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Review Article

Integrated Risk Assessment of Manufacturing Processes, Safety, and Nitrosamine Contaminants in the Pharmaceutical Industry: A Comprehensive Review

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ABSTRACT

Risk assessment in pharmaceutical manufacturing has become an essential component of modern pharmaceutical operations due to increasing regulatory requirements, complex supply chains, and growing quality and safety concerns. The three dimensions in which risk management, occupational and operational safety and nitrosamine impurity risk management are interlinked constitute the current risk ecosystem prevailing in the pharma sector. Risk assessment for the process utilizes FMEA, HAZOP and a QbD-based analytical approach for ensuring that such processes are well charted, well-structured and reliable. Safety Risk Assessment dissects process safety, equipment hazards, chemical hazards and environmental exposure in order to avoid accidental injury, ensure people are not injured and the regulation standards are met. Ranitidine, as well as the other recalls before it have revealed the worldwide nitrosamine crisis and emphasized the need for focused risk assessments of genotoxic N-nitroso drugs that can emerge in synthesis routes, reagents, packaging or from degradation. In the present review, we provide an overview of the standards, laws, tools and methods that govern these three major risk areas. It emphasizes the importance of linking proactive and reactive risk approaches, identifies shortcomings in the current commercial situation, and outlines possible ways forward, including digitalization, AI-based predictive modelling methods, and lifecycle-integrated risk management. The review demonstrates the potential of a consolidated holistic risk-assessment approach to offer extended product quality reproducibility, enhanced security, and intentional impurity control in alignment with ICH Q9(R1), ICH Q10, FDA, EMA, EDQM, and worldwide GMP norms.

Keywords: Risk assessment, Process safety, Nitrosamine impurities, ICH Q9(R1), QRM, Pharmaceutical manufacturing, FMEA, HAZOP, Proactive and reactive risk management.

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INTRODUCTION

Risk assessment has evolved into an integral part of current pharmaceutical manufacturing practice in support of QbD and patient safety and regulatory compliance under ICH Q9(R1), ICH Q8, and ICH Q10 guidelines. Such an approach to structured risk assessment enables an organization to systematically identify, analyze, and control the potential risks relating to processes, materials, equipment and emerging challenges such as nitrosamine contamination. Taking methods such as risk ranking and filtering to quantify risks by severity (what happens if it fails), probability (how likely it is to happen), and detectability (the chance that the failure is detected before it reaches the patient), effective risk evaluation is at the center of these activities (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2023). When integrated into frameworks such as FMEA, these metrics provide a Risk Priority Number (RPN), giving objective criteria to help compare and prioritize measures to control risk. Severity rankings vary from minor effects to major consequences that may affect the patient or regulatory action, and probability scales address how often the failure is likely to occur in typical manufacturing settings. Alternatively, detectability scales measure the strength of existing controls-whether a failure will be detected through in-process testing, PAT tools, or innovative digital monitoring. Pharma embeds these ranking systems into a methodology so that you can see the rationale and repeat the process in order to help the whole risk management system be more resilient and compliant and based on data instead of opinion. This integrated basis is consistently important because the industry moves into

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complex manufacturing technologies, digitalized quality systems, and more stringent product safety factors, such as the control of nitrosamine impurities (Figure 1) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2008).

Risk Ranking Scales (Severity, Probability, Detectability)

Risk rankings (scales) are core elements of many of the quantitative and qualitative methodologies for risk assessment utilized in the pharmaceutical manufacturing site, including Failure Mode and Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP), Hazard Analysis and Risk Assessment (HIRA) and a number of the Quality Risk Management (QRM) frameworks described under ICH Q9(R1). These scales allow for the quantification of the three key dimensions of risk (severity, probability, and detectability, or their equivalents) to give an RPN or equivalent risk values. This structured ranking method maximizes consistency, objectivity, and reproducibility of the decision-making process across cross-functional teams, including members from quality assurance, production, engineering, and regulatory affairs (Figure 2) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2019).

Severity (S)

Severity is based on the adverse impact that a failure mode would result in a product not meeting its requirements or specifications, affecting patient safety, regulatory compliance, or operational performance. In particular, signaling to the severity score-the key determinant of determination placed in pharmaceutical operations is evident; severity scoring is driven by the nature of the defect, the criticality of the process step and patient impact/finished-product specification. Usually, less serious deviations that do not significantly impact safety or efficacy get a low severity score, while high severity ratings indicate critical negative impacts such as batch rejection, product recall, critical deviations from GMP, and risk of patient harm. Approaches to severity assessment are closely aligned with risk-to-patient principles inherent to ICH Q8, Q9 and Q10 with an emphasis on identification of Critical Quality Attributes (CQAs) and Critical Process Parameters

Figure 1: Key steps in pharmaceutical risk assessment.

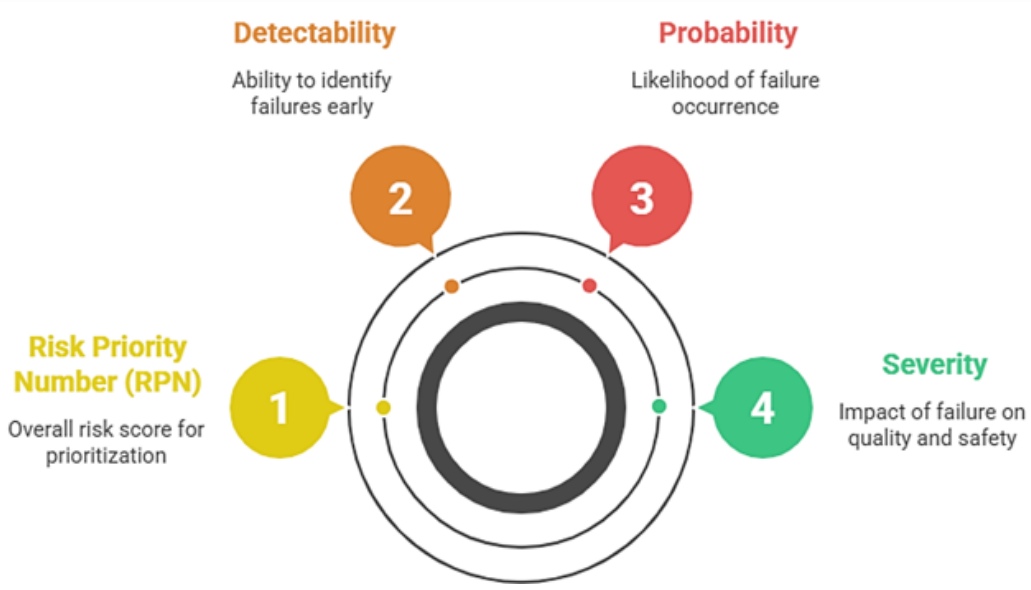

Figure 2: Risk Ranking Scales in Risk Assessment.

