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Hazard Operability Analysis (Hazop): A Quality Risk Management Tool for the Protection of Quality Drugs.

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ABSTRACT:
Hazard and operability study is a systematic and structured technique which is used to identify the potential hazards and evaluate the problems associated with systems. The health ministry's largest-ever survey to assess drug quality revealed that more than 10% of medications in the government supply chain were "Not of Standard Quality" (NSQ). Comparatively, samples collected from retail locations nationwide showed an estimated 3% of NSQ medications, whereas 0.023% of the samples were determined to be fake.According to the survey, the combined prevalence of NSQ and fake medications nationwide was estimated to be 3.16% and 0.0245% for both government and retail sources."In India, the estimated percentage of NSQ drugs from official sources was 10.02%, while the percentage of spurious drugs was 0.059%." The following pattern was noted in civil hospital shops during the examination of samples from the government supply chain that were deemed NSQ: 10.44% NSQ, ESI dispensaries, 11.03% NSQ, state government medical store depots CGHS dispensaries: 4.11% NSQ and 9.01% NSQ, according to a National Institute of Biologicals (NIB) survey conducted in Noida.States like Meghalaya, Mizoram, Arunachal Pradesh, Nagaland, Telangana, Uttarakhand, Uttar Pradesh, and Punjab had higher NSQs (11.39–17.39%) in terms of the government supply chain, whereas Chandigarh, Delhi, Orissa, Tamil Nadu, and West Bengal had lower NSQs (0–7.93%).The country's retail establishments were projected to have a 3% and 0.023% NSQ and bogus medication proportion, respectively.Tools for Quality Risk Management (QRM) are crucial for detecting and reducing these risks, but the pharmaceutical industry has yet to fully utilize Hazard Operability Analysis (HAZOP), a methodical and structured approach that has long been employed in the chemical and processing industries. The potential of HAZOP as a proactive QRM tool to pinpoint manufacturing failure spots for non-standard quality medications is assessed in this study. CAPA Is also applied to the risk to identify the cause.

Keywords: Consequence, Medications, Survey ,CAPA ,Examination , Methodical

I. INTRODUCTION:

The concepts of risk management are effectively used in a number of government and industrial sectors, including banking, insurance, public health, safety-related activities, pharmacovigilance, and organizations that oversee these sectors. Despite the fact that the pharmaceutical business does have certain instances of quality risk management (QRM) in action. They are constrained and fall short of capturing the full potential of risk management[2]. Furthermore, the pharmaceutical sector has acknowledged the value of quality systems, and it is becoming clear that a strong quality system includes quality risk management as a crucial element. These goods may be the consequence of inferior production procedures, insufficient quality assurance, or supply chain breakdowns, which might lower medicinal efficacy and raise patient safety risks. Tools for Quality Risk Management (QRM) are crucial for detecting and reducing these risks, but the pharmaceutical industry has yet to fully utilize Hazard Operability Analysis (HAZOP), a methodical and structured approach that has long been employed in the chemical and processing industries. The potential of HAZOP as a proactive QRM tool to pinpoint manufacturing failure spots for non-standard quality medications is assessed in this study. A typical oral solid dosage manufacturing process was subjected to a HAZOP study, which looked at distortions pertaining to important process parameters and quality features. Inconsistencies in raw materials, equipment failure, and operational process human error were among the major risk areas highlighted by the evaluation. Process control, employee education, and

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equipment validation were the main topics of the recommendations created for risk minimization. The findings show that HAZOP can efficiently reveal hidden hazards and provide organized information for CAPAs (corrective and preventative measures).

Principles of Quality Risk Management:

- The degree of effort, formality, and documentation of the quality risk management process should be proportionate to the degree of risk; and
- The assessment of the risk to quality should be grounded on scientific knowledge and ultimately linked to patient protection.

