World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO good manufacturing practices considerations for the prevention and control of nitrosamine contamination in pharmaceutical products

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.943:

WHO good manufacturing practices considerations for the prevention and control of nitrosamine contamination in pharmaceutical products.

Description of Activity	Date
Preparation of first draft working document.	December 2023
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Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	April 2024
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	May – June 2024
Discussion of the feedback received on the working document in a virtual meeting with an informal consultation group.	June – July 2024
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Presentation to the Fifty-seventh meeting of the ECSPP.	October 2024
Any other follow-up action as required.	

WHO good manufacturing practices considerations for the prevention and control of nitrosamine contamination in pharmaceutical products.

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1. Introduction

1.1. Nitrosamines and their precursors are found in food products and other consumer products such as processed meats, alcoholic beverages, and cosmetics. In these cases, they are normally present in small quantities.

1.2. Foods such as meats, dairy products and vegetables as well as drinking water may contain low levels of nitrosamines. There is no immediate health risk associated with the use of pharmaceutical products containing levels of a nitrosamine impurity below recommended acceptable intake limits. The actual health risk varies from person to person and also depends on the chemical structure of the nitrosamine contaminant. Nitrosamine impurities may increase the risk of cancer in case of exposure above acceptable levels and over long periods of time (i.e., lifetime intakes below acceptable limit is not expected to significantly increase cancer risks). The risk further depends on several factors, such as:

- the daily dose of the medication;
- how long the medication is taken;
- the level of the nitrosamine impurity in the finished product.

1.3. In recent years, some manufacturers of pharmaceutical products have identified that their products were contaminated with N-nitrosodimethylamine (NDMA), hereafter referred to in general, as nitrosamines). This has led to worldwide recalls of certain products that contained levels of nitrosamines above acceptable limits.

1.4. Nitrosamines is a group or class of compounds which have the chemical structure of a nitroso group bonded to an amine (R1N(-R2)-N=O). The compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (coming from nitrite salts under acidic conditions) *(1).*

1.5. Nitrosating agents include nitrites (e.g. sodium nitrite, $NaNO_2$) and nitrous acid (HNO_2), nitric oxide (NO), nitrosyl halides (e.g. ClNO, BrNO), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4) and organic nitrites (e.g. t-BuONO). Some can arise from recycled solvents or reused catalysts from different processes or across manufacturing lines with inadequate control and inappropriate monitoring.

1.6. N-Nitrosamines are a class of substances of concern to international regulators and the pharmaceutical industry. This is because many nitrosamines are highly potent mutagenic agents that have been classified as probable human carcinogens. In order to control the presence of nitrosamines in pharmaceutical products, manufacturers should be familiar with the root causes of nitrosamine impurities in their products. A comprehensive risk management plan should be established and implemented.

1.7. Manufacturers should perform risk assessments to determine whether their products are at risk of containing nitrosamine impurities, and ensure that the levels of impurities do not exceed the acceptable limits. Risk assessment should include the assessment of information relating to excipients, active pharmaceutical ingredients (APIs) and finished pharmaceutical product manufacture. It should cover potential formation and presence of nitrosamine impurities, as well as the potential for contamination of other products from e.g. materials, other products or residue on commonly used equipment.

1.8. New impurities of concern may be identified on an ongoing basis. The following nitrosamine impurities are currently of concern: (Note: This not an exhaustive list)

- N-nitrosodimethylamine (NDMA)
- *N*-nitrosodiethylamine (NDEA)
- *N*-nitrosodiisopropylamine (NDIPA)
- *N*-nitroso-N-methyl-4-aminobutanoic acid (NMBA)
- 1-methyl-4-nitrosopiperazine (MNP)
- *N*-nitrosoethylisopropylamine (NEIPA)
- *N*-nitrosodibutylamine (NDBA)

1.9. Materials, equipment and utilities, may contain contaminants that may be carried over into another material, intermediate, excipient or finished product resulting in contamination or in the formation of nitrosamines. This may result in an adulterated product which could be harmful to patients.

1.10. Traces or residue of unwanted substances present in materials, on surfaces of equipment, in the environment, or in carrier material such as water - may be difficult to remove. These may also be difficult to detect through conventional analytical procedures and basic tests.

Validated, sensitive, selective analytical procedures may have to be used to detect these contaminants.

2. Scope

This guideline is applicable to all manufacturers of excipients, active pharmaceutical ingredients and finished pharmaceutical products.

3. Glossary

Acceptable Intake Limit. The maximum Intake level that poses negligible cancer risk, or for serious/life-threatening indications where risk and benefit are appropriately balanced. The acceptable intake limits can be bound to a specific time-period e.g. daily or cumulative.

