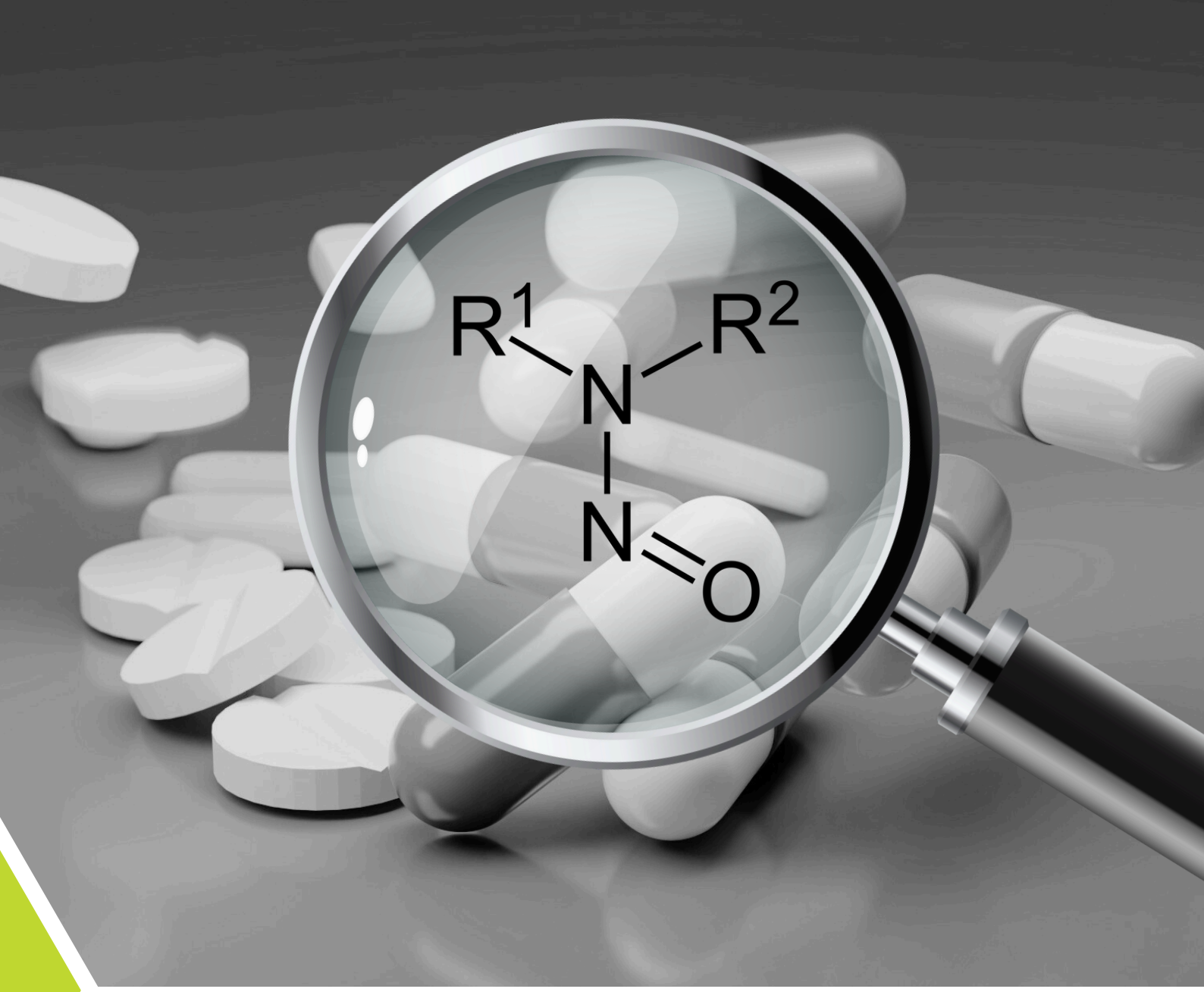



# The High-Stakes Nature of Nitrosamine Impurities in APIs

White Paper

solvias

# Executive Summary

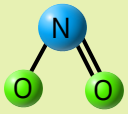
Nitrosamines are a group of chemical compounds known for their carcinogenic properties. These compounds can unintentionally form as impurities during the manufacturing of various substances, including active pharmaceutical ingredients (APIs). With the FDA and global health authorities strengthening regulatory requirements after several prominent recalls of widely used medications, the spotlight on nitrosamines has intensified.

For pharmaceutical companies, the stakes are high. The presence of nitrosamines in drug products on the market can trigger recalls, causing severe financial and reputational damage. Moreover, during the approval process of a new drug, insufficient data on nitrosamines can lead to costly delays. Proactively managing nitrosamine risks is an imperative for drug developers to ensure compliance with regulations, maintain product safety, and uphold public trust.