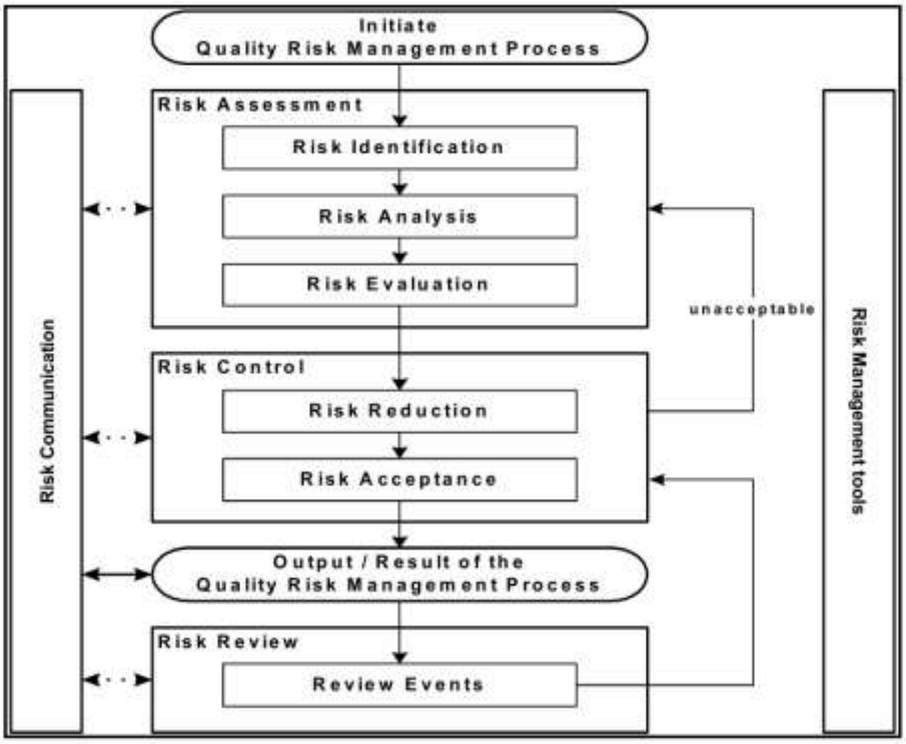

Figure 1: Overview of a typical quality risk management process. Taken from: ICH Q9: Quality Risk Management. This figure is also available on the ICH website www.ich.org.

Risk Management Tools

A wide range of tools, either separately or in combination, can be employed for QRM. When using a QRM technique, it is crucial to remember that no one tool or set of tools is appropriate for every circumstance. Regulatory advice lists some examples of tools, although neither list is comprehensive. If the tool or instruments are employed to support the essential characteristics of a sound risk assessment, it is a crucial criterion for acceptance[7-9].

A number of working tools to promote uniformity in the use of ICH Q9 in daily RM decision-making, a summary of common RM principles and best practices, and a number of examples of RM applications currently being used by significant pharmaceutical companies have all been produced by the Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) [10-11]. Additionally, they have created highly useful risk tool training courses for HACCP, failure modes and effects analysis (FMEA), hazard operability analysis (HAZOP), and risk rating and filtering.

Origin of HAZOP study :

- The term HAZOP was first used in the literature in the early 1970s and was 'developed' by ICI in the UK.
- After the 1974 Flixborough tragedy, which claimed 28 lives and damaged several others, HAZOP became more popular in the chemical processing sector.

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- The petroleum sector, which has a comparable risk of catastrophic events, later adopted the concept.
- The food and water sectors came next, with similar potential hazards but of a different kind, with contamination rather than explosions or chemical spills being the main worry.
- International Standard IEC61882 (HAZOP Studies Application Guide 2001)

The acronym for Hazard and Operability analysis is HAZOP. The term 'HAZOP' was first used by ICI, and Skelton, B. (1997) defined it as a formal, systematic, critical, rigorous examination of the manufacturing intentions and process of new and existing facilities to determine the hazard potential of individual pieces of equipment malfunctioning and the resulting consequences [5]. HAZOP is a formal, systematic analysis of a processing plant to find risks, failures, and operability issues and evaluate the repercussions of such mal-operation (Wells, G., 1996).

List Of the not Standard drugs in the year of 2024(as per cdsco)
Amoxicillin AndPotassium Clavulanate Tablets IP (Clavam 625)

1. Amoxycillin & Potassium Clavulanate Tablets (Mexclav 625)
2. Calcium And Vitamin D3 Tablets IP Shelcal 500 (Shelcal)
3. Metformin Hydrochloride Sustained-release Tablets IP (Glycimet-SR-500)
4. Vitamin B Complex with Vitamin C Softgels
5. Rifmin 550 (Rifaximin Tablets 550 mg
6. Pantoprazole Gastro-Resistant and Domperidone Prolonged-Release Capsules IP (Pan- d)
7. Paracetamol Tablets IP 500 mg
8. Montair LC Kid (Montelukast Sodium &Levocetirizne Hydrochloride Dispersible Tablets)
9. Compound Sodium Lactate Injection I.P. (Ringer Lactate Solution for Injection) (RL 500 ml)
10. Fexofenadine Hydrochloride Tablets IP 120 mg

Principles of HAZOP:

A study is a comprehensive, team-based approach for identifying hazards and operability issues. HAZOP addresses the detection of probable violations from the design intent, investigation of their potential causes, and evaluation of their effects.

