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HOLISTIC MARKET COMPLAINT INVESTIGATION IN PHARMACEUTICAL INDUSTRY: A FISHBONE DIAGRAM- BASED APPROACH

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ABSTRACT

This paper outlines a comprehensive market complaint investigation methodology for the pharmaceutical industry, leveraging the fishbone (Ishikawa) diagram as a primary tool for systematic root cause analysis. Effective complaint handling is critical for ensuring product quality, patient safety, and regulatory compliance, adhering to guidelines from USFDA, MHRA, PIC/S, ICH, and WHO. We highlight the inherent challenges in investigating routine commercial market complaints, where superficial analysis often leads to misinterpretation of the root cause. This misdiagnosis results in ineffective Corrective and Preventive Actions (CAPA), perpetuating product defects and leading to repeated complaints, eroding consumer trust and inviting heightened regulatory scrutiny. The paper emphasizes the crucial need for a holistic investigation approach that transcends immediate symptoms to identify underlying systemic failures across all contributing factors (Man, Machine, Material, Method, Measurement, and Environment). Two detailed case studies illustrate this point: one involving a half-tablet in a blister pack and another concerning missing label information on a liquid product. Both cases demonstrate how focusing solely on apparent issues, like human error, can obscure the true mechanical or procedural deficiencies. By adopting a thorough, fishbone-driven methodology, pharmaceutical manufacturers can develop robust CAPA, prevent recurrence, and uphold the highest standards of pharmaceutical quality.

Keywords: Market Complaint, Pharmaceutical Industry, Fishbone Diagram, Root Cause Analysis, CAPA, USFDA, MHRA, PIC/S, ICH, WHO.

INTRODUCTION

Market complaints represent a critical indicator of product quality and system effectiveness within the pharmaceutical industry. Their diligent management and thorough investigation are not merely operational necessities but fundamental requirements mandated by global regulatory bodies, including the United State Food and Drug Administration (USFDA), Medicines and Healthcare products Regulatory Agency (MHRA), Pharmaceutical Inspection Co-operation Scheme (PIC/S), International Council for Harmonization (ICH), and the World Health Organization (WHO). Prompt and accurate resolution of these complaints is paramount to safeguarding patient safety, maintaining product integrity, and ensuring continuous regulatory compliance. Despite their significance, routine commercial market complaints often pose unique investigative challenges, particularly when complex issues are masked by seemingly straightforward symptoms. A superficial or misguided investigation can lead to an erroneous determination of the root cause, subsequently resulting in the implementation of ineffective Corrective and Preventive Actions (CAPA). This perpetuates the underlying defect, leading to recurrent complaints, eroding consumer trust, and inviting heightened regulatory scrutiny. This paper proposes a comprehensive market complaint investigation methodology centered on the fishbone diagram (Ishikawa diagram), a powerful tool for systematic root cause analysis. Our objective is to detail this holistic investigative approach, highlight the common challenges encountered in routine commercial market complaints, and underscore the detrimental impact of incorrect root cause interpretation on CAPA efficacy and complaint recurrence. Through two illustrative case studies, we aim to demonstrate the critical importance of a thorough and multi-faceted investigation in alignment with stringent international pharmaceutical quality guidelines.

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REGULATORY FRAMEWORK GOVERNING MARKET COMPLAINT INVESTIGATIONS:

Effective handling of market complaints in the pharmaceutical industry is anchored in a robust regulatory framework. Regulatory authorities across the globe have emphasized the necessity of establishing well-documented and scientifically sound procedures for the receipt, investigation, and resolution of such complaints. This section outlines the key expectations set forth by major international regulatory agencies:

USFDA (United State Food and Drug Administration):

Under 21 CFR Part 211, Subpart J, the USFDA mandates that all drug product quality complaints be documented and thoroughly investigated. Section 211.198 specifically requires written records of complaints and their investigation, emphasizing the need for adequate review, root cause identification, and Corrective and Preventive Actions (CAPA)[1,8].

MHRA (United Kingdom):

MHRA guidelines, rooted in EU Good Manufacturing Practices (GMP), necessitate a structured Quality Management System (QMS) that includes a comprehensive complaint handling system. Chapter 8 of the EU GMP Guidelines specifies that all complaints concerning quality must be recorded and thoroughly investigated, and trends must be evaluated[6,7].

PIC/S(Pharmaceutical Inspection Co-operation Scheme):

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) outlines complaint management procedures in its Guide to GMP, particularly in Annex 16, which emphasizes batch release responsibilities. A qualified person (QP) must evaluate all complaint

investigations to ensure that product quality has not been compromised[2].

ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) Q10 and Q9:
ICH Q10 outlines the Pharmaceutical Quality System, advocating a lifecycle approach to quality. Market complaint investigation aligns with its pillars of process performance and product quality monitoring. ICH Q9, on the other hand, underscores the need for risk-based approaches to decision-making during investigations[3,4].

WHO (World Health Organization) Guidelines:

WHO's GMP guidelines stress that quality defects, particularly those leading to potential product recalls, must be investigated using scientifically validated procedures. Adequate documentation, trending, and recall readiness are crucial components of complaint handling. In summary, global regulatory expectations converge on the importance of a robust, scientific, and risk-based approach to complaint investigation, necessitating tools such as the fishbone diagram to ensure comprehensive root cause analysis[5].

MARKET COMPLAINT INVESTIGATION METHODOLOGY: THE FISHBONE DIAGRAM APPROACH

The fishbone diagram, also known as the Ishikawa or cause-and-effect diagram, serves as an invaluable quality tool in pharmaceutical investigations. It systematically explores potential root causes across multiple domains, providing a visual pathway for investigators.

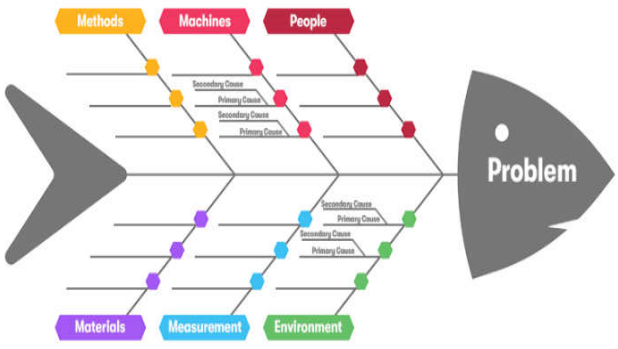
Anatomy of the Fishbone Diagram :

The diagram visually represents the "effect" (the market complaint) at the fish's head, with the primary "bones" signifying key cause categories:

1. Man (People)
2. Machine (Equipment)
3. Material (Raw/Packaging)
4. Method (Processes/SOPs)
5. Measurement (Testing, Sampling, Calibration)
6. Environment (Facility, Temperature, Humidity, Vibration)

A model of Fishbone Diagram is outlined in the diagram (Figure 1):

Figure 1: Fishbone Diagram illustrating the six key domains (6Ms) used in root cause investigation.



Stepwise Investigation Approach:

- **Step 1: Complaint Receipt and Classification**
  All complaints must be logged, triaged, and classified (critical vs. non-critical) per QMS procedure.
- **Step 2: Data Gathering and Preliminary Assessment**
  Investigators must collect relevant information, including the complaint sample (if available), batch records, in-process records, and historical complaint trends.
- **Step 3: Problem Definition**
  Clear articulation of the complaint, including defect description, location, and potential implications on safety or efficacy.
- **Step 4: Cause Identification via Brainstorming**
  Cross-functional teams conduct brainstorming sessions using the fishbone structure, ensuring every "M" is scrutinized.
- **Step 5: Evidence Collection and Hypothesis Testing**
  Each potential cause is verified with available documentation, testing, interviews, and historical data analysis.
- **Step 6: Root Cause Confirmation**
  Root causes are narrowed using methods such as the 5 Whys, Pareto analysis, and control chart evaluations.
- **Step 7: Risk Assessment**
  Evaluate the potential impact on product safety, patient health, and regulatory compliance based on ICH Q9 principles.

This structured methodology enhances investigation quality, minimizes bias, and improves CAPA effectiveness.

CHALLENGES IN ROUTINE COMMERCIAL MARKET COMPLAINT INVESTIGATIONS

Despite well-established systems, routine market complaint investigations often face practical challenges:

Limited Sample Availability
Returned samples may be insufficient or degraded, complicating physical or chemical analysis.

Delayed Reporting
Long intervals between production, market distribution, and complaint reporting may lead to loss of traceability.

External Influences
Storage or handling at the pharmacy or consumer level can contribute to the defect, blurring root cause attribution.

Business Pressure and Resource Constraints
Companies often aim for quick complaint closures to satisfy business needs, risking superficial investigations.

Data Fragmentation
Relevant information may be scattered across multiple departments or systems, reducing investigation efficiency.
These challenges necessitate a robust, cross-functional, and tool-driven approach to ensure investigation depth and accuracy.