# Formation of Nitrosamines in APIs

Nitrosamines are formed by a reaction between amines and nitrite sources. In the context of APIs, nitrosamines can arise as unintentional by-products of manufacturing process in the presence of amines and nitrite precursors. The common nature of the precursors and the ease with which nitrosation reactions occur have rendered nitrosamines common and unwelcome entities in APIs.


Amines can be naturally occurring in starting materials or can result from the breakdown of other compounds during synthesis.




Nitrite sources can be introduced inadvertently or originate from specific reagents or environmental factors.

While the following sources have been identified as potential contributors to nitrosamine impurities, this list is not exhaustive:

- Utilization of sodium nitrite ($NaNO_2$) or other nitrosating agents in conjunction with secondary or tertiary amines
- Combination of $NaNO_2$ or other nitrosating agents with reagents, solvents (such as DMF, DMAc, and NMP), and catalysts that are prone to degradation, resulting in the formation of secondary or tertiary amines
- Use of contaminated raw materials, including solvents, reagents, and catalysts
- Impurities in recovered or recycled materials, such as solvents, reagents, and catalysts, especially when outsourced to third parties or when non-dedicated equipment is employed

# Risk and Regulatory Response

The presence of nitrosamines in APIs has raised global regulatory concerns as exposure to these impurities may increase the risk of cancer. Nitrosamines came into the spotlight when their presence was discovered in certain Sartan drugs, which are commonly used to treat hypertension. This prompted regulatory authorities, such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), to initiate comprehensive investigations that identified nitrosamine impurities in antidiabetic drugs, antihistamines, and antibiotics, leading to recalls, stricter quality control requirements, and new regulatory guidelines.

Failing to detect nitrosamine impurities in drug products can cause enormous financial losses. Morgan Stanley estimated that the presence of nitrosamines in Zantac, one of the best-selling drugs in history, could cost the manufacturers between $10.5 billion to $45 billion in recalls and trial judgments.[1] Since 2018, pharmaceutical companies have filed over 250 recall reports with the FDA due to nitrosamine impurities. For drugs awaiting approval to enter the market, the stakes are equally high, as delays in drug approvals cost an average of USD $1 million a day.[2]

The FDA's guidance on nitrosamine testing recommends that manufacturers conduct testing on all their drug products and APIs to ensure they do not have unacceptably high levels of nitrosamines. Specifically, the FDA recommends a three-step process that manufacturers should take to mitigate nitrosamine impurities in their products (see box).

**$ 45B**

in potential recalls and trial judgements in a single nitrosamine contamination case

**250+ recall reports**

filed with the FDA due to nitrosamine impurities since 2018

**$ 1M/day**

in costs related to delays in drug approvals by regulatory authorities

## FDA Guidelines

1) conduct risk assessments for nitrosamines contamination in APIs, marketed products, and products under approved and pending applications

2) conduct confirmatory testing if risks are identified

3) report changes implemented to prevent or reduce the presence of nitrosamine impurities in drug products in approved and pending new drug applications (NDAs) and abbreviated new drug applications (ANDAs)

1) Bloomberg - http://tinyurl.com/55udmamm
2) University of Texas - http://tinyurl.com/28tk34h3

Trusted Solutions

# Solvias' Expertise in Nitrosamine Quantification

Detecting nitrosamines poses a significant challenge as highly sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb) range are required to meet regulatory standards. Moreover, extensive expertise is needed for sample preparation and cleanup procedures, preventing matrix interferences and in situ formation of nitrosamines that could affect the results.

Solvias stands out as a unique solution provider, combining unparalleled expertise with cutting-edge technology to overcome all challenges associated with nitrosamine analysis.

### UNPARALLELED EXPERTISE

With a long-standing history in the analysis of impurities, Solvias boasts a team of highly skilled experts with extensive knowledge in nitrosamine analysis. Our experts navigate the entire analytical process independently of the matrix type. This adaptability ensures that we consistently meet the criteria set by regulatory authorities.

