, quality, and purity.

This does not include lack of effect. This can be calculated as follows:

Product Quality Complaint Rate (PQCR) = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.

As per ISPE Quality metrics initiative, quality metrics pilot program wave 2, the following calculations can help in analysis.

1. **Total Complaint Rate per million packs excluding lack of effect =**

   Total complaints excluding Divided by Total number of packs Divided by 106 for a site

2. **Critical Complaint Rate per million packs =**

   Number of critical complaints (based on final investigation classification) Divided by Total number of packs produced per site Divided by 10^6

Explanation

Substantiated and Confirmed Complaints

Consider those complaints for which final categorization are assigned. Consider only confirmed & substantiated complaints.

Total No. of complaints

All complaints received on the site irrespective of their categorization.

Above two does not include ADE.

Total No. of FG lots approved

Total No. of Finished Goods for which QA has taken the decision to release the lots.

Total number of FG + Salable Intermediate lots Dispatched

Total number of Finished API and Saleable Intermediate dispatched to customer by manufacturer.

7. Abbreviations

- **ADE**—**A**dverse **D**rug **E**ffect
- **ADR**—**A**dverse **D**rug **R**eaction
- **AN**—**A**lert **N**otification
- **API**—**A**ctive **P**harmaceutical **I**ngredient
- **BMR**—**B**atch **M**anufacturing **R**ecord
- **BPR**—**B**atch **P**roduction **R**ecord
- **CAPA**—**C**orrective **A**ction **P**reventive **A**ction
- **CEO**—**C**hief **E**xecutive **O**fficer
- **CFR**—**C**ode of **F**ederal **R**egulations
- **CMO**—**C**ontract **M**anufacturing **O**rganization
- **DP**—**D**rug **P**roduct
- **DS**—**D**rug **S**ubstance
- **EIR**—**E**stablishment **I**nspection **R**ecord
- **FAR**—**F**ield **A**lert **R**eport
- **GMP**—**G**ood **M**anufacturing **P**ractices
- **HHE**—**H**ealth and **H**azard **E**valuation
- **IPA**—**I**ndian **P**harmaceutical **A**ssociation
- **KPI**—**K**ey **P**erformance **I**ndicators
- **LOE**—**L**oss **o**f **E**ffect
- **OOS**—**O**ut **o**f **S**pecification
- **OSD**—**O**ral **S**olid **D**osage
- **OTC**—**O**ver **t**he **C**ounter
- **PV**—**P**harmacovigilance
- **QA**—**Q**uality **A**ssurance
- **QF**—**Q**uality **F**orum
- **QRM**—**Q**uality **R**isk **M**anagement
- **QS**—**Q**uality **S**ystems
- **UKMHRA**—**U**nited **K**ingdom **M**inistry of **H**ealth and **R**egulatory **A**ffairs
- **US FDA**—**U**nited **S**tates **F**ood and **D**rug **A**dministration
- **WHO**—**W**orld **H**ealth **O**rganization

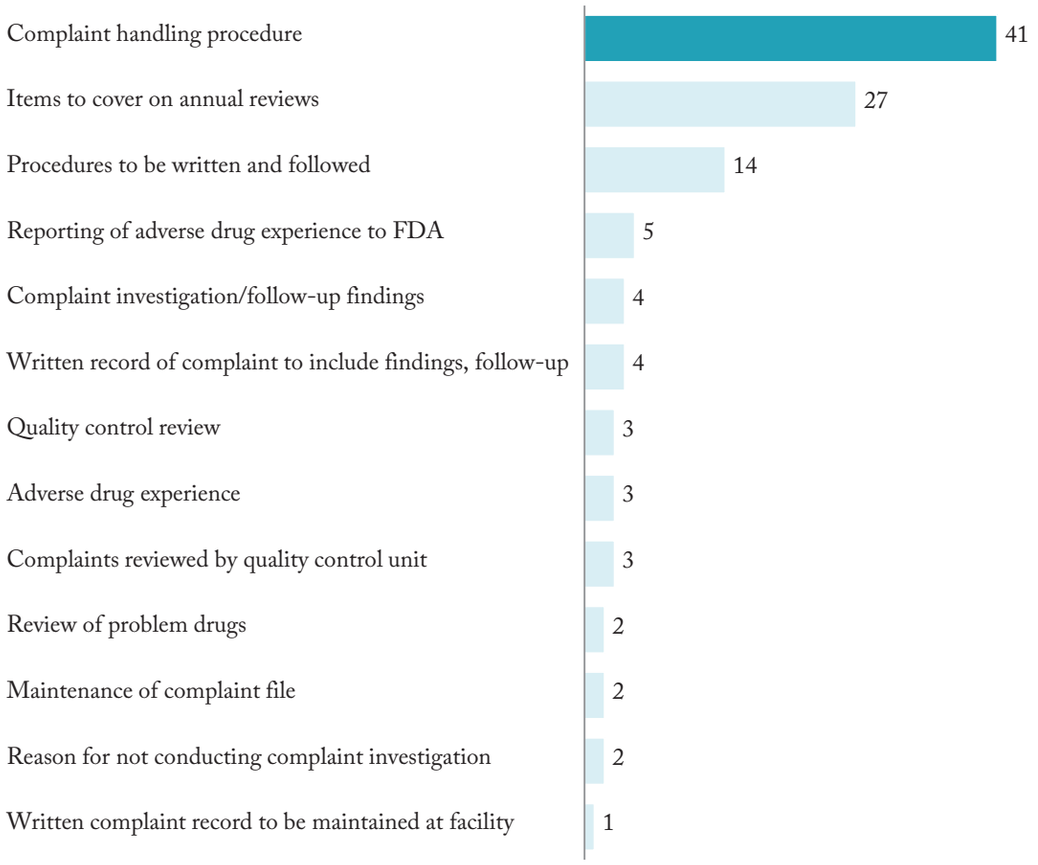
(This page is intentionally left blank)

