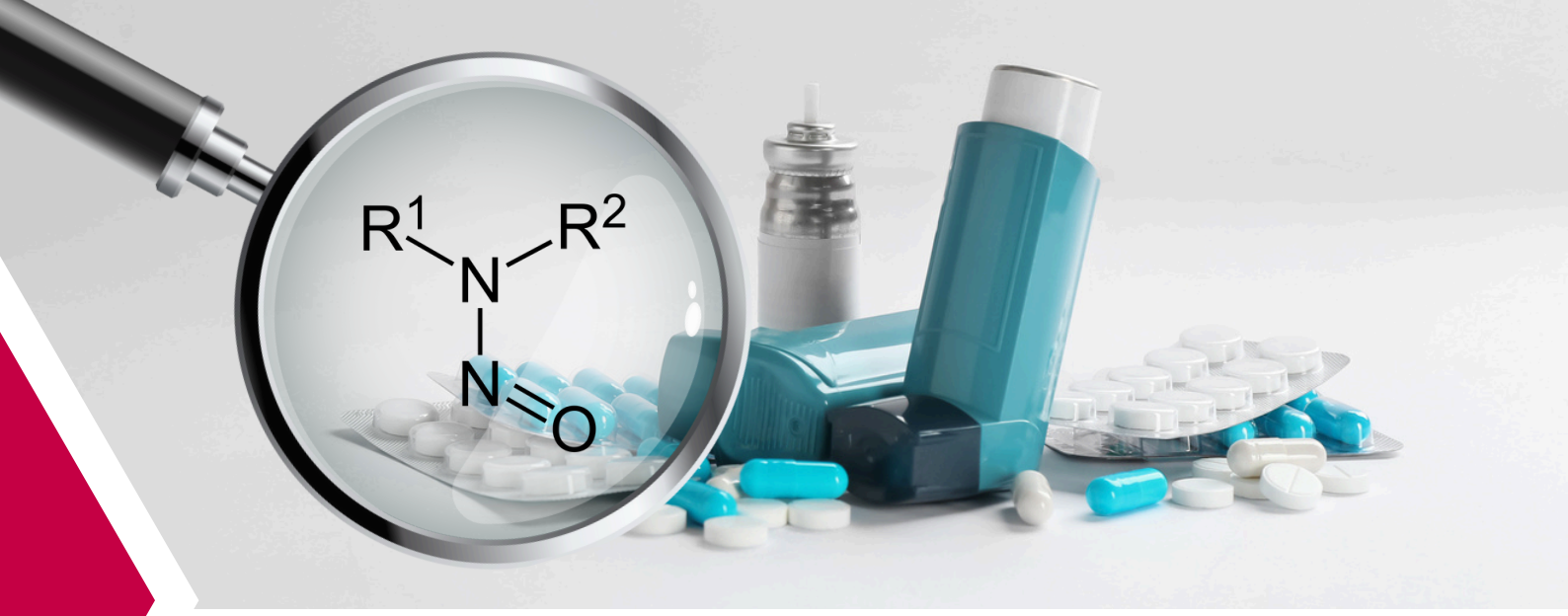

New FDA Nitrosamine Impurities Guide

What Drug Developers Need to Know

Nitrosamine impurities are highly toxic compounds with potential to increase the risk of cancer, even at trace levels. These findings have prompted significant concern among regulatory agencies worldwide, including the FDA. In September 2024, the FDA released its much-anticipated **Control of Nitrosamine Impurities in Human Drugs guidance**, marking the second major update since the original guidance in 2020 and its first revision in 2021. Below is a table summarizing the key changes introduced in this revision:

Aspect	2021 Guidance	2024 Guidance
Scope	Focused on small-molecule nitrosamines in APIs and drug products.	Expanded to include Nitrosamine Drug Substance-Related Impurities (NDSRIs), biologics with chemically synthesized fragments, and at-risk packaging.
Nitrosamine Classes Addressed	Only small-molecule nitrosamines (e.g., NDMA, NDEA).	Includes both small-molecule nitrosamines and NDSRIs (e.g., impurities sharing structural similarities with APIs).
Acceptable Intake (AI) Limits	AI limits provided for small-molecule nitrosamines with strict individual thresholds.	Flexible limits introduced for multiple nitrosamines; new methodologies for calculating NDSRI limits.
Risk Assessment	Required risk assessment for nitrosamine formation in APIs and drug products.	Expanded to require inclusion of NDSRIs in assessments; periodic reassessments recommended throughout the product lifecycle.

Aspect	2021 Guidance	2024 Guidance
Mitigation Strategy	General recommendations for prevention and reduction of nitrosamines, without detailed steps.	Mandates a structured 3-step strategy: (1) Risk assessment, (2) Confirmatory testing with advanced methods, (3) Implementation of control measures.
Testing Requirements	Sensitive analytical methods recommended for detection and quantitation of nitrosamines.	Specific requirements for highly sensitive chromatographic and mass spectrometric methods; mandatory for risk confirmation.
Reporting Requirements	Submission of changes required for APIs and drug products with new specifications or limits.	Mandatory reporting of all NDSRI-related changes, including specifications, stability data, and mitigation strategies.
Supplier and Manufacturing Controls	General advice to audit supply chains and review processes for nitrosamine risk.	Detailed requirements to audit suppliers, control nitrosamine precursors, monitor excipients and packaging, and ensure consistent API specifications.
Additional Risk Factors	Focused on nitrosamines forming in APIs during synthesis.	Highlights risks from excipients, water sources, packaging, and storage conditions contributing to nitrosamine formation in finished products.

From fast screening to fully validated quantification in drug substances and drug products

Solvias provides rapid nitrosamine screening, development and cGMP validation of control methods for small nitrosamines, nitrosamine drug substance related impurities (NDSRIs), and any other genotoxic impurities with unparalleled sensitivity and selectivity.

- ✓ Generic methods available for **screening** samples at single digit ppb levels (R&D)
- ✓ Method **development** and **validation** of product specific methods, using LC/MS/MS or GC/MS/MS (**cGMP**)
- ✓ **Quantification** of N-nitrosylated APIs or intermediates in drug products including the synthesis of stable isotope-labeled reference standards
- ✓ Additional Investigation services available include: **HRAM Spectrometry**, Nitrite/Nitrate Screening, and Pharmacopeial approaches **USP<1469>** and **Ph. Eur. 2.5.42.**

Contact us to speak with an expert: info@solvias.com

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