Managing Nitrosamine Risks Across the Product Lifecycle

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Nitrosamine impurities have emerged as a significant challenge in the pharmaceutical industry due to their carcinogenic potential and unexpected presence in various drug products. Regulatory authorities including the FDA, EMA, and WHO have responded with strict requirements for identification, risk assessment, and control of these impurities. While guidance continues to evolve, implementation remains complex. Jason Brown and Kim Huynh-Ba present a practical, science-based approach to managing nitrosamine risks throughout the product lifecycle—grounded in ICH Q9 and Q10 principles. (1)

Nitrosamines typically form when secondary or tertiary amines react with nitrite under acidic conditions. These reactions can occur during synthesis, storage, or even packaging. Common sources of risk include APIs with amine groups, excipients or raw materials containing nitrite, and manufacturing conditions such as pH, moisture, or temperature. Unexpected contamination events have led to global recalls, making nitrosamine control a high priority for industry.

Step 1: Risk Identification

The first step in a robust control program is a thorough risk assessment. Each material used—API, excipients, solvents, and packaging—should be reviewed for potential to form nitrosamines. Risk identification is most effective when driven by a cross-functional team that understands raw material properties, synthetic routes, and storage conditions. Using a structured framework, companies can prioritize high-risk products and processes for further investigation.

Step 2: Risk Evaluation and Root Cause Analysis

If risk is identified and observed to be present during preliminary testing, a root cause investigation should follow. This includes evaluating known nitrosation mechanisms, process conditions, and structural vulnerabilities in ingredients. For example, if secondary amines and nitrites coexist under acidic conditions, formation is likely. To fully understand these pathways, companies may need to review batch records, test raw materials for nitrite levels, and conduct small-scale experiments. These insights support the development of a focused and effective control strategy that will stand the test of time.

Step 3: Confirmatory Testing and Toxicology

When a credible risk exists, confirmatory testing is required to determine actual nitrosamine levels in the product. Validated analytical methods such as LC-HRMS, LC-

MS/MS, and GC-MS are commonly used, depending on the analyte's properties. Testing should cover multiple batches and span the full product shelf life.

If nitrosamines are detected, acceptable intake (AI) limits must be applied. For compounds lacking full toxicological data, predictive tools such as structure-activity relationship (SAR) modeling or the Carcinogenic Potency Categorization Approach (CPCA) can help establish provisional limits if they are not already provided by the appropriate regulatory agency. These limits guide both specification setting and risk management decisions.

Step 4: Control Strategy Development

The heart of nitrosamine mitigation is a control strategy tailored to the specific risks identified. This includes preventive actions such as redesigning synthetic routes, sourcing low-nitrite materials, or altering process parameters like pH. When formation cannot be appropriately prevented, mitigation measures—like adding antioxidants or tightening process controls—should be implemented. While this redesign is in progress, temporary limits may be agreed upon in order to maintain drug supply.

Control strategies must be documented, regularly reviewed, and integrated into the broader pharmaceutical quality system. They should clearly define critical materials and process inputs, along with their control limits and justification.

Step 5: Monitoring and Lifecycle Management

Long-term monitoring is essential to verify that the strategy remains effective. Raw material testing, routine in-process checks, and final product stability testing are all tools to detect changes over time. Regulatory guidance suggests adjusting the frequency of nitrosamine testing based on observed levels: minimal testing may be acceptable if levels are consistently below 10% of the AI; values above 30% require more frequent testing.

Lifecycle management ensures that any changes to materials, suppliers, or processes prompt a reassessment of risk. All updates should be documented, and control strategies revised accordingly. Maintaining current and accurate records is key for compliance and readiness for inspections.

Implementation and Cross-Functional Execution

Implementing control strategies requires collaboration across departments. SOPs must be updated, suppliers informed of new expectations, and analytical labs prepared for the demands of new techniques. Changes should be integrated into existing quality systems—including change control, supplier qualification, and training programs. It's critical that teams work in alignment to ensure timely execution and regulatory compliance.

Culture of Prevention

Beyond process controls, the paper emphasizes the need for a culture of proactive quality. Nitrosamine control is not just a technical fix; it reflects an organization's broader commitment to product safety. Encouraging risk-based thinking and cross-functional engagement helps ensure that control strategies are both effective and sustainable.

Conclusion

Nitrosamine control is now an integral part of pharmaceutical manufacturing and quality systems. It demands a science-based, lifecycle-focused approach—starting with thorough risk assessments and ending with long-term monitoring and continuous improvement. Preventive design, confirmatory testing, and cross-functional implementation are key to staying compliant and protecting patients.

As regulatory expectations continue to evolve, companies that embed nitrosamine control into their development and commercial operations will be better positioned to respond quickly, reduce risk, and maintain trust.

Reference:

1. Nitrosamine Control Strategies: From Risk Identification to Implementation, Jason Brown*, Adare Pharma Solutions and Kim Huynh-Ba, Pharmalytik, LLC, AAPSNewsMagazine, September 2025.