ANNEXURES

Annexure 1: Trending of market complaints

Frequency of citation of market complaint (YYYY)

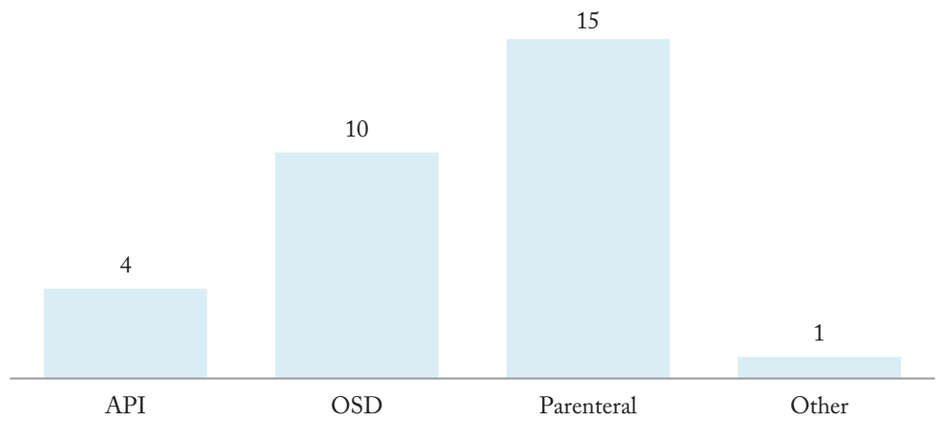
ILLUSTRATIVE



Market complaints related to dosage forms (YYYY)