(CPPs) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2022).

Probability (P)

Probability (or occurrence or likelihood): This is the estimation of the frequency that a failure mode is expected to occur during normal operating conditions. Probability is driven by historical variation data, Capability Indices (Cp/Cpk), actual preventive maintenance results, supplier quality performance, and process noise. The probability score (1-2, failures are incredibly low because of strong control, well-validated systems and preventive measures, etc.; 4-5, frequent/repeating events, usually due to poor control, bad equipment design, manual processes, and/or lack of training). Add SPC data and historical trending for greater probability scoring accuracy to enable data-driven risk mitigation (European Medicines Agency [EMA], 2020).

Detectability (D)

A lack of detectability quantifies the chance that a failure will go undetected until it affects the patient or product quality. Inversely proportional to detection mechanism efficiency the highest detectability (lowest score of 1-2) means that the deviation will be identified by monitoring systems, in-process controls, automated alarms or PAT tools with high ability. On the other hand, a low detectability (high score of 4-5) means weak detection controls, detection performed slowly, manually, or no real time feedback. Digital quality systems benefit immensely from early-warning capabilities provided by AI-enabled anomaly detection and advanced sensors, as well as Real-Time Release Testing (RTRT), thereby improving detectability scores (the ability to detect defects) (U.S. Food and Drug Administration [FDA], 2023).

Integration into Risk Scoring Models

Multiplying these three parameters derives the Risk Priority Number (RPN=S×P×D), allowing for risk prioritization based on numerical value. Critical risks that need prompt treatment (CAPA) or process redesign score higher, whilst lower scores only need monitoring. More recent times have seen many of these pharmaceutical organizations start to combine these scales with digital dashboards, often found in automated risk-ranking tools or QRM platforms, to deliver a far greater consistency and also traceability of the risk rating process (World Health Organization [WHO], 2020).

Interpretation

- **Low Risk (Green):** Acceptable; routine controls adequate.
- **Medium Risk (Yellow):** Requires monitoring and targeted mitigation.
- **High Risk (Orange):** Formal CAPA or process redesign needed.
- **Very High Risk (Red):** Unacceptable; immediate corrective action required (Parenteral Drug Association [PDA], 2021).

Why Detectability Is Not Included in a 5×5 Risk Acceptance Matrix

The 5×5 Risk Acceptance Matrix in pharmaceutical Quality Risk Management (QRM) relies solely on Severity (S) and Probability (P) because ICH Q9(R1) defines risk strictly as the combination of these two factors. Detectability (D), although central to FMEA, is intentionally excluded from standard risk matrices due to its high subjectivity, dependence on analyst or method

capability, and potential to artificially downgrade high-severity risks. Moreover, detectability is more appropriately addressed during risk control and monitoring strategy development (e.g., PAT, sampling, analytical methods) rather than during the initial risk estimation phase. Therefore, excluding D ensures regulatory alignment, avoids misleading risk scores, and simplifies decision-making in cross-functional pharmaceutical operations (Table 1) (European Directorate for the Quality of Medicines and HealthCare [EDQM], 2022).

Proactive and Reactive Risk Assessment Concepts

Proactive Risk Assessment

The proactive approach is concerned with preemptive failure prevention by systematically identifying weaknesses in processes, raw materials, facilities and safety systems. During development, technology transfer and routine operations, FMEA, HACCP, DoE, PAT-based monitoring and HIRA ensure that quality, safety and nitrosamine-related risks are envisaged and offset in defense during such processes. With this future-based approach, a potential risk can be minimized, structural control strategies developed, and properly informed decisions can be executed to lower the risk of deviations, safety breaches, or contaminants in the final product when manufacturing in real time (U.S. Food and Drug Administration [FDA], 2021).

Reactive Risk Assessment

On the other hand, reactive risk assessment is a response to an event-such as deviations, batch failures, OOS/OOT results, equipment failures, safety events, and nitrosamine detections, for example. It uses Root Cause Analysis (RCA), CAPA, incident investigation, and trending analysis tools to find the root cause, corrective actions, and to prevent recurrence. Reactive assessments help in closing loopholes and resolving underlying issues but are generally as cost-effective as proactive assessments. Together, reactive and proactive approaches form a synergy in which risk management becomes life-cycle oriented to enhance the robustness of the processes, ensure safety for our operations, and keep pace with the rapidly evolving regulations around impurity control such as nitrosamines (American Industrial Hygiene Association [AIHA], 2022).

METHODOLOGY

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies, regulatory guidelines, and technical reports related to process risk assessment, safety risk assessment, and nitrosamine risk assessment in the pharmaceutical industry. Electronic databases including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect were searched. In addition, official guidance documents from FDA, EMA, WHO, ICH, MHRA, and ISO were reviewed. Keywords used included *"pharmaceutical risk assessment," "process risk assessment," "safety risk management," "nitrosamine impurities," "NDMA," "NDEA," "NDSRI," "ICH Q9,"* and *"quality risk management."*

Inclusion and Exclusion Criteria

Peer-reviewed articles, regulatory guidelines, and authoritative technical reports published in English between 2010 and 2025 were included. Publications focusing on non-pharmaceutical industries or lacking regulatory or scientific relevance were excluded.

Data Extraction and Analysis

Relevant information was extracted, critically analyzed, and synthesized to develop integrated frameworks, decision trees, and comparative tables aligned with current regulatory expectations.

Safety Risk Assessment In Pharmaceutical Operations

Safety risk assessment ensures identification and control of chemical, mechanical, thermal, ergonomic, and environmental hazards throughout pharmaceutical processes (Table 2). Risk is assessed for consequence and likelihood, using tools such as HAZOP, PHA, HIRA, OEB evaluation, etc., to prioritize mitigation. Applied engineering controls, SOPs, LOTO programs, and PPE to mitigate risks to an acceptable threshold. Such a systematic approach can enhance workplace safety and eliminate incidents to stay compliant with global safety regulations (National Institute for Occupational Safety and Health [NIOSH], 2020).

Table 1: 5×5 Risk Acceptance Matrix (Severity × Probability) For Process, Safety, and Nitrosamine Risk Assessment.

Probability / Likelihood	1 - Negligible	2 - Low	3 - Moderate	4 - High	5 - Very High
5 - Almost Certain	Medium	High	High	Very High	Very High
4 - Likely	Medium	Medium	High	High	Very High
3 - Possible	Low	Medium	Medium	High	High
2 - Unlikely	Low	Low	Medium	Medium	High
1 - Rare	Low	Low	Low	Medium	Medium

Table 2: Safety Risk Assessment Steps and Control Measures.