CONSEQUENCES OF INCORRECT ROOT CAUSE ANALYSIS ON CAPA AND RECURRENCE

Root cause misidentification can severely impair CAPA and lead to persistent complaints. Key consequences include[8,9]:

Ineffective CAPA Implementation
Actions may target symptoms instead of the actual cause, failing to prevent recurrence.

Reputational and Regulatory Risks
Recurring complaints can erode customer confidence and trigger regulatory audits, warning letters, or import alerts.

Financial and Operational Impact
Investing resources in inappropriate CAPA leads to cost inefficiencies and potential legal liabilities.

Systemic Vulnerabilities
Failure to address deeper systemic issues (e.g., process validation gaps) can affect multiple products or sites. Thus, a sound root cause methodology is indispensable for effective pharmaceutical quality systems.

CASE STUDIES: APPLICATION OF FISHBONE ANALYSIS IN REAL-WORLD SCENARIOS

Case Study 1: Half Tablet in Blister Pack

Complaint: A customer reported finding a blister pack with one socket containing a broken (half) tablet during dispensing by a pharmacist.

Initial Investigation and Assumption: Upon receipt of the complaint, the immediate and seemingly obvious focus of the internal investigation leaned towards human error. It was initially assumed that "Man"—specifically, the packing line operators responsible for visual inspection of the blisters—had either been negligent or had simply missed the defect. This initial interpretation suggested that enhanced vigilance or retraining for the inspection personnel would be the primary corrective action.

The Pitfall of Tunnel Vision: Had the investigation concluded at this stage, the proposed CAPA would likely have focused solely on re-training, stricter supervisory oversight, or increased manual inspection. While seemingly logical, such actions would have addressed a symptom (the missed defect) rather than the true underlying cause. This wrong interpretation of the root cause would inevitably lead to ineffective CAPA and a high probability of repeated market complaints in subsequent batches, as the fundamental issue remained unaddressed.

Holistic Investigation using Fishbone Diagram: Recognizing the limitations of a narrow focus, a comprehensive investigation employing the fishbone diagram was initiated to ensure a holistic analysis across all potential contributing factors.

- **Effect:** Half tablet identified in a blister pack.
- **Man:** Was the operator adequately trained on defect identification? Were the inspection criteria clear? Was there fatigue or distraction impacting vigilance? (This was the initial focus, but broader factors were explored).
- **Machine:** This became a critical area of focus. Was there damage in the tablet feeding mechanism of the blistering machine? Were there excessive vibrations during tablet transfer or blistering that could cause breakage? Was there wear and tear on the forming or sealing tools, or even within the hopper or tablet path leading to the blister pockets? This category indicated potential for mechanical issues causing breakage before or during packaging.
- **Material:** Was the tablet inherently brittle? Could this be due to issues like over-compression during tablet manufacturing or insufficient lubrication during tablet formulation, making it prone to breakage under minimal stress?
- **Method:** Was the in-process quality check for blister integrity and tablet presence sufficiently robust? Was the frequency of checks adequate? Was the packaging line speed optimized for tablet integrity?
- **Measurement:** Were the quality control instruments for tablet hardness or friability properly calibrated? Were the in-process inspection systems (if automated) functioning correctly?
- **Environment:** Could factors like high humidity at the packing stage affect tablet integrity, making it more susceptible to breakage? Were there external vibrations impacting machine stability?

Root Cause Determination (Holistic Approach): The holistic analysis, particularly the in-depth investigation into the "Machine" category, revealed that while human inspection might have failed to detect the defect, the primary root cause was a mechanical defect within the blister packing machine's tablet feeding or sealing section. Investigation traced the breakage to specific points where tablets were subjected to undue stress or impact due to a worn or misaligned part. The tablets, while within specifications, were susceptible to this specific mechanical stress. Therefore, the issue was fundamentally a machine performance problem, not solely an operator oversight.

Proposed CAPA (Holistic and Effective): Based on the revised root cause, the CAPA was comprehensive and targeted:

- **Equipment Maintenance and Replacement:** Immediate repair and replacement of the identified worn or damaged machine parts. Implementation of a robust preventative maintenance schedule for critical components of the blistering machine.
- **Online Camera-Based Defect Detection:** Installation and validation of an automated vision system on the packing line capable of real-time detection of broken or half tablets in blisters, significantly reducing reliance on manual inspection.
- **Parameter Optimization:** Review and optimization of blister machine operating parameters (e.g., speed, pressure) to minimize tablet stress during packaging.
- **Retraining and Awareness:** While not the primary cause, operators were retrained on heightened vigilance and awareness of potential machine-related issues, empowering them to identify and report machine anomalies promptly.