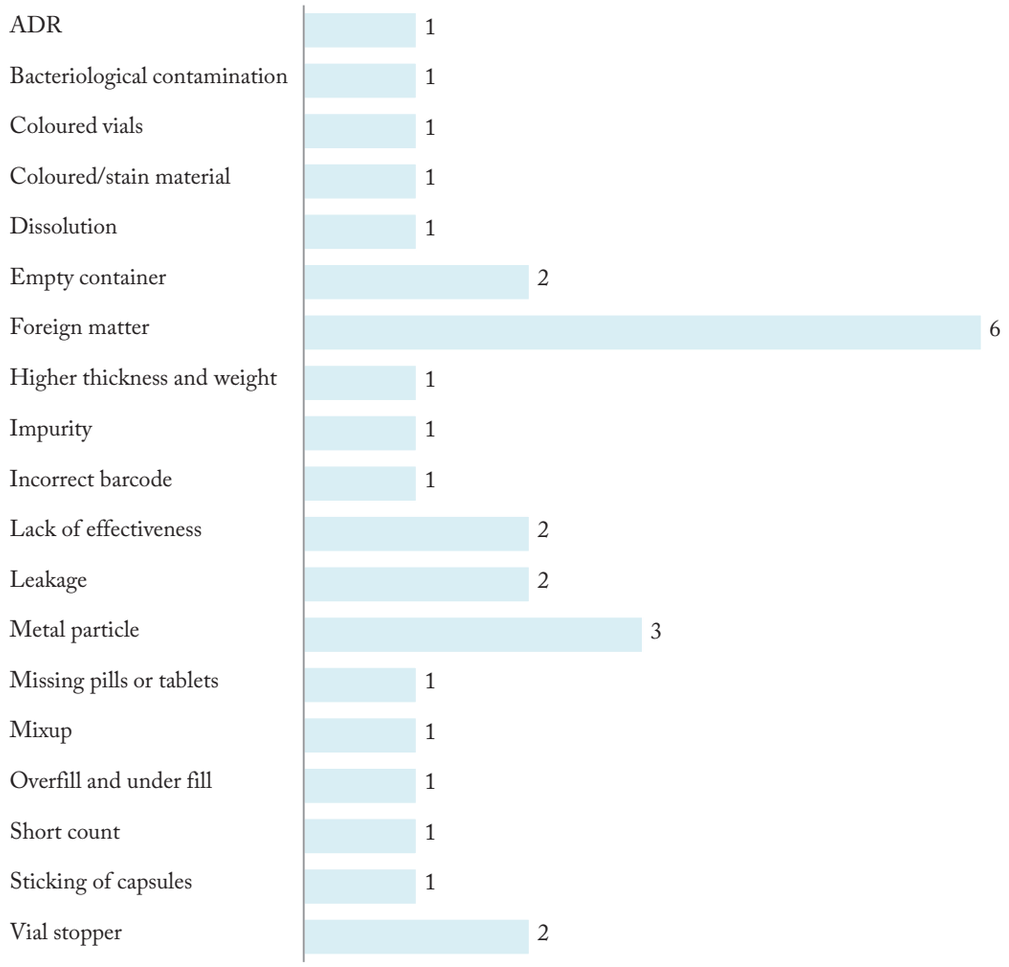
ILLUSTRATIVE

Number of complaints



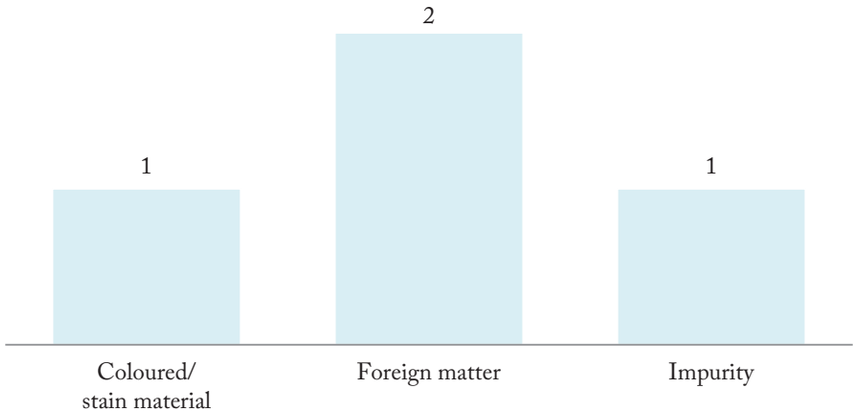
Market complaints related to nature (YYYY)
Number of complaints

ILLUSTRATIVE



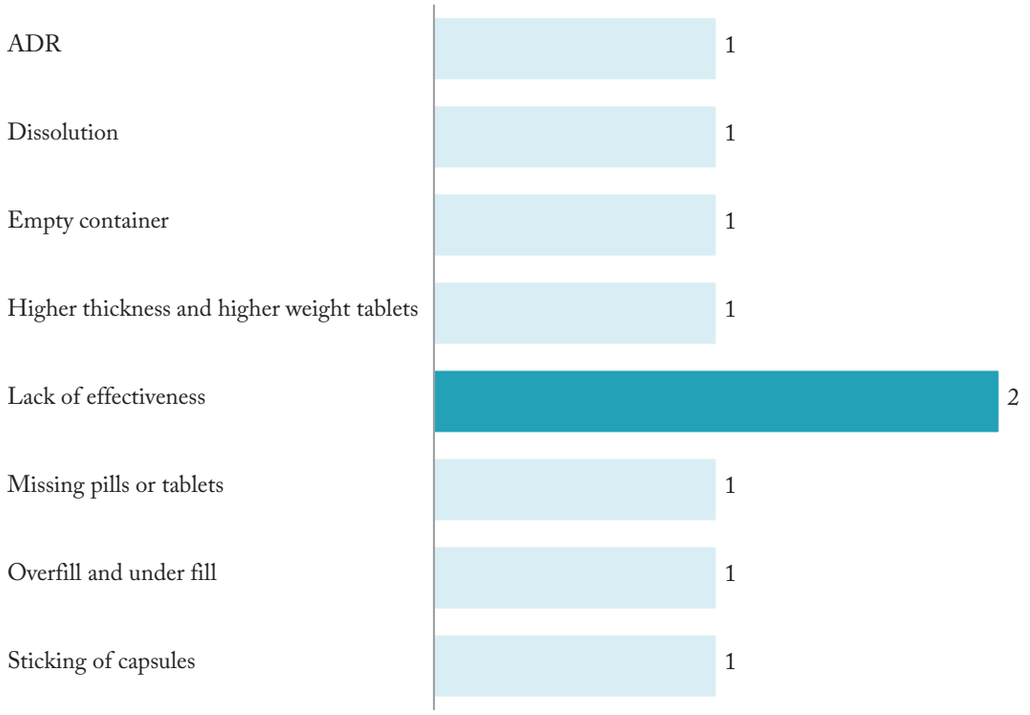
Market complaints related to API (YYYY)
Number of complaints

ILLUSTRATIVE



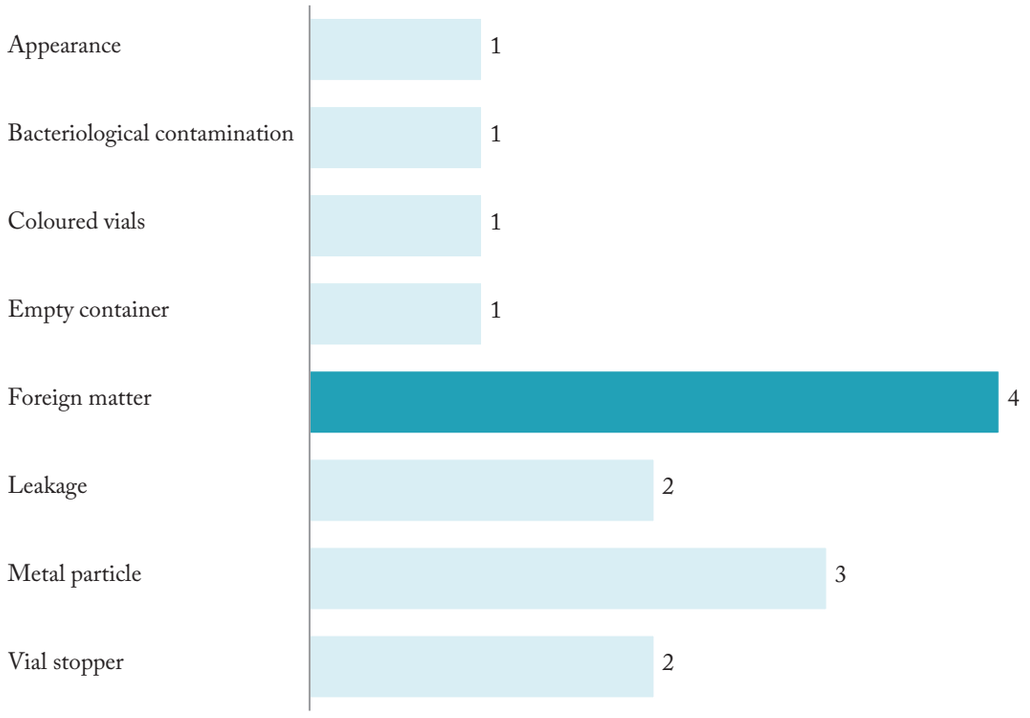
Market complaints related to OSD manufacturing
Number of complaints

ILLUSTRATIVE



Market complaints related to parenteral manufacturing
Number of complaints

ILLUSTRATIVE



Annexure 2: Risk assessment

Context

- The criteria for initial and final classification of complaints into critical, non-critical, major and minor categories are, to some extent, subjective, and may vary across different pharma companies.
- The decision to raise FAR and/or initiate product recall is evaluated on a case-by-case basis given the lack of a standard industry approach towards categorizing complaints for which FAR needs to be initiated.
- There were many cases where failing to initiate FAR/recall le-d to regulatory observations.