Step	Description	Control Measures/Examples
Risk Identification	Recognize potential safety hazards in operations.	Chemical hazards, mechanical hazards, thermal hazards, occupational exposure, environmental hazards.
Risk Analysis	Assess likelihood and potential severity of identified hazards.	Historical incident data, exposure limits, process review, lab simulations.
Risk Evaluation	Prioritize risks based on likelihood and severity.	Risk matrix (e.g., 5×5), categorized as high, medium, or low.
Risk Acceptance	Decide which residual risks are tolerable.	Documented justification, cross-functional approval, alignment with regulatory standards.
Risk Reduction	Implement strategies to lower risk probability or severity.	Engineering controls (isolators, ventilation), administrative controls (SOPs, lockout/tag-out), training and competency development.
Control Measures	Continuous monitoring and mitigation of safety risks	Emergency preparedness, incident investigation, CAPA, regular audits, PPE compliance.

Types of Safety Risks in Pharmaceutical Operations

Chemical Hazards

Chemical hazards are among the most important sources of safety risk due to exposure to Active Pharmaceutical Ingredients (APIs), solvents, reagents, intermediates, cleaning agents, and Volatile Organic Compounds (VOCs) in pharmaceutical manufacturing. Such chemicals can have hazardous properties, including toxicity, carcinogenicity, corrosiveness, flammability, or reactive instability. Under containment, Highly Potent APIs (HPAPIs), nitrosamine precursors, and sensitizing compounds (e.g., β-lactams) all benefit from CTELs. Dispensing, charging, reaction steps, filtration, drying, and waste disposal are the major sources of risk. Quantitative exposure assessments, when coupled with engineering containment and concomitant monitoring against Occupational Exposure Limits (OELs), are required to minimize hazards. OSHA, NIOSH, and EMA recommend exposure control strategies based on the Hierarchy of Controls, including elimination, substitution, engineering controls, administrative controls, and personal protective equipment (PPE), to minimize worker exposure to hazardous substances. Continuous industrial hygiene monitoring, including airborne concentration monitoring and occupational exposure assessment against established Occupational Exposure Limits (OELs), is also recommended to ensure worker safety and regulatory compliance (Montgomery, 2020).

Mechanical Hazards

Mechanical hazards happen due to machinery in motion and the presence of equipment components, rotating shafts, blenders, tablet presses, centrifuges, mills, and conveyors. Such hazards comprise entanglement, crushing, shearing, and impact traumas. Pharmaceutical industries may consist of highly intricate automated machines where improper guarding, lack of interlocks, or access during machine operation can result in an accident. There are also risks involved with equipment handling during installation, cleaning, and maintenance. Mechanical hazards: Protective measures include engineering controls such as machinery guarding, emergency stops, ergonomic design, preventive maintenance, and lockout/tag-out (Renard *et al.*, 2021).

Thermal Hazards

Thermal hazards refer to the potential risk associated with processes that involve high-temperature chemical reactions, steam sterilization, autoclaving, drying ovens, lyophilization, and hot transfer lines. Employees may be exposed to the danger of being burnt or under the effect of thermal shocks or thermal cold (cremation freezer, refrigerated rooms). Image by Dan Hennessey from Pixabay Exothermic reactions in API synthesis can cause runaway reaction hazards if there is a failure in temperature control because heat generated is concerned. Precautionary measures including accurate heat transfer control, employing thermal jackets to regulate desired heat flux, continuous monitoring of temperature, and knowing proper PPE are all foundational interventions to control thermal hazards. Thermal safety is also reinforced through the use of emergency cooling systems, temperature alarms, and by validating heat-based sterilization cycles (Dwivedi *et al.*, 2022).

Environmental Hazards

Environmental hazards may arise from improper waste disposal, solvent emissions, microbial contamination, water supply failures, and the release of hazardous chemicals or untreated effluents. Ecosystems may also be impacted by API residues in wastewater. Environmental safety, adhering to EPA and CPCB standards, demanding waste separation, neutralization, solvent recovery, emission controls, and environmental monitoring programs. Additionally, in order to ensure environmental safety as well as product quality, preventing cross-contamination of

manufacturing sectors and reducing biohazard risk are also keys to success (Alexander *et al.*, 2021).

Key Safety Assessment Tools

HAZOP (Hazard and Operability Study)

HAZOP is a team-oriented and systematic analytical technique for assessing deviations of real results from planned functions and their possible consequences. It applies guide words such as "more," "less," "as well as," "reverse," and "other than" for identification of risk in chemical processes, equipment operation and utility systems. HAZOP is commonly used to study API synthesis plants, solvent-handling units, sterile operations, and high-energy reactions in pharmas, as shown in the text box. It allows hazards such as pressure buildup, temperature deviations, flow blockages, mixing failures, contamination points, etc., to be identified. Hazards identified in HAZOP are implemented through engineering controls, alarms, interlocks, and procedural safeguards (Jones *et al.*, 2021).

Hazard Identification and Risk Assessment (HIRA)

Hazard Identification Risk Assessment (HIRA) is a systematic process for the identification of hazards and an assessment of the risk associated with those hazards in the pharmaceutical process. HIRA stands for Hazard Identification and Risk Assessment, an approach to identifying and scoring possible hazards in the workplace, including chemical, mechanical, ergonomic, and environmental hazards by determining their potential severity and likelihood for occurrence in order to prioritize risk control measures. It is "widely utilized in manufacturing facilities as part of routine safety assessments, engineering projects, maintenance planning, pre-startup reviews." HIRA assists in proactive safety management by allowing for the rapid deployment of engineering controls, administrative procedures, PPE requirements and training interventions to minimize the likelihood of accidents, near misses, and occupational exposures (Figure 3) (Matysik, 2022).

Process Hazards Analysis (PHA)

Process Hazards Analysis (PHA)-This is a risk-based approach that assesses hazards related to processes, materials, and equipment. Some PHA methods are what-if analysis, checklist analysis, Failure Mode and Effects Analysis (FMEA), and Fault Tree Analysis (FTA). For chemical operations with a hazardous substance, methodologies to carry out Process Hazard Analysis (PHA) are required in applicable regulatory frameworks, such as OSHA's Process Safety Management (PSM). PHA, in pharmaceutical manufacturing, finds hazards like fire hazards, explosion hazards, toxic release, and failure in operation. This activity is done on a periodic basis during lifecycle safety management, especially at process design, scale-up, or changes in equipment or materials (Moser, 2020).