This case study profoundly illustrates how an initial focus on human error, without a holistic fishbone analysis, would have led to an ineffective CAPA. By correctly identifying the "Machine" as the primary root cause, the company was able to implement targeted, effective actions that prevented the recurrence of half-tablet complaints, ensuring product quality and consumer trust.

Case Study 2: Missing Batch Details on Liquid Product Label :

Complaint: Commercial product liquid bottles were identified in the market with labels completely missing critical information, specifically the Batch Number, Manufacturing Date, and Expiry Date.

Initial Investigation and Assumption: The immediate response to this complaint, similar to Case Study 1, initially focused on human error within the packaging department. The assumption was that the "Man" (packing personnel) responsible for applying the labels and performing in-process quality checks had simply failed to verify the presence and correctness of the printed information before the

product was released. This initial interpretation suggested a need for retraining or disciplinary action for the individuals involved in the labeling and verification process.

The Peril of Superficial Analysis: Limiting the investigation to a single aspect like operator error would have been a significant oversight. Addressing only the packing personnel's verification process (e.g., through retraining) would not resolve the fundamental issue of "Why" the information was missing in the first place. This wrong interpretation of the root cause would lead to ineffective CAPA, leaving the core problem untouched. Consequently, the company would likely experience repeated market complaints for subsequent batches, damaging its reputation and inviting severe regulatory consequences.

Holistic Investigation using Fishbone Diagram: A comprehensive investigation utilizing the fishbone diagram was critical to uncover the true, systemic root causes beyond the immediate human interface.

- **Effect:** Labels on finished product liquid bottles missing Batch No., Mfg. Date, and Exp. Date.
- **Man:** Was the packing person adequately trained on label verification? Was there fatigue or distraction? Was the in-process verification SOP clear and robust? (Initial focus, but broader system issues explored).
- **Machine:** This emerged as a primary suspect. Was the inkjet printer (or other printing device) used for applying variable data malfunctioning? Was there an intermittent nozzle clog? A software glitch in the printer settings? Was the printer due for maintenance or calibration? Was the printer's data input system prone to errors?
- **Method:** This was another crucial category. What was the SOP for label printing? Was there a defined in-process quality check at the printing stage itself, before labels were released to the packing line? Was the approval process for label artwork and variable data entry sufficiently controlled? Was the verification step for printed information prior to label application robust enough, or was it a mere visual check?
- **Material:** Was the label stock compatible with the printer's ink/ribbon? Was the ink cartridge running low or expired? Was the quality of the label material itself affecting print adhesion or clarity?
- **Measurement:** Were there clear specifications for print quality and data presence? Was there an automated print quality audit trail or vision inspection system at the printing stage? Were verification tools (e.g., scanners) being used effectively?
- **Environment:** Could factors like temperature or humidity in the printing area affect ink drying or printer performance?

Root Cause Determination (Holistic Approach): The holistic fishbone analysis definitively pointed towards a combination of "Machine" and "Method" as the primary root causes, rather than solely human error at the packing stage. It was discovered that the inkjet printer was experiencing intermittent nozzle clogs, leading to incomplete printing of characters. Furthermore, a significant procedural gap ("Method") was identified: the in-process verification for printed variable data was heavily reliant on visual checks only at the point of label application in the packing area, with an insufficient or absent robust verification step at the actual label printing facility. The labels were essentially "released" without proper confirmation of complete printing. While the packing personnel's verification did fail, it was a secondary failure, stemming from the fact that the defect originated much earlier in the process.

Proposed CAPA (Holistic and Effective): Based on the accurate root causes, the CAPA was comprehensive:

- **Printer Maintenance and Upgrade:** Immediate service and calibration of the inkjet printer. Implementation of a robust preventive maintenance schedule for all printing equipment. Evaluation for upgrade to printers with self-cleaning nozzles or real-time print verification.
- **Revised SOP for Label Printing and Verification:** Development and implementation of a new, stringent SOP requiring mandatory, automated (e.g., vision system-based) verification of all variable data immediately after the labels are printed, before they are released to the packing line. This included clear acceptance/rejection criteria.
- **Enhanced In-Process Checks at Packing Line:** While the primary issue was upstream, in-process checks at the packing line were also strengthened, potentially incorporating scanner-based verification of batch details to act as a final safeguard.
- **Digital Label Tracking System:** Implementation of a system to link printed labels to specific batches digitally, providing a clear audit trail.
- **Operator Training:** Comprehensive training for both printing operators and packing personnel on the new SOPs, use of verification equipment, and the critical importance of each verification step.