Introduction

- Risk assessment is an approach to standardize the process of complaint classification (into critical/major/minor categories) which helps to arrive at a logical conclusion on the need to raise FAR or initiate product recall.
- It is based on the concept of assessing important aspects of 'substantiated market complaints' – severity of the complaint, frequency of occurrence and detectability of defect - in order to bucket the complaint into a pre-defined category and subsequently evaluate the need for raising FAR/product recall.

Pre-requisites

- Checklists, prepared as per dosage forms, mapping the usual kind of defects/complaints most commonly observed in a particular dosage form and the severity of implication of the respective defect (bucketed into critical/major/minor).
- Database of previous 'substantiated' market complaints classified by date of receipt of complaint, product, dosage form and action taken to address the complaint.

Definitions

- **Risk Assessment:** A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
- **Risk Analysis:** Estimation of the risk associated with the identified hazards.
- **Risk Evaluation:** Comparison of the estimated risk against given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.
- **Severity:** A measure of the possible consequences of a hazard.
- **Occurrence:** Identification of repetitive nature of the hazard.
- **Detectability:** The ability to discover or determine the existence, presence, or occurrence of a hazard.

Methodology

- At the time of receipt of complaint, all the required information including source, description of defect observed, etc. is captured in the query template (Annexure no. 3).
- This information forms the basis of initial classification of complaint into critical and non-critical categories on the basis of information available at hand and the implication of observed defect on patient safety and product efficacy.
- Initial classification as Critical and Non-Critical can be performed on qualitative basis considering the severity of complaint and its occurrence as per table I.
- Occurrence of complaint must be captured for particular batch in terms of dosage unit.
- Occurrence of a complaint received without batch number must also be captured in terms of dosage unit.
- Severity and occurrence can be assessed as per the description given in the subsequent respective part of scoring methodology in Table II and Table III.
- On completion of initial classification, all the critical complaints must be evaluated whether there is a need to raise FAR or not.
- For other non-critical complaints, decision regarding of FAR can be taken based on repeatability of defect.

Table I: Initial Category of complaint based on Severity and Occurrence

		Severity		
		Critical	**Moderate**	**Low**
Occurrence	Almost certain/High	Critical	Critical	Non-Critical
	Moderate	Critical	Non-Critical	Non-Critical
	Rare/Unlikely	Critical	Non-Critical	Non-Critical

- Final categorization of complaint can be based on Quantitative Risk Assessment.
- Decision for recall can be based on final categorization of complaints after investigation.
- Risk assessment for final categorization of complaint can be performed based on a scoring methodology for severity, occurrence and detectability of defect in the product. Scoring for severity, likelihood of occurrence and detectability can be done on scale of 1 to 3.
- The scoring methodology for risk assessment is described as below:

Severity: Each complaint can be assessed for its extent of impact on, quality, efficacy and patient safety and thereby its severity rank. Quality impact assessment (outcome of investigation), scientific knowledge and Health Hazard evaluation (HHE) can be performed to determine severity. Scoring methodology is as below:

Table II: Severity

Qualitative parameter	Description	Quantitative parameter
Critical	Critical impact on product quality, safety and efficacy	3
Moderate	Medium impact on product quality, safety and efficacy	2
Low	Minor/no impact on product quality, safety and efficacy	1

Likelihood of Occurrence: Retrospective review of market complaints must be conducted for identification of repetitive nature. Depending on the frequency of recurrences, likelihood of occurrence is ranked.

Table III: Likelihood of Occurrence

Qualitative parameter	Description	Quantitative parameter
Almost certain/High	1 defect in 100 dosage units	3
Moderate	1defect in 10000 dosage units	2
Rare/Unlikely	1defect in 1000000 dosage units	1

- For the products/complaints where less data is available, occurrence could be considered as 'moderate' level in order to assign a quantitative parameter.

Detectability: Depending on the level of detection strength, its detection risk can be ranked. Here detection risk rank is inversely proportional to the level of detection strength. Criteria to be used for "Detectability of risk" ranking are tabulated below.

Table IV: Detectability

Qualitative parameter	Description	Quantitative parameter
Low	The defect is not detectable	3
Moderate	Defect can be detected but the assurance of detection is not 100%	2
High	100% detectable and sufficient measures are available to control	1

Risk Evaluation: For each complaint, based on the score for severity, detectability and likelihood of occurrence, the Risk Priority Number (RPN) must be derived as a product of these three factors. (i.e., RPN = SxLxD).

- Based on the Risk Priority Number (RPN) obtained, decision for recall can be considered. This is detailed in the table below:

Tablet V: Final Categorization

Complaint	Risk analysis			Risk evaluation
	Severity (S)	Likelihood of Occurrence (L)	Detectability (D)	Total score/ RPN (SxLxD)

- If any individual parameter (severity, likelihood of occurrence and detectability) is ≥ 3, it could be a potential case for recall and can be so evaluated.
- If any substantiated complaint has RPN ≥ 6, the complaint qualifies for a re-call decision.