Chemical Reactivity Hazard Assessment

A chemical reactivity hazard assessment assesses the potential for harmful reactions by heat of formation (e.g., thermal decomposition, polymerization, oxidation) or dangerous reactions between chemicals. Differential Scanning Calorimetry (DSC), Reaction Calorimetry (RC1), Accelerating Rate Calorimetry (ARC), and Thermogravimetric Analysis (TGA) are some of the techniques to evaluate reaction energetics and thermal stability. These evaluations are especially important for API synthesis, scale-up, and solvent changes, as insufficient knowledge of these may result in thermal runaway and/or gas evolution. To address risks associated with Li-ion chemistries,

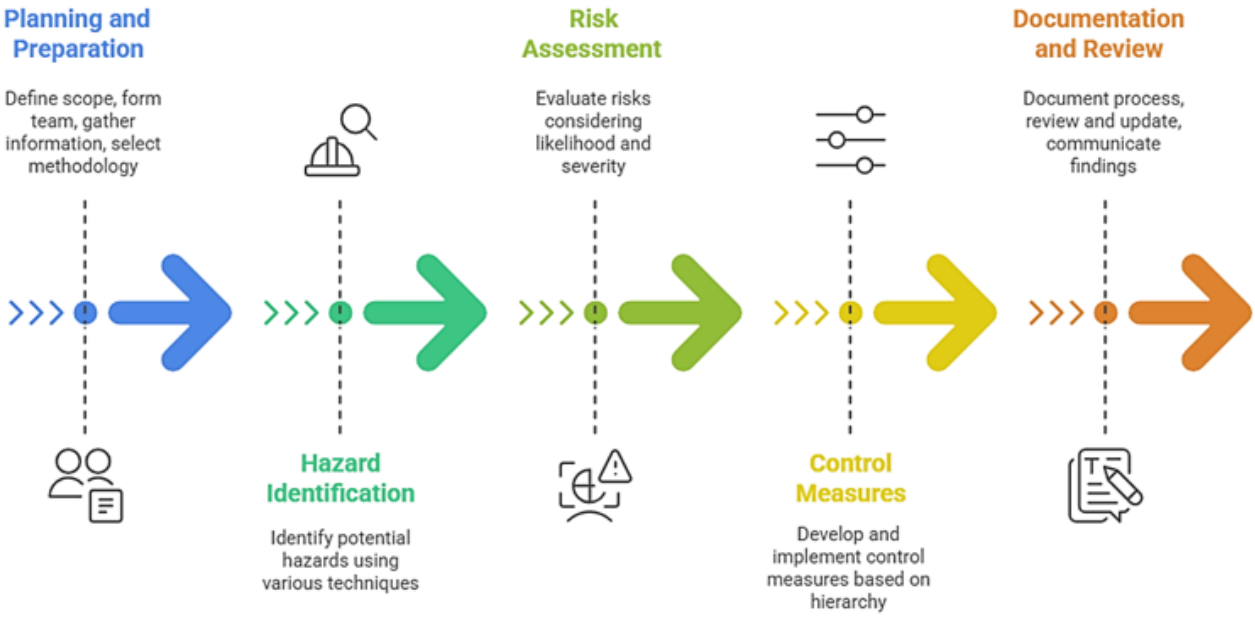

Figure 3: Process Steps for Hazard Identification and Risk Assessment (HIRA).

risk mitigation strategies can be developed that include control of reaction kinetics, validated thermal propagation control systems, safe charging sequences, venting of escape products, and segregation of incompatible chemicals and other hazards (Elder *et al.*, 2020).

Safety Management Strategy in Pharmaceutical Operations

Training and Competency Development

The first step of all safety management systems is to have a competent training system, which is also applicable to personnel. Which includes chemical hazards, safe equipment operation, emergency, PPE, containment systems, regulatory, etc. To ensure consistency and reduce or eliminate human error, competency assessments, refresher training, and job-specific certifications are performed. Safety culture is solidified even more throughout your organization with behavioral safety programs.

Engineering Controls

Engineering controls, which are the first line of defense against workplace hazards, include containment isolators, glove boxes, laminar airflow hoods, negative-pressure rooms, dust collectors, HEPA filtration, pressure relief systems, explosion-proof equipment, and interlocks. Such systems limit the exposure of workers to toxic chemicals, high-potency active pharmaceutical ingredients, thermal hazards, and mechanical hazards. Engineering controls are the first line of defense in a containment strategy for high-potency manufacturing (Griesenauer *et al.*, 2021).

Administrative Controls

Administrative controls can include procedures described in the SOPs, Work Permits, LOTO (Lockout/Tag-Out) procedures, shifts and access control procedures, housekeeping standards, and signage. These controls mitigate risk when engineering controls are not possible. Standardized procedure documentation is important for ensuring consistency across processes, especially concerning solvent handling, cleaning of equipment, changeover between batches, and maintenance work. Administrative controls also help ensure compliance with regulatory frameworks like OSHA and GMP obligations (Teasdale, 2020).

Incident Investigation and CAPA

Part of the safety management process, incident investigation is the process of determining the root cause of a near miss, accident, equipment failure, and deviation. Root Cause Analysis (RCA), 5-Why analysis, and fishbone diagrams are some of the tools that can give clarity to what is causing the problems. The CAPA (Corrective and Preventive Action) system makes sure that corrective action is about the root cause and preventive action is to avoid recurrence. Investigation findings inform training, SOPs, processes, and risk assessments, and a feedback loop builds the new knowledge in the safety culture (Crowl and Louvar, 2021).

PROCESS RISK ASSESSMENT IN PHARMACEUTICAL MANUFACTURING

Process risk analysis as an element of worldwide pharmaceutical Quality Risk Management (QRM) lays out the application of both quantitative and qualitative methods to ensure that manufacturing processes will always produce products with required quality, safety and efficacy. Based on ICH Q8, Q9(R1), Q10 and Q11 concepts, it permits a systematic understanding of process variability, identification of potential failure modes, and robust control strategy design over the product life cycle. Five key activities comprise this process: risk identification, risk analysis, risk evaluation, risk acceptance and risk reduction, each of which plays an important part in developing a simple, compliant, and scientific basis for a controlled manufacturing system. The fundamental purpose of process risk assessment is to develop a thorough, scientifically rational knowledge of the impact of formulation variables, material properties, and process parameters on the Critical Quality Attributes (CQAs) of

Table 3: Process Risk Assessment Steps and Control Measures.

Step	Description	Control Measures/Examples
Risk Identification	Identify potential process hazards affecting quality, safety, or compliance.	Mapping CPPs/CQAs, reviewing raw materials, equipment, human factors, historical deviations.
Risk Analysis	Assess likelihood and impact of identified risks.	FMEA scoring, statistical analysis, DoE, historical process data.
Risk Evaluation	Prioritize risks based on predefined criteria.	Risk matrix (5×5), RPN ranking, categorized as high, medium, or low.
Risk Acceptance	Decide which residual risks are tolerable.	Documented justification, cross-functional approval, alignment with regulatory requirements.
Risk Reduction	Implement strategies to lower risk severity or probability.	Process optimization, material controls, equipment/facility controls, PAT monitoring, human reliability measures.
Control Measures	Continuous monitoring and mitigation to maintain process robustness	Real-time PAT monitoring, SPC/trend analysis, SOPs, training, preventive maintenance, CAPA.

a drug product. This facilitates the definition of Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) that need to be controlled in order to achieve reproducible product performance and quality (Table 3) (European Medicines Agency [EMA], 2020).

