EFCG Briefing Note on Nitrosamines

1. What are nitrosamines?

Nitrosamines are a class of organic compounds that are formed when nitrites react with secondary or tertiary amines. Nitrosamines can occur naturally in some foods and in the environment.

Low levels of nitrosamines have been found in some cosmetics and pharmaceuticals where they constitute **unintentional impurities.**
They can be formed during the manufacturing process of APIs[1] and/or drug products due to processing conditions, cross-contamination (e.g. when processes are running in parallel on the same production lines), solvent recovery, or simply the substance degradation in the process.[2] Nitrosamines can be formed also during the storage conditions and shelf-life.

2. How Are Nitrosamines Formed?

Starting Materials: Medicines often contain amines (organic compounds) and nitrites, which can react under certain conditions.
Chemical Reaction: When amines and nitrites combine, especially in the presence of acids or heat, nitrosamines can form.
Manufacturing Process: Contamination may occur during synthesis, purification, or storage of medicines.
External Factors: Exposure to environmental nitrites (such as during packaging or storage) can increase risk.

Amines + Nitrites + Acid/Heat → Nitrosamines

Step	Description	Risk Points
Raw Materials	Amines and nitrites present	Contamination from sources
Manufacturing	Mixing, heating, acid exposure	Unintentional chemical reactions
Storage	Packaging, environmental exposure	Nitrites entering from surroundings
Final Product	Medicine contains nitrosamines	Patient exposure risk

[1] New strategy for N-nitrosamine impurities in Ph. Eur. monographs - European Directorate for the Quality of Medicines & HealthCare

[2] N-nitrosamine contamination in brief - European Directorate for the Quality of Medicines & HealthCare

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3. Why do they require careful consideration?

Nitrosamines may represent **health risks for the patients**, as two of the most commonly occurring ones (*N*-nitrosodiethylamine – NDEA – and *N*-nitrosodimethylamine – NDMA) are classified as **category 1[3] carcinogens.**

At a **low level**, nitrosamines **do not cause any harm** to patients. The Food and Drug Administration (FDA) estimates that taking medication containing nitrosamines at or below the acceptable daily intake level every day for 70 years does not increase cancer risk[4]. However, the impurities have a potential carcinogenic risk when patients are exposed to above acceptable limits levels of nitrosamines, especially in the long term.

4. Why is this important?

The issue of nitrosamines gained attention in mid-2018, when batches of Valsartan (a blood pressure medicine) manufactured by a Chinese company were recalled after detection of NDMA, a probable human carcinogen, prompting global recalls and regulatory reviews.[5] Since then, drug manufacturers have been requested to assess the level of nitrosamines in their products, following **guidance from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency** (EMA).[6]

5. Our sector's approach to nitrosamines

Nitrosamines could be formed during manufacturing of pharmaceuticals. We therefore focus on the best practices for **risks assessment and detection**, at all steps of the supply chain, from APIs to excipients to the Finished Dosage Form, to ensure that impurities are identified and controlled.

In the absence of strict monitoring, elevated nitrosamine levels can constitute a health risk for patients and lead to economic consequences for companies, with comprehensive batch recalls and increased compliance efforts.

6. Cooperation with APIC

To address these complexities, APIC, the Active Pharmaceutical Ingredient Committee (a sector group of Cefic dealing with regulatory issues linked to Active Pharmaceutical Ingredients and working closely with EFCG) has established a dedicated Nitrosamine Task Force. Through active engagement with industry associations and Health Authorities, APIC maintains access to the latest scientific insights and regulatory developments, while proactively contributing to the shaping of future requirements.

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[3] NDMA and NDEA are classified as Class 1 impurities in ICH M7 / NDMA is classified as Carc 1b (H350) according to the harmonised classification of CLP Annex 3

[4] Information about Nitrosamine Impurities in Medications | FDA

[5] Medical Product Alert N°4/2018: impurity discovered in valsartan

[6] Nitrosamine impurities: guidance for marketing authorisation holders | European Medicines Agency (EMA)

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A core objective of the APIC Nitrosamine Task Force is to harmonise and standardise the approach to risk assessment, and to facilitate the sharing of outcomes with health authorities and customers. To support this, APIC has developed:

- A "How-to" guidance document for conducting risk assessments[7]
- A template report for nitrosamine evaluations[8]

  A position letters on nitrosamines[9], reaffirming its commitment to support and collaborate with Marketing Authorization Holders (MAHs).

[7] APIC-Nitrosamines-Risk-management_Guidance-for-API-Manufacturers_Final.pdf

[8] APIC_Template_for_report_on_Nitrosamine_Risk_Evaluation_Update-January-2026_V4.pdf

[9] 00206B4ABDF1231207102025 and 00206B4ABDF1240826150150

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