Benefits

- This is a standardized approach which helps to minimize the element of subjectivity while classifying complaints and assessing the need to initiate recall.
- Trend analysis of complaints evaluated using the risk assessment approach can also help to identify potential process improvements that could offer a long-term solution to a repetitive market complaint.

Annexure 3: Query template

(for collecting information from complainant)

Date of receipt	
Mode of complaint receipt	Mail/Courier/Fax/Telephonic/Other (Specify:_____)
Market	
Complainant information	
Greeting/salutation	
Name of complainant	
Occupation/relation to the patient	
Company	
Address	
Telephone	
Email	
Complaint related to	Packaging/Quality/ADE/Other (Specify:_____)
Response Letter requested by Complainant	Yes/No/NA
Did the complainant request monetary reimbursement?	Yes/No
Any additional information	
Product information	
Brand name	
Generic name	
Dosage form	Tablet/Capsule/Dry Powder Injection/Dry Powder Suspension/Drops/ Inhaler/Cream/Spray/Liquid Injection, Other (Specify:_____)
Controlled substances product	Yes/No
Strength	
Pack type	
Batch No	
Expiry Date	
Manufacturing site	
NDC Number	
Storage condition	

Complaint sample availability	Yes/No
Product bought from (Address of Pharmacy)	
Complaint description	
Patient information	
Patient Name	
Age	
Address	
Therapy/treatment details	
Date of prescription	
Date of dispensing	
Type of dispensing	
Self-administering	Yes/No
Storage condition followed	Yes/No
Total Daily Dose	
Any alternative therapies/treatment	
Other information	

Annexure 4: Dosage form wise investigation checklists

Manufacturing related complaints – OSD

Type of complaint	Bitter taste of tablet	Smell defect of product	Broken capsule	Black spots on tablet	Coating peel off	Product not dissolving	Difficult to swallow	Lack of effect
Severity	Low	Medium	Medium	Medium	Medium	High	Low	Medium
Training	✓	✓	✓	✓	✓	✓	✓	✓
Change to procedure	✓	✓	✓	✓	✓	✓	✓	✓
Incident	✓	✓	✓	✓	✓	✓	✓	✓
Annual Product Quality Review	✓	✓	✓	✓	✓	✓	✓	✓
Operating instructions				✓	✓			
Equipment log book	✓			✓				
Qualification	✓	✓	✓	✓	✓		✓	✓
Complaint log	✓	✓	✓	✓	✓	✓		
Calibration/PMP			✓	✓	✓			
Procurement of raw material	✓	✓	✓	✓	✓	✓		✓
In-process checks	✓	✓	✓	✓	✓	✓	✓	✓
Wear and tear of change parts					✓			
Method/Process	✓	✓	✓	✓	✓	✓	✓	✓
Stability Data	✓	✓	✓	✓	✓	✓	✓	✓
Check weigher			✓					
Analysis of complaint/ Reserve sample				✓	✓	✓		✓
Physical Inspection of complaint/ Reserve Sample	✓	✓	✓	✓	✓	✓	✓	
Analytical results of RM/PM/FP	✓	✓	✓	✓	✓	✓		✓
BPR	✓	✓	✓	✓	✓			✓
BMR	✓	✓	✓	✓	✓	✓	✓	✓

Training	✓	✓	✓	✓	✓	✓	✓	✓
Change to procedure	✓	✓	✓	✓	✓	✓	✓	✓
Incident	✓	✓	✓	✓	✓	✓	✓	✓
Annual Product Quality Review								
Operating instructions	✓	✓	✓	✓			✓	✓
Equipment log book						✓		✓
Qualification	✓	✓	✓	✓	✓	✓	✓	✓
Shape and dimensions of rejection pusher			✓					✓
Complaint log	✓	✓	✓	✓	✓	✓	✓	✓
Rejections handling				✓	✓		✓	✓
Calibration/PMP	✓	✓	✓	✓	✓		✓	✓
Challenging of sensors Counting sensors/burnt seal sensor/OCR/No label sensor/metal detector	✓		✓			✓	✓	✓
In-process checks	✓	✓	✓	✓	✓	✓	✓	✓
Angle of dropping of blister				✓	✓			
Physical condition of change parts	✓	✓			✓	✓		
Method/Process	✓	✓	✓	✓	✓	✓	✓	✓
Stability Data								
Analysis of complaint/Reserve sample			✓			✓		
Check weigher	✓			✓			✓	
Physical Inspection of Complaint/ Reserve Sample	✓	✓	✓	✓	✓	✓	✓	✓
Analytical results of RM/PM/FP		✓	✓		✓	✓		
BPR	✓	✓	✓	✓	✓	✓	✓	✓
BMR						✓		
Severity	Low	Medium	Medium	Low	Low	Medium	Low	Medium
Type of complaint	Less count	Broken desiccant	Burnt seal	Empty blister	Damaged blister	Foreign matter	Missing blister	Missing coding