Tools and Methods for Process Risk Assessment

Failure Mode and Effects Analysis (FMEA)

FMEA (Failure Mode Effects Analysis) FMEA is a prevalent quantitative risk assessment tool in pharmaceutical manufacturing because it provides a structured approach to numerically score failure modes, their potential impact on product quality, and the likelihood of occurrence using a defined scoring scale and logic. The output is a Risk Priority Number (RPN=Severity × Occurrence × Detectability), which can be used to prioritize the most serious risks that need to be mitigated. The FMEA is used in unit operations such as weighing, blending, granulation, drying, tableting, capsule filling, coating, sterilization, filtration, lyophilization, and packaging. It is similarly employed in Analytical Method Development (AM-FMEA), Equipment Qualification (EQ-FMEA), Cleaning Validation (CV-FMEA), as well as supplier risk evaluation. FMEA forms a critical QbD tool for a selection of factors for DoE, a definition of design space, and justification of CPP-CQA relationships (European Medicines Agency [EMA], n.d.).

Hazard Analysis and Critical Control Point (HACCP)

HACCP is a rational, preventive, and systematic risk assessment tool that was originally developed for the food industry through a collaborative program involving NASA, the Pillsbury Company, and the U.S. Army Laboratories to ensure food safety for space missions. It has since been widely adopted in pharmaceutical manufacturing, vaccine production, biotechnology operations, and other high-risk processes. Instead of identifying all potential hazards, HACCP narrows it down to those that would impact the sterility, integrity, or purity of a product, while also establishing Critical Control Points (CCPs), the parameters of which must be monitored to avoid contamination or a deviation from the process. Example CCPs cover aseptic connections, filtration steps, sterilization cycles, bioburden control, lyophilization parameters, transport packages, environmental monitoring, and container closure integrity. HACCP is the key for prevention of microbial contamination, endotoxin, and adventitious agent and introduction which are the requirements of EU GMP Annex 1 (Sterile Products), WHO TRS, and FDA aseptic guidelines (U.S. Food and Drug Administration [FDA], 2020).

Process Analytical Technology (PAT) Integration

PAT is one of the key contributions to process risk mitigation in modern operations practice, forging real-time monitoring of critical process variables or quality attributes. PAT tools consist of spectroscopy (NIR, Raman, UV-vis), particle-size analyzers, in-line moisture probes, automated sampling systems, chemometric models (PCA, PLS), multivariate data analytics software, etc. PAT lowers risk by removing uncertainty, reducing human sampling errors, forecasting deviations, and facilitating Real-Time Release Testing (RTRT). Addition of PAT enables support of FDA Process Validation Stage 3 requirements related to Continued Process Verification (CPV) and ICH Q8-Q10 expectations of broader process knowledge. PAT is crucial in enhancing process robustness and providing greater control than traditional offline testing by delivering rapid feedback on blend uniformity, granule moisture, crystallization end-point determination, coating thickness, and other critical manufacturing parameters.

Process risk assessment combines risk identification, risk analysis, risk evaluation, risk acceptance, and risk reduction, which guarantees the manufacturable process is controlled and predictable throughout the product lifecycle and adheres to compliance. Structured QRM tools as well as data-driven methods allow for identifying vulnerabilities early on, and decisions in pharmaceutical manufacturing can be supported by science (Medicines and Healthcare products Regulatory Agency [MHRA], n.d.).

NITROSAMINE RISK ASSESSMENT IN PHARMACEUTICAL PRODUCTS

Pharmaceutical quality control requires the risk assessment of nitrosamine impurities like NDMA and NDEA, which are suspected human carcinogens. Beyond NDMA and NDEA, several other small-molecule nitrosamines have been found in APIs and drug products up to 2025, including NMPA, NDIPA, NIPEA, NDBA, NMBA, and NDSRIs formed from API structural moieties. The systematic risk assessment method identifies API synthesis routes, residual solvents and reagents, nitrite-containing excipients, packaging interactions, solvent recycling, and degradation pathways as potential sources of nitrosamines. Amine functionalities, nitrosating agents, critical process parameters, and storage conditions drive risk evaluation, supported by mechanistic nitrosation chemistry. International regulatory requirements like ICH M7(R2), EMA, and US-FDA guide product classification and control according to strict Acceptable Intake (AI) limits. Risk mitigation includes procedure modification, elimination of amine-nitrite coexistence, enhanced raw material nitrite specifications, process optimization, and supplier qualification. High-sensitivity analytical methods (GC-MS, LC-MS/HRMS) ensure nitrosamine levels stay below regulatory limits. To prevent patient exposure to carcinogenic impurities (Figure 4), nitrosamine risk assessment uses chemical insight, advanced analytics, and quality risk management (Tables 4 and 5) (U.S. Food and Drug Administration [FDA], n.d.).