Key features:

- The process of inspection is creative.
- In order to find any possible departures from the design goal, the investigation is conducted methodically utilizing a set of reference phrases.
- The examination relies on seasoned experts from a range of disciplines and is conducted under the direction of a leader who guarantees thorough coverage of the system being studied [2-3].
- It should be conducted in an environment that encourages candid communication and optimistic thinking. Although they are not the main goal, solutions to difficulties are noted for the designers to take into account [5-8].

HAZOP Methodology:

The methodology is divided into Four Phases:

1. Definition Phase:

The risk assessment team members are usually identified in advance to start the Definition Phase. HAZOP is designed to be a cross-functional team effort and depends on experts (SMEs) from many fields who exhibit strong judgment and intuition along with the necessary training and expertise. SMEs (Specialists) with a thorough and up-to-date understanding of system aberrations should be carefully selected [6-7]. HAZOP should always be conducted in anatmosphere of open communication and optimistic thinking. The risk assessment team must precisely define the assessment scope during the Definition Phase in order to concentrate their efforts. This entails outlining the parameters of the research, important interfaces, and the fundamental presumptions that will guide the evaluation.

2. Preparation Phase:

The following tasks are commonly included in the preparation phase:

- Finding and identifying relevant information and data.
- Determining the users and audience for the study's results.
- Preparations for project management, such as setting up meetings and recording sessions, etc.
- Agreement on a template format for documenting research results.

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- Agreement on the HAZOP guide terms to be utilized throughout the research [9].

3. Examination Phase:

- Finding every component (step or section) of the system or process that needs to be investigated is the first step in the examination phase [6].
- As an illustration, physical systems may be divided into smaller components as needed, and processes can be divided into distinct stages or phases.
- To make evaluation easier, related components or procedures might be grouped together. Each element is subsequently subjected to the HAZOP guiding words.
- In this way, a comprehensive and methodical search for aberrations is conducted.
- It should be mentioned that not every set of guidelines and components will produce logical or plausible deviation options [2].

4. Documentation Phase or follow -up:

As indicated in IEC Standard 61882, using a template recording form to document HAZOP analyses is frequently helpful. Depending on a number of circumstances, including regulatory requirements, risk assessment teams may need to make changes to the template.

More precise risk rating or prioritizing is required (for example, rating deviation probability, severities, and/or detection). · Company documentation policies requirements for audit preparation or traceability of other elements.

Role of CAPA in HAZOP Based Risk Management:

The Corrective and Preventive Action (CAPA) system is essential to a Hazard and Operability Study (HAZOP) because it makes sure that hazards that have been identified are adequately controlled and reduced. Although HAZOP is a methodical and organized approach for identifying possible risks and problems with process operability, CAPA offers the means by which the results of the HAZOP are converted into useful enhancements [5].

Existing problems found during the HAZOP analysis, such as equipment breakdowns, procedural gaps, or design faults, are addressed by corrective measures. These steps are taken to get rid of or lessen the chance that dangers that have been identified may manifest. Conversely, preventive actions are proactive measures done to stop similar risks from happening again in other parts of the system or process. To reduce human error, this might entail improving training programs, changing standard operating procedures (SOPs), or rethinking equipment interfaces.

CAPA Process Flow Chart:

CAPA PROCESS
HAZOP Identifies Deviation or Risk ↓
Record Finding in Risk Log or HAZOP Report ↓
Initiate CAPA Request
Root Cause Analysis (e.g., 5 Whys, Fishbone)] ↓
Develop CAPA Plan ↓ ↓
Corrective Action Preventive Action ↓ ↓
Implement Actions (Procedures, Design, Training, etc.) ↓
Verify Effectiveness of CAPA ↓
Close CAPA (Document and Archive) ↓
Feed Lessons Learned into Future Risk Assessments

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Case Study 01:

- **Background:**

A batch of 500 mg paracetamol tablets failed weight variation and dissolving tests during normal quality control. A comprehensive risk assessment of the production process was necessitated by the failures. A HAZOP analysis was started because of the operation's complexity and the requirement for a methodical approach.