Training	✓	✓	✓	✓	✓	✓
Change to procedure	✓	✓	✓	✓	✓	✓
Incident	✓	✓	✓	✓	✓	✓
Annual Product Quality Review				✓	✓	
Operating instructions	✓	✓				✓
Equipment log book	✓		✓			
Qualification	✓	✓	✓	✓	✓	✓
Shape and dimensions of rejection pusher	✓			✓		
Complaint log	✓	✓	✓	✓	✓	✓
Rejections handling	✓					✓
Calibration/PMP	✓	✓	✓	✓	✓	✓
Challenging of sensors Counting sensors/burnt seal sensor/OCR/No label sensor/metal detector	✓					
In-process checks	✓	✓	✓	✓	✓	✓
Angle of dropping of blister						
Physical condition of change parts		✓				
Method/Process	✓	✓	✓	✓	✓	✓
Stability Data				✓	✓	
Analysis of complaint/Reserve sample						
Check weigher		✓	✓	✓		
Physical Inspection of Complaint/Reserve Sample	✓	✓	✓	✓	✓	✓
Analytical results of RM/PM/FP				✓	✓	✓
BPR	✓	✓	✓	✓	✓	✓
BMR			✓	✓	✓	
Severity	High	Medium	Low	Low	Medium	Low
Type of complaint	Missing label	Empty bottle	Commingling	Broken tablet	Crumbling of tablets	Improper sealing of blister

Market complaints – Dermal

Dosage Form	Type of complaints	Severity	History/repeatability of complaint	Duration of treatment	Dispensing date to patient	Date of reporting of complaint to pharmacy	Age of patient/if the patient self-administering the drug	Complaint sample available or not	Photograph of complaint sample available	Physical evaluation of complaint sample	Chemical/Microbial evaluation of complaint sample	Physical evaluation of control sample	Chemical/Microbial evaluation of control sample	Simulation study	Appearance of carton	Extrusion	BMR review	BPR review	Challenge test	AQL checks	Check weighing operation review	In-process tests review	Reconciliation of rejections for less weight bottles
Dermal Patches	Foreign matter	Low	✓	✓	✓	✓		✓	✓	✓		✓					✓	✓	✓	✓		✓	
	Improper size/ Incomplete patch	Medium	✓	✓		✓		✓	✓	✓		✓					✓	✓	✓	✓		✓	
	Poor adhesion	Medium	✓	✓	✓	✓	✓	✓		✓		✓		✓			✓	✓		✓		✓	
	Crystallization/ Liquefaction	Medium	✓	✓	✓	✓		✓	✓	✓		✓					✓	✓				✓	
	Separation of liner	Low	✓	✓	✓	✓		✓	✓	✓		✓		✓			✓	✓		✓		✓	
	Colour change	Low	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓				✓				✓	
Ointments, Creams, Gels, Lotions	Phase separation	Medium	✓	✓	✓	✓		✓		✓		✓		✓				✓	✓				
	Grittiness	Medium	✓	✓	✓	✓		✓		✓	✓	✓	✓					✓	✓				
	Colour change	Medium	✓	✓	✓	✓		✓		✓	✓	✓	✓					✓	✓				
	Odour issue	Medium	✓	✓	✓	✓		✓		✓	✓	✓	✓					✓					
	Texture Change/ Solidification/ Lump Formation/ Consistency Issue/ Agglomeration	Medium	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓		✓		✓				✓	
	Floating.	Low	✓	✓	✓	✓		✓		✓	✓	✓	✓					✓	✓			✓	
	Sedimentation	Low	✓	✓	✓	✓		✓		✓	✓	✓	✓					✓	✓			✓	

Dosage Form	Type of complaints	Severity	History/repeatability of complaint	Duration of treatment	Dispensing date to patient	Date of reporting of complaint to pharmacy	Age of patient/if the patient self-administering the drug	Complaint sample available or not	Photograph of complaint sample available	Physical evaluation of complaint sample	Chemical/Microbial evaluation of complaint sample	Physical evaluation of control sample	Chemical/Microbial evaluation of control sample	Simulation study	Appearance of carton	Extrusion	BMR review	BPR review	Challenge test	AQL checks	Check weighing operation review	In-process tests review	Reconciliation of rejections for less weight bottles
Tinctures, Solutions	Particles in solution	Medium	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓				✓	✓		✓		✓	
	Crystallization	Medium	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓				✓	✓		✓		✓	
General	Leakage/Open tube	Low	✓	✓	✓	✓		✓	✓	✓		✓			✓			✓		✓	✓	✓	✓
	Empty tube/Bottle	High	✓	✓	✓	✓		✓	✓	✓		✓						✓	✓	✓	✓	✓	✓
	Dented tube	Low	✓	✓	✓	✓		✓	✓	✓		✓			✓			✓		✓		✓	
	Layer separation of tube/Liner separation	Low	✓	✓	✓	✓		✓	✓	✓		✓						✓	✓	✓		✓	
Dry Powders	Grittiness/Lump formation	Medium	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓				✓	✓				✓	

Checklist for market complaints

Type of complaints/ Investigation checklist	Defective device/Non-operative device	Device Leakage/ Integrity breach	Device Auto-activation	Low/High volume	Damaged needle	Without needle/ wrong size needle	Plunger not in position	Foreign particles	Turbidity/Precipitation, sedimentation/ Discoloration	Mix up
Severity	**Low**	**High**	**Low**	**Low**	**High**	**Low**	**Low**	**High**	**High**	**High**
Trend of similar complaint reported for the batch	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Trend of similar complaint reported for the product	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Past history of supplier	✓	✓	✓		✓		✓	✓	✓	✓
Patient history, if available	✓	✓	✓							
PFS dispensing date to patient (for information only)	✓	✓	✓						✓	✓
Date pharmacy was informed of the issue by the complainant (for information only)	✓	✓	✓					✓	✓	✓
Date the issue was communicated to company by pharmacy (for information only)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Age of patient, if the patient is self-administering the drug	✓	✓	✓				✓			
Has the patient followed the instruction guide?	✓	✓	✓				✓		✓	
Is complainant (patient, nurse, doctor) a frequent user of the device or a first-time user?	✓	✓	✓				✓	✓	✓	✓
Complaint sample photograph availability	✓	✓	✓	✓			✓	✓	✓	✓
Complaint sample availability	✓	✓	✓	✓			✓	✓	✓	✓
Authenticity of the sample	✓	✓	✓	✓			✓	✓	✓	✓