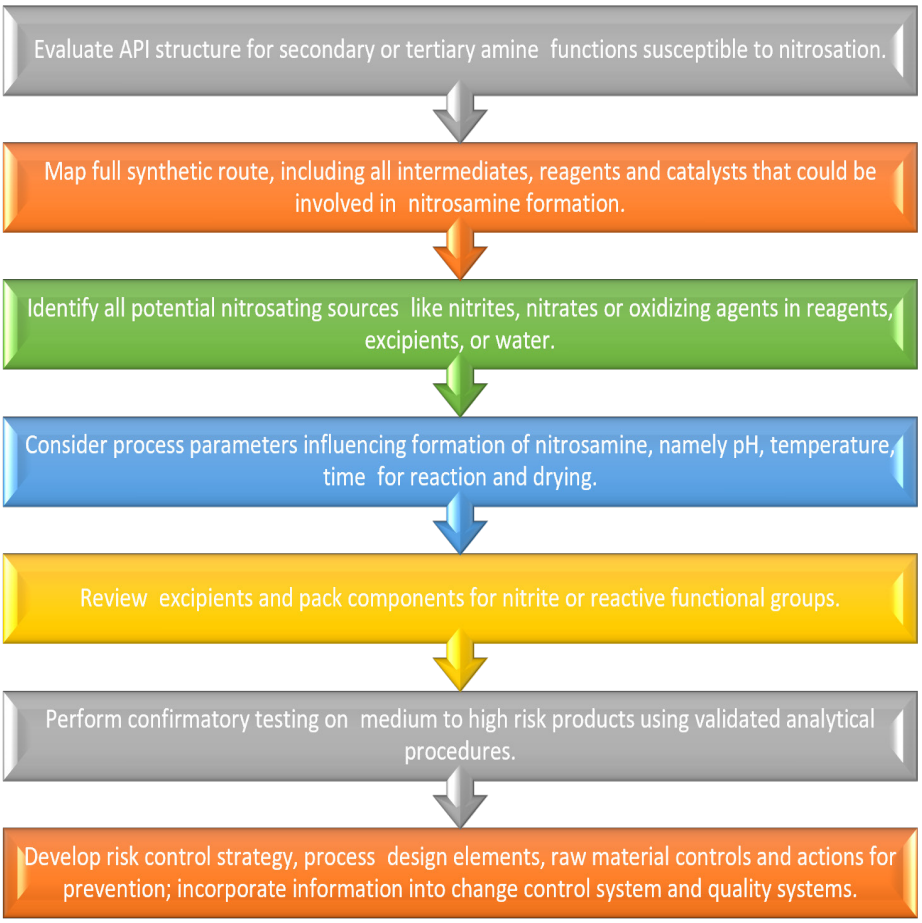

Figure 4: Methodology of Nitrosamine Risk Assessment.

Sources of Nitrosamine Contamination

Nitrosamine formation in pharmaceutical products can occur from multiple sources:

- **API synthesis pathways:** Secondary and tertiary amines in the synthetic route may react with nitrosating agents under acidic or high-temperature conditions. Intermediates or reaction by-products may also generate nitrosamines.
- **Solvents and reagents:** Contaminated or recycled solvents and nitrite-containing reagents can introduce nitrosating species during reactions or workup steps.
- **Excipients:** Some excipients may contain residual nitrites or react with amine groups, contributing to nitrosamine formation during processing or storage.
- **Packaging components:** Materials such as rubber stoppers or plasticizers may release nitrosating agents that interact with drug substances.
- **Degradation pathways:** Environmental factors like heat, humidity, or light can induce chemical degradation of amine-containing APIs or excipients, leading to nitrosamine formation during storage or shelf life (World Health Organization [WHO], n.d.).

FDA Recommendations

The FDA requires API and drug product manufacturers to assess and prioritize nitrosamine risks based on dose, treatment duration, and patient exposure due to their carcinogenicity. The Agency has strict acceptable intake limits for single nitrosamines and overall assessment for multiple impurities. FDA initially expected confirmatory testing and submission of the required modifications for products at risk of Nitrosamine Drug Substance-Related Impurities (NDSRIs) through August 1, 2025, but it recognizes that this timeline may not be achievable for all products and allows affected applicants to submit a progress update by August 1, 2025 (Figure 5) (U.S. Food and Drug Administration [FDA], n.d.).

Regulatory Expectations

Risk assessment of all nitrosamine-related drugs should be conducted by regulatory bodies, including the US-FDA, EMA, MHRA, WHO and ICH, across APIs, drug products, excipient systems, devices, or packaging components from the

manufacturing source. High-risk products need to be analyzed with ultralow limits of quantification (LC-HRMS, GC-MS) and producers should justify the lack of risk in such cases. All identified nitrosamines are required to be controlled below Acceptable Intake (AI) limits with appropriate control throughout the life cycle, including timely reporting of findings in accordance with ICH M7(R2) and international regulatory expectations (Health Canada, n.d.).

Methodology of Nitrosamine Risk Assessment

A systematic approach is applied to assess and mitigate nitrosamine risk:

Control and Mitigation Measures

The following control measures are recommended to avoid or reduce the formation of nitrosamines:

- Consider substitution of nitrite reagents with a safer alternative, or include removal of the nitrosating agent in your process.
- Amines should not be allowed to coexist with nitrites in any reactions or storage.
- Employ new solvents, not recycled streams with possible traces of nitrites or contamination.

Figure 5: Decision tree with control options for products containing multiple N-nitrosamines. Adapted from Swissmedic guidance on nitrosamine risk evaluation.

- Establish strict nitrite content specifications for raw materials to apply pressure on incoming materials against challenging quality requirements.
- Add scavengers or change processes to mitigate nitrosation, including pH adjustment, temperature change, changes in order of reaction or addition of quench (Therapeutic Goods Administration [TGA], n.d.).

INTEGRATED APPROACH: LINKING PROCESS, SAFETY, AND NITROSAMINE RISK ASSESSMENT

Why Integration Is Essential

It's essential to consolidate your process, safety and nitrosamine risk assessment methods to maintain the quality of products, employee protection and regulatory adherence over time as drugs evolve (Figure 6). Stand-alone risk evaluations can generate disparate, or potentially conflicting, measures for mitigation, whereas a consolidated approach enables comprehensive analysis of the interaction between process parameters, equipment design and arrangements, materials used and operations. Such modification of a process with the purpose of being able to achieve higher yields or to decrease impurity levels may introduce unintended chemical, thermal, or mechanical hazards or environments that are favorable for nitrosamine formation. Likewise, if equipment is modified or there are updates to the cleaning process then product quality may be affected in parallel with contamination risk, and when changing suppliers, then the potency of raw material, the profile of impurities and the potential for nitrosamines can also vary. By having a unified framework for sizing all possible risks, decisions can be made in an informed and science-based manner that integrates safety, quality, and regulatory expectations (Table 6) (Pharmaceuticals and Medical Devices Agency [PMDA], n.d.).

Components of an Integrated Framework

Comprehensive integrated risk assessment system: multiple tool cross-functional collaboration and digital surveillance range to realize the strong control of risk:

Table 4: Nitrosamine Risk Assessment Steps and Control Measures.

Step	Description	Control Measures/Examples
Risk Identification	Identify potential sources of nitrosamine contamination.	API synthesis pathways, solvents/reagents, excipients, packaging components, degradation pathways.
Risk Analysis	Assess likelihood and severity of nitrosamine formation.	Evaluate API structure, map synthetic route, identify nitrosating agents, review process conditions.
Risk Evaluation	Prioritize risks based on potential patient exposure.	Use a risk matrix or risk scoring; consider Acceptable Intake (AI) limits.
Risk Acceptance	Decide which residual risks are tolerable.	Justification based on analytical data, regulatory guidance (ICH M7(R2)), and product safety.
Risk Reduction / Control	Implement measures to minimize nitrosamine formation.	Replace nitrite-containing reagents, avoid amine-nitrite coexistence, use fresh solvents, use tight raw material specs, and introduce scavengers or process modifications.
Monitoring and Verification	Continuous monitoring to ensure mitigation effectiveness.	Analytical testing (LC-MS, GC-MS), in-process sampling, trend analysis, change control updates.

Table 5: Historical Emergence and Acceptable Intake Limits of Key Nitrosamine Impurities.

