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Pharma still hasn't solved its nitrosamine problem

A cascade of high-profile drug recalls and evolving FDA and EMA guidance have pushed nitrosamine risk assessment from a late-stage afterthought to an early-development priority

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The pharmaceutical industry's reckoning with nitrosamine impurities began in 2018, when contamination with N-nitrosodimethylamine (NDMA) triggered the recall of valsartan products and set off a chain of regulatory action that has not stopped since.

Ranitidine was withdrawn from the US market in 2020, with similar regulatory scrutiny occurring internationally. Recalls of certain metformin extended-release products followed. By the time the FDA published its final revised guidance on the control of nitrosamine impurities in human drugs in September 2024, the scope of the problem had expanded well beyond the sartan class that first brought it to light, and the deadline pressure on drug manufacturers had

become acute.

FDA's August 1, 2025 implementation milestone for NDSRIs intensified the pressure on approved and marketed products. Although FDA later allowed progress updates where full implementation was not achievable by that date, the expectation remained clear: Companies needed to show they had assessed risk, advanced confirmatory testing, and defined a credible mitigation path.

"The latest regulatory guidance has added an urgency to nitrosamine mitigation requiring drug developers to provide a defined plan to address nitrosamine formation," Brian Wilson, director of sales and business development at Aptar Active Material Science, told DDN. "Reformulation and synthesis redesign are expensive, carry regulatory risk because they involve reopening the filing, and can take years. Multiply that across ten or more drug products that all require remediation and it becomes unmanageable."

Where nitrosamines actually come from

The early framing of the nitrosamine problem as primarily a synthesis issue — contaminated solvents, recycled reagents, specific process conditions — was accurate for the initial sartan cases but incomplete as a picture of the full risk picture. A 2025 review in Regulatory Toxicology and Pharmacology on nitrosamine risk assessment described a more distributed set of formation pathways: excipients carry nitrite impurities, packaging materials contribute nitrosating species, and the headspace environment within a package — moisture, oxygen, volatile precursors — can drive nitrosamine formation throughout shelf life rather than only during manufacturing.

Wilson described the same picture from the development side. "Excipients like microcrystalline cellulose carry nitrite impurities, packaging materials contribute nitrosating species, and moisture and oxygen in the headspace act as enablers," he told DDN. "These reactions don't stop at release — they continue during storage, which is why nitrosamine levels climb throughout shelf life."

That shelf-life dimension is what makes the challenge structurally different from a conventional process impurity problem. A synthesis contamination can be identified and controlled at

source. A nitrosamine that forms slowly in a finished product over its two- or three-year shelf life may not be detectable at release and may not surface until accelerated stability studies or post-market testing. "These issues are still typically caught late," Wilson said. "The gap between knowing the science and operationalizing it across development programs remains significant."

How risk varies across compound classes

The FDA's September 2024 guidance revision introduced an important structural distinction: between common, smaller nitrosamines arising from reagents and solvents, and the larger, more complex NDSRIs that derive from the drug substance itself through dealkylation or excipient-mediated pathways. NDSRIs are harder to predict, often lack established acceptable intake limits based on carcinogenicity data, and require compound-specific toxicological assessment using approaches like the Carcinogenic Potency Categorization Approach (CPCA).

Structural risk varies considerably across drug classes. Secondary and tertiary amine-containing compounds — including piperazines, piperidines, and morpholines — are among the most susceptible to nitrosation. But the ranitidine case demonstrated that self-nitrosation can occur in compounds that don't fit the obvious risk profile. "Each API brings its own structural risk," Wilson noted. "No single risk model fits every drug class, and drug developers must conduct compound-specific assessments early enough to actually do something about the results."

The FDA and the European Medicines Agency (EMA) have largely converged on a shared three-step framework — risk assessment, confirmatory testing, and implementation of controls — though differences remain in how they approach NDSRIs specifically. The EMA focuses on lifecycle reassessment and portfolio-wide evaluation, while the FDA places more emphasis on predictive toxicological assessment for NDSRIs without sufficient carcinogenicity data, a distinction that has practical implications for how companies prioritize remediation across different markets.

What best practice looks like now

For formulation scientists and development teams, the regulatory pressure has changed when

nitrosamine risk enters the conversation. The most prepared organizations are building risk assessment into candidate selection rather than treating it as a late-stage quality exercise — evaluating the amine functionality of the API, the nitrite burden of proposed excipients, and the packaging environment as part of the stability equation from the outset.

That also means acknowledging that formulation changes alone may not be sufficient. "Excipient interactions, headspace volatiles, and storage conditions continue to drive formation regardless," Wilson added. "No company can reformulate their way through their entire nitrosamine risk exposure."

The field's maturation on this front has been uneven. "The default response is still reactive: find a problem, reformulate," he said. "That takes 12 to 18 months, can cost millions, and carries its own failure risk." What best practice increasingly looks like is a portfolio-level approach that identifies where risk is concentrated, prioritizes remediations by severity and timeline, and deploys scalable controls across multiple products without triggering unnecessary regulatory filings.

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Wilson said, 'The packaging environment — volatile precursors, moisture, and oxygen inside the package that can drive nitrosamine formation during shelf life — remains among the most underestimated risk factors. If developers are not addressing that aspect, they are leaving a significant risk factor uncontrolled, regardless of what they have done to a formulation."

The broader lesson from the past several years of nitrosamine regulatory activity is that the challenge is no longer only analytical. Sensitive detection methods are essential, but the larger strategic challenge is building the organizational infrastructure to assess, prioritize, and remediate nitrosamine risk across complex portfolios before regulators or post-market surveillance force action.