Type of complaints/ Investigation checklist	Defective device/Non-operative device	Device Leakage/ Integrity breach	Device Auto-activation	Low/High volume	Damaged needle	Without needle/ wrong size needle	Plunger not in position	Foreign particles	Turbidity/Precipitation, sedimentation/ Discoloration	Mix up
Severity	**Low**	**High**	**Low**	**Low**	**High**	**Low**	**Low**	**High**	**High**	**High**
Retain sample evaluation (If complaint sample is not available)	✓	-	✓	✓	✓	✓	✓	✓	✓	✓
Single-use device or multiple-use device?	✓	✓	✓							
Simulation performed with complaint device	✓	-	✓							
Any unplanned event reported?	✓	✓	✓							
Batch document review	✓	✓	✓							
Vial/PFS design/Dimensions	-	✓	✓							
Filling operation review	-	✓	-							
In-process tests review, i.e., leak test	-	✓	-							
In-process tests review, i.e., visual inspection test	-	-	-							
In-process tests review, i.e., device functionality parameters	✓	-	✓							
Challenge test	-	✓	-							
AQL checks	-	✓	-							

Market complaints – OSD

Type of complaint	Severity for FAR	Occurence for FAR	BMR	BPR	Analytical results of RM/ PM/FP	Physical sample of complaint/ Reserve sample	Analysis of complaint/ Reserve sample	Check weigher	Stability Data	Method/Process	Wear and tear of change parts	In-process checks	Procurement of raw material	Calibration/PMP	Complaint log	Qualification	Equipment log book	Operating instructions	Annual Product Quality Review	Incident	Change to procedure	Training
Bitter/Bad taste of tablet	Low		✓	✓	✓	✓			✓	✓		✓	✓		✓	✓	✓		✓	✓	✓	✓
Smell defect of product	Low		✓	✓	✓	✓			✓	✓		✓	✓		✓	✓			✓	✓	✓	✓
Broken tablet/ capsule	Low	More complaint from a single batch or lot/ product, without historical data	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓			✓	✓	✓	✓
Black spots on tablet	Low		✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Metallic particle/ Shiny/Insect	High		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mould-like observation/ Microbial growth	High		✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Coating peel off – functional	Medium		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Coating peel off – non-functional	Low			✓		✓			✓	✓		✓	✓	✓	✓	✓	✓	✓			✓	✓

Type of complaint	Severity for FAR	Occurrence for FAR	BMR	BPR	Analytical results of RM/ PM/FP	Physical sample of complaint/ Reserve sample	Analysis of complaint/ Reserve sample	Check weigher	Stability Data	Method/Process	Wear and tear of change parts	In-process checks	Procurement of raw material	Calibration/PMP	Complaint log	Qualification	Equipment log book	Operating instructions	Annual Product Quality Review	Incident	Change to procedure	Training
Product not dissolving	High		✓		✓	✓	✓		✓	✓		✓	✓		✓				✓	✓	✓	✓
Difficult to swallow	Low		✓			✓			✓	✓		✓				✓			✓	✓	✓	✓
Lack of effect	Low	Historical data	✓	✓	✓		✓		✓	✓		✓	✓			✓			✓	✓	✓	✓
Mix up of different stages for a single product	High																					

Market complaints – Opthalmic

Type of complaints	Less drops/Empty bottle	Very hard/difficult to get the drop	Multiple drops	Drying/Precipitation of the ophthalmic solution	Black/Foreign particle in the bottle	Seal attached to the collar on the neck of bottle was open	Over-printing missing on label
Analysis of the complaint sample upon receipt				✓	✓		
Reconciliation of rejections for less weight bottles	✓			✓	✓		
In-process tests review, i.e., visual inspection test	✓		✓		✓	✓	
In-process tests review, i.e., leak test	✓		✓	✓			
Check weighing operation review	✓						
Filling operation review	✓		✓	✓	✓		
Nozzle design/dimensions	✓	✓	✓	✓	✓		
Mechanism of getting a drop out of bottle	✓	✓	✓				
Review of retention samples	✓	✓	✓	✓	✓	✓	
AQL checks	✓		✓		✓	✓	
Challenge test	✓		✓		✓		
BPR review	✓	✓	✓	✓	✓	✓	✓
BMR review				✓	✓		
If gap is observed between screwed cap and the bottle	✓						
Marks on the bottle	✓	✓	✓		✓		
label print condition/Smudging of over printed text	✓						
Appearance of carton	✓						
Simulation performed with complaint bottle			✓		✓		
Evaluation of complaint sample/nozzle upon receipt	✓	✓	✓		✓		
Photograph of complaint sample available or not	✓	✓	✓	✓	✓	✓	✓
Complaint sample available or not	✓	✓	✓	✓	✓	✓	✓
Age of patient/If the patient self-administering the drug	✓		✓	✓	✓		
Date of reporting of complaint to pharmacy	✓	✓	✓	✓	✓	✓	✓
Dispensing date to patient	✓	✓	✓	✓	✓	✓	✓
Duration of treatment	✓	✓	✓	✓	✓	✓	
History/Repeatability of complaint	✓	✓	✓	✓	✓	✓	✓
Severity	Low	Low	Low	High	High	Low	