Nitrosamine Impurity	Year First Reported	Associated Drug Class/Product	Acceptable Intake (AI)
NDMA (N-nitroso dimethylamine)	2018	ARBs (e.g., valsartan)	96 ng/day
NDEA (N-nitrosodiethylamine)	2018	ARBs and antihypertensive products	26.5 ng/day
NMPA (N-nitrosomethylphenylamine)	2019	Amine-containing small-molecule APIs	34 ng/day
NDIPA (N-nitrosodiisopropylamine)	2019	APIs involving diisopropylamine impurities	26.5 ng/day
NIPEA (N-nitrosoisopropylphenylethylamine)	2019-20	Complex amine-containing APIs	26.5 ng/day
NDBA (N-nitrosodibutylamine)	2020	Products with dibutylamine intermediates/excipients	26.5 ng/day
NMBA (N-nitroso-N-methyl-4-aminobutyric acid)	2020	H_2-receptor antagonists (e.g., ranitidine)	96 ng/day

Combined FMEA + HAZOP + Nitrosamine Checklist

A mixed approach as this enables the quantitative and qualitative benefits of the tools to be harnessed, thus being able to study risk-related (like process, safety and nitrosamine) risks concurrently for which previously separate studies were conducted. Thus, FMEA can provide the degree of the severity impact on CQAs, whereas HAZOP generates the deviations and operational hazards, and nitrosamine checklists help to be foresightful in assessing likely sources of contamination.

Cross-functional Risk Review

QA, QC, Production, EHS, RA, and R&D teams are involved to have an interdisciplinary perspective. By doing so, this collaboration enables the identification of risks that might not be captured within a single silo and thereby promotes collective responsibility for mitigating strategies (European Medicines Agency [EMA], n.d.).

Digital Dashboards for Real-Time Monitoring

Process Analytical Technology (PAT), automated sensors, and data analytics platforms combine to ensure there is continuous tracking of CPPs, CQAs, environment parameters and nitrosamine indicators. Through digital dashboards, trends and deviations can be visualized along with early warnings and allow you to intervene proactively before risks affect your product quality or safety.

Table 6: Process Hazards, Safety Risks, and Nitrosamine Risk Assessment in Pharmaceutical Manufacturing.

Risk Category	Type of Hazard/Risk	Key Sources/Examples	Risk Assessment Tools	Control and Mitigation Measures
Process Risk	Process variability	CPP/CMA drift, scale-up changes, operator intervention.	FMEA, DoE, PAT, HACCP.	Control strategy, process optimization, SPC, PAT monitoring.
	Raw material risk	Variable API quality, excipient impurities.	Supplier risk assessment, FMEA.	Supplier qualification, tighter specs, incoming testing.
	Equipment risk	Aging equipment, cross-contamination.	FMEA, HACCP.	Preventive maintenance, closed systems, cleaning validation.
	Analytical risk	Method variability, low sensitivity.	QbD for analytics, Q14.	Method robustness, validation, lifecycle management.
Safety Risk	Chemical hazards	Solvents, reagents, potent APIs.	HAZOP, PHA, HIRA, OEB.	Containment, isolators, LEV, PPE.
	Mechanical hazards	Moving equipment, pressure systems.	HIRA, PHA.	Machine guarding, interlocks, LOTO.
	Thermal hazards	High-temperature reactions, steam systems.	HAZOP, HIRA.	Insulation, alarms, temperature control.
	Occupational exposure	HPAPIs, dust, vapors.	OEB, HIRA.	Engineering controls, SOPs, PPE.
	Environmental hazards	Waste solvents, emissions.	EHS risk assessment.	Waste treatment, emission control.
Nitrosamine Risk	Synthetic route risk	Amine + nitrite coexistence.	Nitrosamine risk mapping, FMEA.	Route redesign, reagent substitution.
	Raw material contamination	Nitrite in excipients, solvents.	Supplier risk assessment.	Tight nitrite limits, vendor audits.
	Solvent recycling	Amine carryover.	Process risk assessment.	Use fresh solvents, purification.
	Degradation pathways	Heat, oxidation, pH.	Stability risk assessment.	Formulation optimization, antioxidants.
	Packaging interaction	Rubber stoppers, inks.	Migration risk assessment.	Packaging change, compatibility studies.
	Multiple nitrosamines	Cumulative carcinogenic risk.	Cumulative exposure assessment (ΣR).	Mitigation, regulatory engagement.

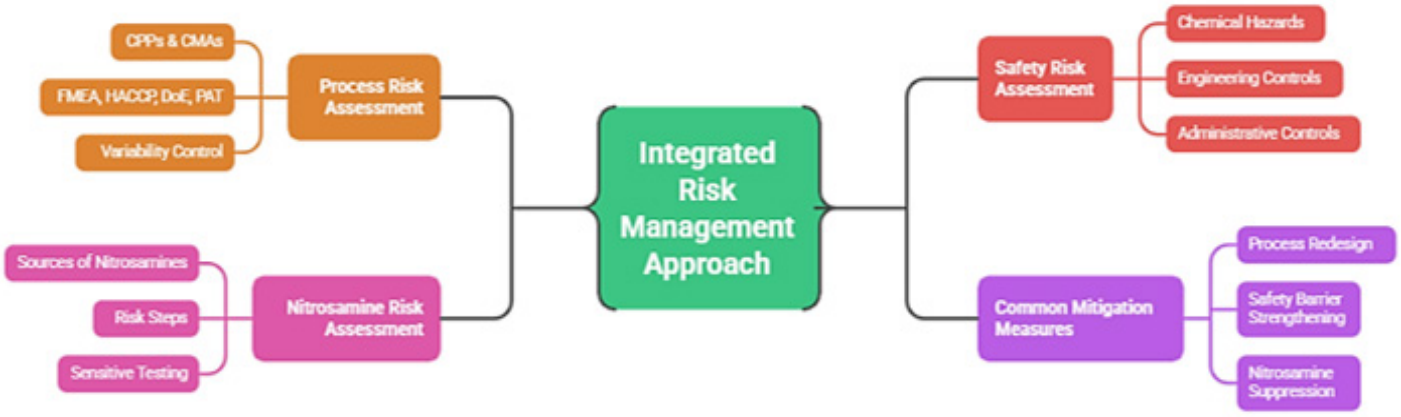

Figure 6: Integrated risk management approach.

Continuous Improvement through Trend Analysis

As the situation changes and historical information becomes available, risk is reassessed through logs, deviation reports in CAPA investigation and environmental monitoring to allow model evolution. Trend analysis enables the identification of developing risks as well as the optimizing of control measures (U.S. Food and Drug Administration [FDA], n.d.).

Documented Lifecycle Risk Management (ICH Q10)

All risk assessments, mitigation plans and reassessment results are documented to maintain alignment with the regulations outlined in ICH Q10 for a pharmaceutical quality system. Traceability and accountability are preserved, even supporting regulatory submissions, inspections, and post-approval change management (International Agency for Research on Cancer [IARC], n.d.).