- **QRM Team Composition:**

✓ QA Supervisor (Assistant)
✓ Manager of Production
✓ Process Engineer
✓ Formulation Scientist
✓ Maintenance Technician and QC Analyst

- **Objective of HAZOP study :**

To find process variations that might result in poor outputs, such as:

✓ Changes in dose strength
✓ Failure of tablet integrity
✓ Inconsistencies in the dissolution profile
✓ Failure to comply with regulations

- **HAZOP Execution (Risk Identification and Analysis):**

Parameter	Guide Word	Deviation	Possible Cause	Consequence	Risk Level	Existing Controls	Recommended Action
Tablet weight	More	Overfilled tablets	Feeder surge, poor granule flow	Overdosage, batch rejection	High	Manual weight checks	Install in-line weight monitoring
Tablet weight	Less	Underfilled tablets	Hopper bridging	Sub-potent tablets	High	Visual checks, sampling	Granule size optimization
Compression force	More	Overcompression	Excessive machine settings	Slow disintegration, hard tablets	Medium	Compression records	Limit setting alarms
Compression force	Less	Undercompression	Mechanical wear, calibration drift	Fragile tablets, capping	Medium	Preventive maintenance	More frequent calibration

Compression Stage :

Parameter	Guide Word	Deviation	Possible Cause	Consequence	Risk Level	Existing Controls	Recommended Action
Spray rate	Less	Incomplete coating	Clogged nozzle, low pump pressure	Non-uniform dissolution	High	Visual inspection	Add nozzle cleaning SOP, flow sensors
Inlet air temperature	More	Excessive heating	Sensor malfunction	API degradation	High	Manual temperature control	Install automated temperature alarms

Coating Stage :

- **Risk Evaluation and Prioritization :** In accordance with FMEA principles, the team categorized weight variation and dissolving inconsistencies as high-risk concerns based on their severity, incidence, and detectability.

- **Risk Control Actions:**

✓ Systems for tracking pill weight and spray rate are implemented in-line.
✓ Updated SOPs for nozzle maintenance and feeder calibration
✓ Improved instruction for operators of coatings and compression
✓ The frequency of preventive maintenance has risen.

- **Risk Review and Outcome:** The efficacy of the controls was assessed in the following batches:

✓ Complete adherence to the weight and dissolution requirements
✓ Follow-up regulatory inspections revealed no deviations.
✓ Auditors valued documented proof of systematic risk control.

Protective Measure For Quality Drugs:

A. Inherent Safety Measures:

Definition: By design, eliminate or drastically lower the risk.

Examples:

- include the use of less dangerous materials.
- reducing complexity through process simplification.
- lowering the temperature or operating pressure.

B. Engineering Controls:

Definition: Making tangible changes to machinery or procedures in order to isolate or lessen risks.

Examples:

- systems for containment (e.g., enclosures, glove boxes).
- systems for automated shutdown.
- systems for ventilation.

C. Administrative Controls:

Definition: Methods and techniques to direct safe operation and lower the likelihood of human mistake.

Examples:

- Standard operating procedures (SOPs)
- programs for training.
- Work permit systems.
- Change the handover procedures.

D. Personal Protective Equipment :

Definition: Gear that employees wear to protect themselves from dangers.

Examples:

- Respirators
- lab coats or full body suits
- goggles
- gloves and hearing protection.

II. CONCLUSION:

It has been demonstrated that using HAZOP as a Quality Risk Management (QRM) tool in pharmaceutical production is a proactive, organized, and successful method of detecting and reducing risks related to non-standard quality medications. This case study, which concentrated on the tablet manufacturing process, showed how HAZOP may be utilized to address important quality qualities including dose consistency, dissolving, and tablet integrity in addition to its conventional application in process safety.

The HAZOP team was able to identify hidden reasons for product non-conformance, put specific risk management measures in place, and increase the overall resilience of the production system by methodically examining potential deviations at each stage of the process—in this example, compression and coating. The process improvements were in accordance with ICH Q9 standards and GMP requirements thanks to the integration of cross-functional knowledge and data-driven decision-making.

In the end, the HAZOP study not only fixed the urgent quality problems but also promoted operational discipline, regulatory preparedness, and a continuous improvement culture. The effectiveness of HAZOP as a QRM tool in guaranteeing the steady manufacture of safe, high-quality medications is demonstrated by its successful application.

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