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Short communication

Application of Quality Risk Management principles in nitrosamine risk assessment and control

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Introduction

Nitrosamine impurities became a major concern for the pharmaceutical industry when they were detected in sartan-based antihypertensives, ranitidine, and metformin. Because nitrosamines are potentially carcinogenic, these findings triggered swift regulatory action, resulting in comprehensive requirements for the identification, assessment, and control of nitrosamine impurities across the entire product lifecycle (EMA, 2020; FDA, 2021).

Because nitrosamines can arise through many pathways and their sources are not always obvious, a systematic, science-based approach is essential. Quality Risk Management (QRM), as outlined in ICH Q9(R1), provides a structured framework for identifying, analysing, controlling, and reviewing quality-related risks (ICH, 2023).

This paper reviews how QRM principles apply to nitrosamine risk assessment and discusses current regulatory expectations for pharmaceutical manufacturers.

Methodology

This paper is based on a review of regulatory guidelines and scientific publications on nitrosamine impurities and pharmaceutical QRM, covering documents from ICH, EMA, and FDA issued between 2018 and 2025. Sources were selected for direct relevance; a comparative, critical evaluation was used to identify areas of agreement and divergence between regulatory expectations and scientific evidence. All findings were then organised within the five-step QRM framework: risk identification, risk analysis, risk evaluation, risk control, and risk review.

Discussion

The reviewed literature confirms that QRM is central to current regulatory expectations for managing nitrosamine risks.

Risk identification

Identifying where nitrosamines might enter a product is the first and arguably the most important step. Potential sources are wide-ranging: active pharmaceutical ingredients (APIs), excipients, solvents, reagents, recovered materials, water systems, manufacturing equipment, and packaging components all need to be considered (EMA, 2020).

APIs containing secondary or tertiary amine groups are particularly susceptible when they come into contact with nitrosating agents, as illustrated by the formation of N-nitrosodimethylamine (NDMA) in valsartan, where dimethylformamide (DMF) used as a process solvent acted as the nitrosamine precursor (Bharate, 2021). Excipients also deserve careful attention, as trace nitrite levels can vary considerably between suppliers and batches (Boetzel et al., 2022).

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Risk analysis

Risk analysis examines both materials and the manufacturing process: high temperatures, acidic environments, and the simultaneous presence of amines and nitrosating agents all increase the likelihood of nitrosamine formation. A thorough analysis combines a review of raw material chemistry with an assessment of critical process parameters (FDA, 2021).

Risk evaluation

Risks are then ranked by priority using structured tools such as Failure Mode and Effects Analysis (FMEA) or risk decision trees, as recommended in ICH Q9(R1) (ICH, 2023). Products combining amine-containing structures with likely nitrosating agents are considered higher risk and typically require confirmatory analytical testing, while products lacking these characteristics may be placed in a lower-risk category.

Risk control and review

Risk control focuses on reducing the probability or severity of nitrosamine risks, for example by substituting problematic solvents such as DMF, setting nitrite specifications on excipients, and implementing targeted analytical testing (EMA, 2020; ICH, 2023). Risk review closes the QRM cycle: outputs must be revisited periodically, triggered by changes to materials, suppliers, or processes, or by new regulatory guidance; given the pace of change around NDSRIs, an annual review is considered good practice (EMA, 2023; FDA, 2021).

Emerging focus: NDSRIs

A significant recent development is the growing regulatory focus on Nitrosamine Drug Substance-Related Impurities (NDSRIs) - nitrosamines originating from the API itself rather than external sources. A well-known example is N-nitroso-lisinopril, formed directly from the lisinopril molecule; because NDSRIs are structurally diverse and toxicological data are often limited, each requires a tailored, product-specific scientific evaluation (EMA, 2023). This marks a broader shift away from generic control strategies towards product-specific assessments rooted in the chemistry of each individual medicine, a more demanding but more accurate approach to managing real-world risk.

Conclusion

Nitrosamine impurities remain one of the most significant quality and safety challenges facing the pharmaceutical industry. Applying QRM principles offers a structured, scientifically credible way to address risk identification, analysis, evaluation, control, and review in a consistent manner. Effective risk management in this area requires a thorough understanding of raw materials, manufacturing processes, and product-specific properties. A proactive QRM approach enables manufacturers to build genuinely robust control strategies across the full product lifecycle - not merely to meet regulatory requirements, but as the most reliable means of keeping nitrosamine risks under sustainable control.

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