Type of complaints	Bottle not found in carton	Mix-ups	Dispensing actuator not available in carton	Dispenser not fitting in container
Severity	Low	High	Low	Low
History/Repeatability of complaint	✓	✓	✓	✓
Duration of treatment		✓		
Dispensing date to patient	✓	✓		
Date of reporting of complaint to pharmacy	✓	✓		
Age of patient/If the patient self-administering the drug				
Complaint sample available or not	✓	✓		✓
Photograph of complaint sample available or not		✓		✓
Evaluation of complaint sample/nozzle upon receipt				✓
Simulation performed with complaint bottle				✓
Appearance of carton	✓	✓	✓	
label print condition/Smudging of over printed text		✓		
Marks on the bottle				
If gap is observed between screwed cap and the bottle				
BMR review				
BPR review	✓	✓	✓	✓
Challenge test	✓	✓		
AQL checks	✓	✓		
Review of retention samples	✓		✓	✓
Mechanism of getting a drop out of bottle				
Nozzle design/dimensions				
Filling operation review				
Check weighing operation review	✓	✓		
In-process tests review, i.e., leak test				
In-process tests review, i.e., visual inspection test				
Reconciliation of rejections for less weight bottles	✓	✓		
Analysis of the complaint sample upon receipt				

Market complaints – MDI

Type of Complaint	Severity	Investigation Criteria															
		BMR	BPR	Analytical record	Physical Inspection of Complaint/Reserve sample	Analysis of complaint/ Reserve sample	Stability data	Method/Process	In-process control	Calibration/PPM	Qualification/Validation	Training	Transportation	Annual product quality review	OOT	OOS	Deviation	Warehouse
Incorrect fill volume	Low	✓	✓	✓	✓			✓	✓			✓	✓	✓	✓	✓	✓	
Broken product	Low	✓	✓	✓	✓		✓	✓	✓			✓	✓	✓	✓	✓	✓	
Leakage	Low	✓	✓		✓		✓	✓	✓			✓	✓	✓			✓	
Missing/Incorrect batch details	High		✓		✓			✓	✓			✓		✓			✓	
Missing component of pack, e.g., enclosure	Low	✓	✓		✓			✓	✓	✓	✓	✓		✓			✓	
Foreign matter	High	✓	✓	✓	✓			✓	✓					✓	✓	✓	✓	
Physical appearance/ cosmetic	Low	✓	✓	✓	✓		✓	✓	✓					✓	✓	✓	✓	
Analytical parameter	High	✓	✓	✓	✓	✓	✓	✓			✓	✓		✓	✓	✓	✓	
Damaged consignment	Low		✓		✓								✓	✓			✓	✓
Defective product Pack	Low	✓	✓		✓			✓	✓					✓			✓	
Adverse drug event	High	✓	✓	✓			✓							✓	✓	✓	✓	

Packing related problems

Type of complaint	Severity	BMR	BPR	Analytical results of RM/ PM/FP	Physical Inspection of Complaint/Reserve Sample	Check weigher	Analysis of complaint/ Reserve sample	Stability Data	Method/Process	Physical condition of Change parts	Angle of dropping of blister	In process checks	Challenging of sensors Counting sensors/ burnt seal sensor/OCR/No label sensor/metal detector	Calibration/PMP	Rejections handling	Complaint log	Shape and dimensions of rejection pusher	Qualification	Equipment log book	Operating instructions	Annual Product Quality Review	Incident	Change to procedure	Training	AQL check limit for FAR
Less count	Low		✓		✓	✓			✓	✓		✓	✓	✓		✓		✓		✓		✓	✓	✓	
Broken desiccant	Low		✓	✓	✓				✓	✓		✓		✓		✓		✓		✓		✓	✓	✓	
Burnt seal	Low		✓	✓	✓		✓		✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	✓	✓	
Empty blister	High		✓		✓	✓			✓		✓	✓		✓	✓	✓		✓		✓		✓	✓	✓	
Damaged blister	Low		✓	✓	✓				✓	✓	✓	✓		✓	✓	✓		✓				✓	✓	✓	
Presence of foreign matter	Low	✓	✓	✓	✓		✓		✓	✓		✓	✓			✓		✓	✓			✓	✓	✓	
Missing blister	Low		✓		✓	✓			✓			✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	
Missing coding for primary pack	High		✓		✓				✓			✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	
Missing label	High		✓		✓				✓			✓	✓	✓		✓		✓	✓	✓		✓	✓	✓	
Empty bottle	High		✓		✓	✓			✓	✓		✓		✓		✓		✓		✓		✓	✓	✓	
Commingling/ mix-up	Na	✓	✓		✓	✓			✓			✓		✓		✓		✓	✓			✓	✓	✓	
Broken tablet	Low	✓	✓	✓	✓	✓			✓			✓		✓		✓	✓	✓		✓	✓	✓	✓	✓	
Crumbling of tablets	High	✓	✓	✓	✓			✓	✓			✓		✓		✓		✓			✓	✓	✓	✓	
Improper sealing of blister	High		✓	✓	✓				✓			✓		✓	✓	✓		✓		✓		✓	✓	✓	

References

- 21 CFR part 211
- ICH Q7 (15 & 17.7): Complaints & Recalls
- ICH Q9: Quality Risk Management

(This page is intentionally left blank)

Published by:
Indian Pharmaceutical Alliance
A-205 Sangam
14B S V Road, Santacruz (W)
Mumbai 400 054 India
E-mail: sudarshan.jain@ipa-india.org