### CUTTING-EDGE TECHNOLOGY

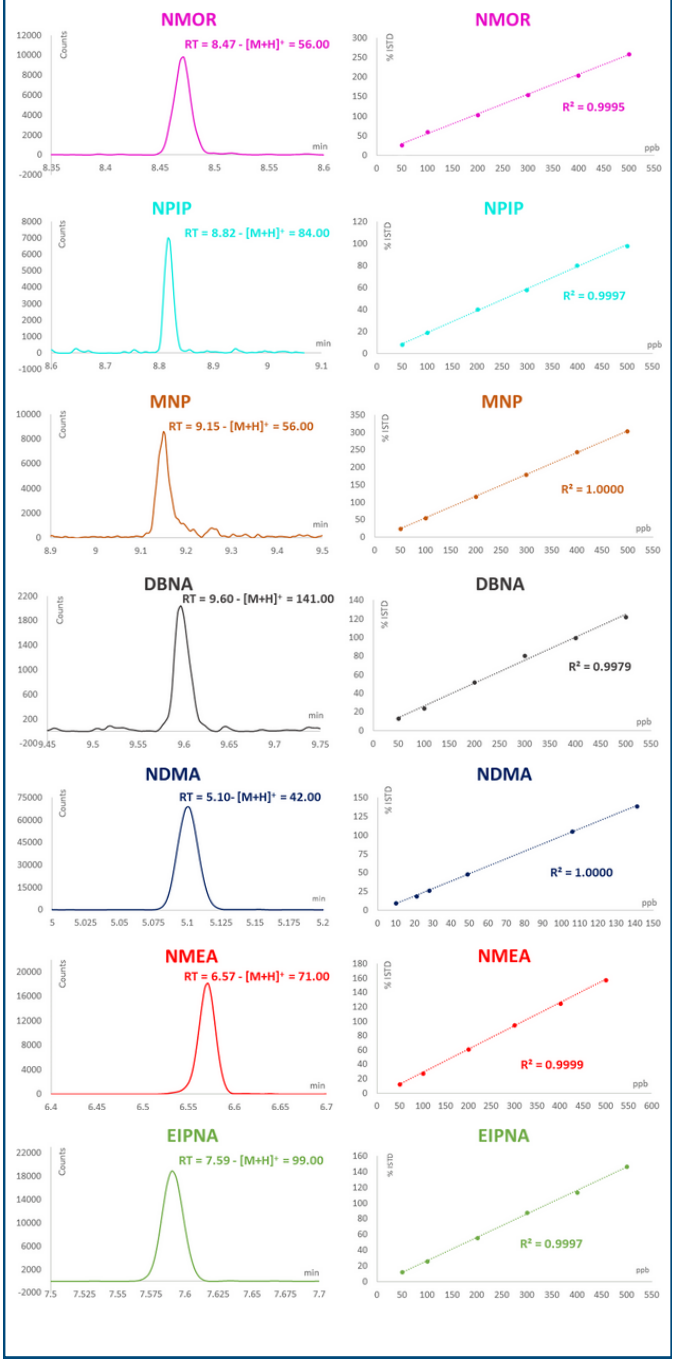
Solvias employs state-of-the-art instrumentation and technology for nitrosamine testing. We utilize well-established GC-MS and LC-MS methods which showcase exceptional accuracy and precision, consistently delivering outstanding performance within the low parts-per-billion thresholds mandated by regulatory authorities.

Solvias understands that different industries and products have unique challenges when it comes to nitrosamine contamination. Our ability to tailor testing methodologies to suit the specific needs of clients ensures a comprehensive and adaptable approach. This spans from generic methods to GMP validated methods for release of commercial products. We are also highly experiences in developing methods for nitrosamines specifically related to your API and tailoring projects to precisely meet your requirements.