This case study powerfully underscores that a superficial investigation, attributing blame solely to packing personnel, would have allowed the systemic issues in printing and upstream verification to persist, leading to a recurrence of the missing label data. The holistic fishbone approach enabled the identification of the true machine and method failures, leading to effective, preventative actions and ensuring future compliance and product integrity.

DISCUSSION

The reviewed methodology and case studies underscore the inadequacy of linear, assumption-driven complaint investigations. A fishbone-based, cross-functional, and data-centric approach offers multiple advantages:

- Captures diverse potential causes and uncovers latent systemic weaknesses.
- Enhances CAPA precision, thereby reducing complaint recurrence.
- Aligns with international QMS principles and satisfies regulatory scrutiny.

In a landscape of increasing regulatory expectations and patient safety imperatives, such methodologies are not optional but critical for operational excellence.

CONCLUSION

Market complaint investigations in the pharmaceutical industry must evolve from reactive exercises to proactive quality improvement tools. The use of the fishbone diagram facilitates this transformation by offering a structured, holistic framework that examines all contributing factors—human, technical, procedural, and environmental.

As shown in the case studies, adopting this approach not only uncovers the true root cause but also ensures meaningful CAPA implementation. This methodology aligns with the principles outlined by USFDA, MHRA, PIC/S, ICH, and WHO, thereby reinforcing compliance, product quality, and patient safety.

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ABBREVATIONS:

- **CAPA:** Corrective and Preventive Actions
- **EU GMP:** European Union Good Manufacturing Practices
- **GMP:** Good Manufacturing Practices
- **ICH:** International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
- **ISO**: International Organization for Standardization
- **MHRA:** Medicines and Healthcare products Regulatory Agency
- **PIC/S:** Pharmaceutical Inspection Co-operation Scheme
- **QMS:** Quality Management System
- **QP:** Qualified Person
- **SOP:** Standard Operating Procedure
- **USFDA**: United State of Food and Drug Administration
- **WHO**: World Health Organization

SUMMARY:

This paper, titled "Holistic Market Complaint Investigation in the Pharmaceutical Industry: A Fishbone Diagram-based Approach," outlines a clear method for investigating market complaints in the pharmaceutical sector. Written by Dr. Nikhil Arun Vyawhare, Quality Assurance Manager at SM Pharmaceuticals Sdn Bhd in Malaysia, the paper promotes the use of the fishbone (Ishikawa) diagram as a key tool for effective root cause analysis. The main point of the paper is that while market complaints are important indicators of product quality, their investigation often faces challenges, especially in normal business situations. A common mistake is misinterpreting the root cause, usually attributing problems to human error without a deeper analysis. Such surface-level investigations lead to ineffective Corrective and Preventive Actions (CAPA), which allow defects to persist and result in repeated market complaints. The paper highlights the need for a thorough investigation approach that goes beyond immediate symptoms. The fishbone diagram helps by systematically examining potential causes across six categories: Man, Machine, Material, Method, Measurement, and Environment. This approach ensures that all possible factors are examined, reducing bias and improving the effectiveness of CAPA. Regulatory guidelines from USFDA, MHRA, PIC/S, ICH, and WHO stress the importance of proper complaint handling. They highlight the need for documented procedures, thorough investigations, root cause identification, and effective CAPA. The proposed method aligns with these international quality management standards. Two detailed case studies are included to show how the methodology works in practice.

- **Case Study 1 (Half Tablet in Blister Pack):** Initially, human error was suspected. However, the fishbone analysis showed a mechanical defect in the blister packing machine as the main root cause. This example illustrates how a narrow focus could have led to ineffective CAPA and ongoing issues.
- **Case Study 2 (Missing Batch Details on Liquid Product Label):** Like Case Study 1, early assumptions pointed to a mistake by packing personnel. However, a comprehensive fishbone analysis uncovered an intermittent printer malfunction ("Machine") and a gap in the print verification process ("Method") as the real systemic root causes. Both case studies clearly demonstrate that focusing only on human error is not enough.

A systemic, fishbone-driven analysis is necessary to find the true root causes. This approach allows for targeted and effective CAPA, preventing future issues, ensuring product quality, and maintaining consumer trust and regulatory compliance. The paper concludes that market complaint investigations should evolve into proactive tools for quality improvement using structured, holistic frameworks.

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