GAPS IN CURRENT INDUSTRIAL PRACTICE

Notwithstanding major advances in regulatory guidance and the increasing availability of systematic methods for risk assessment, important deficiencies remain in the pharmaceutical industry that prevent the implementation of a comprehensive and complete risk management framework. Across organizational, technological, and knowledge limits, there remains a need for increasing compatibilization of process, safety, and nitrosamine risk-assessment paradigms.

Inconsistent Adoption of Proactive Risk Assessment Across Units

Work such as FMEA, HACCP, HAZOP, and nitrosamine risk assessments are established frameworks, but their usage continues to fluctuate between manufacturing locations, departments, and product lines. Much of the activity across units is reactive-investigating deviations after failures have occurred-rather than structured proactive methodologies during development, scale-up and routine manufacturing. Such inconsistencies result in unpredictable quality of identifying risks, insufficient anticipation of deviations in processes, and non-standardized deployment of mitigation measures (Bakeev, 2021).

Limited Integration of Digital Monitoring Tools (AI, ML, PAT)

In many facilities, digital transformation adoption remains slow across many facilities. Despite powerful AI-based and other tools like multivariate PAT models, predictive maintenance algorithms, and machine-learning-enabled impurity prediction, the routine risk assessment does not leverage these to the full extent. This lack of digital data connectivity produces slower process-drift detection, less than optimal control-strategy optimization, and lost opportunities for instant decision-making. Most facilities still depend on human interpretation of data and thus the possibility of overlooking and subjectivity is high (García-Muñoz *et al.*, 2020).

Gaps in Training and Awareness Regarding Nitrosamine Chemistry and Safety Hazards

In production, QA, QC and R&D staffs have almost no knowledge available on the nitrosamine-forming reaction, its degradation pathway and the influence of process parameters such as pH, temperature, presence of amine and nitrite solvent recycle. Similarly, safety knowledge on reactivity hazards, thermal runaway and occupational exposure limits is often inadequate. Inadequate training in the domain of competency building heightens the risk that hazards are scored incorrectly and data is misinterpreted (Li *et al.*, 2023).

DISCUSSION

In this narrative review, the results are presented as thematic syntheses rather than experimental outcomes. The findings derived from the analyzed literature and regulatory guidance are integrated across three major domains: process risk assessment, safety risk assessment, and nitrosamine risk assessment. The review highlights that process-related risks are primarily associated with variability in critical process parameters, raw material quality, and equipment performance, which can be effectively mitigated using

structured tools such as FMEA, DoE, and PAT. Safety-related findings emphasize chemical exposure, mechanical and thermal hazards, and occupational risks, with HAZOP, HIRA, and OEB emerging as key assessment methodologies. Notably, the results underscore a growing regulatory focus on nitrosamine impurities, revealing common sources, risk factors, acceptable intake limits, and the necessity for cumulative exposure evaluation and decision-tree-based control strategies. Collectively, these results demonstrate the importance of an integrated, lifecycle-oriented risk management framework to enhance product quality, patient safety, and regulatory compliance.

CONCLUSION

Effective risk assessment has become central to the successful pharmaceutical manufacturing of today in the climate of increasingly complex processes, with a higher focus on regulation and patient safety scrutiny becoming a way of life. Process risk assessment helps achieve consistent product quality by identifying potential failure modes, determining root causes, optimizing critical process parameters, and establishing science-based control strategies throughout the product lifecycle, including process characterization as well as developing science-based control strategies in a product lifecycle. It is also supplemented by other safety risk assessments to stop warnings in the work area and reduce the threat of chemical and mechanical and increase operational dependability with solid techniques like HAZOP, PHA and HIRA. The later discovery of nitrosamine impurities has further increased the need for powered-by-chemistry risk assessment, backed up by high-sensitivity analytical capabilities and end-to-end supply-chain control. Integrating all three dimensions of process, safety and nitrosamine risk into a single approach offers the strongest foundation for balancing product quality assurance, regulatory compliance and worker protection. NDMA, NDEA, NMBA, and other nitrosamine impurities have shown the need for chemistry-based evaluation, confirmatory testing, and lifecycle control to prevent carcinogenic exposure. Process, safety, and impurity risks are well-managed using proactive identification, analytical monitoring, and reactive mitigation measures. Although some of these data-driven techniques are beginning to flow across complete supply chains, gaping holes persist in end-to-end digital adoption, supplier management inheritances, the maturity of real-time monitoring and harmonized data docs. In order to progress we encourage the wider use of PAT, automation, AI-driven prediction tools and the principles underpinning Continuous Improvement in line with ICH Q9(R1), Q10/Q12. Taken in total, these principles as lifecycle based, data driven and cross- functional risk management framework provide a means to move the industry to focus on prevention of problems rather than reactive problem solving with the intent of ensuring that safe effective medicines are available to patients.

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ABBREVIATIONS

AI: Acceptable Intake; **API:** Active Pharmaceutical Ingredient; **CAPA:** Corrective and Preventive Action; **CPP:** Critical Process Parameter; **CQA:** Critical Quality Attribute; **DoE:** Design of Experiments; **EHS:** Environment, Health and Safety; **EMA:** European Medicines Agency; **FMEA:** Failure Mode and Effects Analysis; **GC-MS:** Gas Chromatography-Mass Spectrometry; **HAZOP:** Hazard and Operability Study; **HIRA:** Hazard Identification and Risk Assessment; **ICH:** International Council for Harmonisation; **LC-HRMS:** Liquid Chromatography-High Resolution Mass Spectrometry; **ML:** Machine Learning; **NDMA:** N-nitrosodimethylamine; **NDEA:** N-nitrosodiethylamine; **NDSRI:** Nitrosamine drug substance-related impurity; **NMBA:** N-nitroso-N-methyl-4-aminobutyric acid; **OEB:** Occupational Exposure Band; **PAT:** Process Analytical Technology; **PHA:** Process Hazard Analysis; **QbD:** Quality by Design; **QC:** Quality Control; **QRM:** Quality Risk Management; **RA:** Regulatory Affairs; **RCA:** Root Cause Analysis; **ROS:** Route of Synthesis; **SOP:** Standard Operating Procedure; **SPC:** Statistical Process Control; **WHO:** World Health Organization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Mayur R. Dandekar contributed to the literature search, data curation, and writing of the original draft. Ms. Swati Satalkar (Senior General Manager, Micro Labs Limited R&D, Mumbai) contributed to the methodology, framework development, manuscript review and editing, visualization, and figure preparation. Dr. Deepak Khobragade (Professor & Dean) provided supervision and critically revised the manuscript. Dr. Pankaj Mandpe (Executive Vice President Micro Labs Limited R&D, Mumbai) contributed to the conceptualization, supervision, and final review of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for the integrity and accuracy of the work.

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