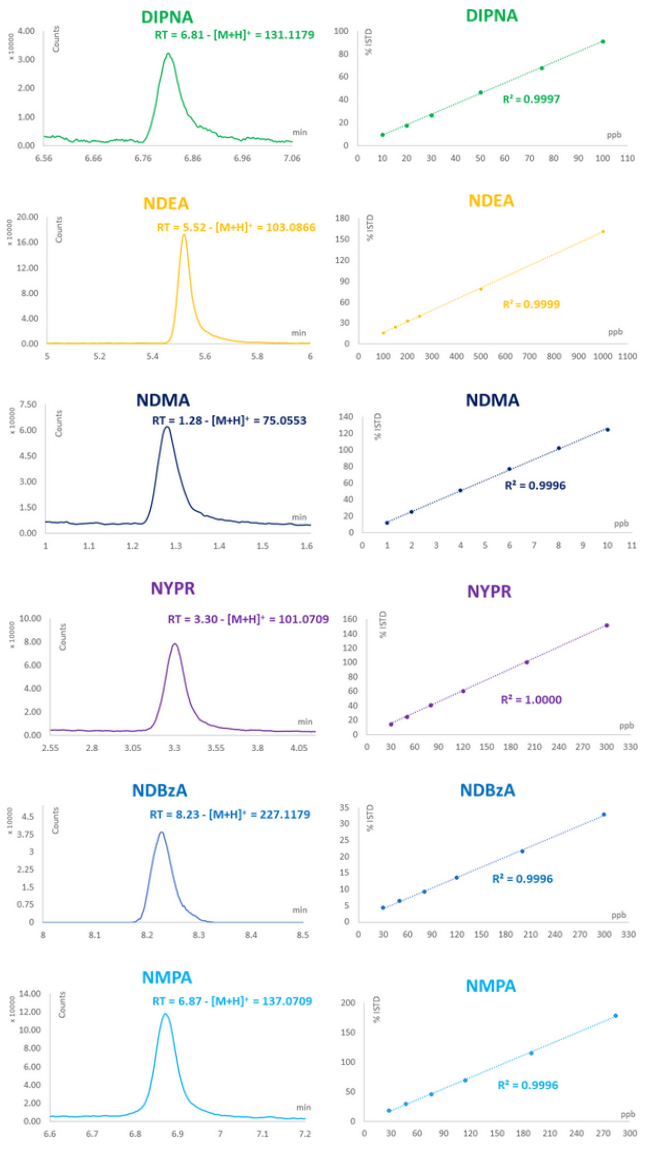
# Unmatched Accuracy

The chromatograms and standard curves below demonstrate the high sensitivity and specificity of our methods, capable of measuring different nitrosamines even at trace levels. The steep slope and high linearity of the standard curves, coupled with R2 values reaching 1.00, showcase the reliability of our results, ensuring that our analytical processes meet rigorous criteria.

## GC-MS




## LC-MS




Numerous other nitrosamines can also be subjected to analysis using either LC-MS or GC-MS, extending well beyond the scope of those discussed here.

# Conclusion

In conclusion, the implementation of nitrosamine GC-MS and LC-MS testing is crucial in ensuring the safety and quality of APIs. Nitrosamines, including those formed from nitrites, are a group of chemical compounds with known carcinogenic properties, posing potential risks to human health.

The utilization of GC-MS and LC-MS technology provides a powerful analytical tool for the detection and quantification of nitrosamines in APIs. This technique allows for precise identification and measurement of these impurities in different solvents and matrices.

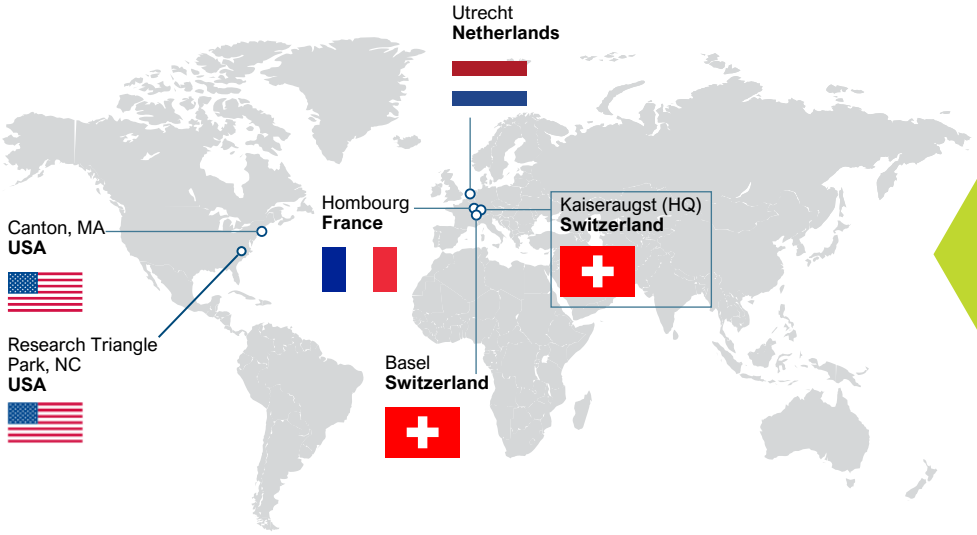
By employing state-of-the-art instrumentation and sophisticated methodologies, Solvias' laboratories can achieve high sensitivity and accuracy in nitrosamine and nitrite analysis. Through rigorous testing, manufacturers can identify the presence of nitrosamine and nitrite impurities in APIs and take appropriate measures to mitigate their levels or eliminate them altogether.

By adhering to regulatory guidelines and continuously monitoring for these impurities, pharmaceutical companies can uphold the highest standards of safety and quality in their API production.

For further information and details about these analytical testing services, or to get in touch with an expert, contact us at info@solvias.com.

## Why partner with us?

- CDMO/CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 22.5K sqm of lab capacity
- 700+ customers worldwide
- 6 centers of excellence




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

**solvias.com**

solvias

A051524