Carcinogenic. Having the potential to cause cancer

Maximum daily dose. Highest dose per day that has been proven to be safe and effective for the intended use, without leading to unacceptable side effects or toxicity.

Mutagenic. Capable of causing changes or mutations in the genetic material of an organism.

Mutagenic impurity. An impurity that has been demonstrated to be mutagenic in an appropriate mutagenicity test model, e.g., bacterial mutagenicity assay.

Nitrosamine. Nitrosamines are organic compounds with the chemical structure $R_2N{-}N{=}O$, where R is usually an alkyl group. They feature a nitroso group bonded to a deprotonated amine

Nitrosamine impurities. Undesired substances which are formed by the reaction of secondary amines, amides, carbamates, derivatives of urea with nitrite or other nitrogenous agents

For other definitions, see the WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guideline (https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database).

4. Points to consider

4.1. Manufacturers of excipients, active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) should comply with current Good Manufacturing Practices. *(2-4).*

4.2. Manufacturers should ensure that a pharmaceutical quality system consisting of e.g. procedures, instructions and specifications is in place to ensure the production and control of materials and products that meet safety, quality, purity and efficacy standards.

4.3. Quality risk management should be an important component of the PQS. Manufacturers should identify risks, assess those risks (harm) and implement appropriate controls to eliminate or mitigate those risks.

5. Risk assessment

5.1. Manufacturers should perform risk assessments to determine whether their products are at risk of being contaminated with nitrosamine impurities.

5.2. The risk assessment should be comprehensive and include but not be limited to the premises, equipment, materials, route of synthesis, production process, interaction between chemicals, excipients, solvents, APIs, packaging components as well as the intended use of the product and route of administration.

5.3. Biological, chemical and physical risks or harms which may be introduced or increased; or should be controlled in each step or stage of production, should be identified.

5.4. An appropriate tool should be used when conducting risk assessment. *(5).*

5.5. As a minimum, the following basic questions should be considered during the risk assessment:

- Is there a possibility of formation of nitrosamine impurities? If so, what are the controls to reduce/eliminate the formation?

- How easy is it to detect these nitrosamine impurities?
- What could be the possible source of the formation of nitrosamine impurities?
- What is the nature of possible risk(s)?
- What is the probability of their occurrence?
- What are the consequences and what is the severity?
- Is a separate, or dedicated facility or equipment needed?
- Has an appropriate supplier qualification been done to ensure that there is no risk of contamination of material at the supplier?
- Are the raw and starting materials, and excipients used, of appropriate purity and quality?

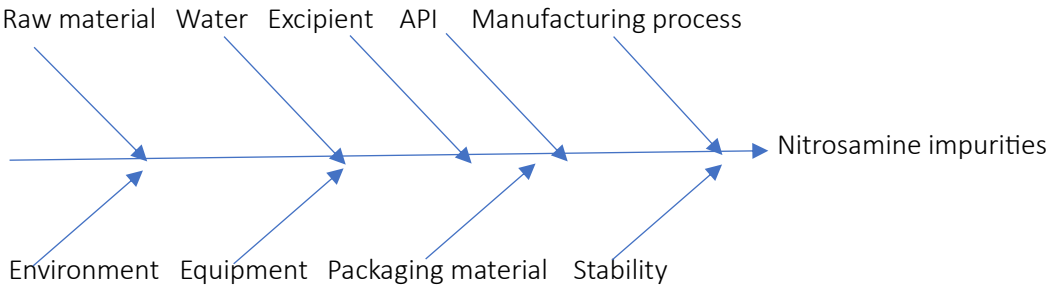

Figure 1. Ishikawa diagram (Example)*

*Include primary, secondary and tertiary causes

6. Root cause analysis

6.1. With the identification and assessment of risks for nitrosamine contamination, manufacturers should also do root cause analysis to determine the possible, or probable cause of the formation of, or contamination with nitrosamine.

6.2. As a minimum, the following questions should be considered:

- Have solvents (fresh and recovered) been considered for possible contamination?
- What is the quality and purity of the solvent used in any step of the processing?
- Are solvents recovered (on-site or off-site/contracted out)?
- did you perform an on-site assessment on contracted facility? Did you assess potential risk of contamination and cross-contamination during the recovery of solvents?

- Is there an appropriate procedure in place to ensure purity of the solvent obtained from the recovery process?
- Is any nitrate such as sodium nitrate used, including in reagents and catalysts?
- Is any nitrosating agent used?
- Is there any risk that nitrates/nitrosating agents can be generated as an impurity during the manufacturing process?
- Are there test results for materials showing nitrites, nitrates and nitrosamines?
- Has water been tested for the presence of potential nitrosamine forming agents, such as chloramines, nitrites and nitrates?
- Is there any secondary or tertiary amine present in the manufacturing process, e.g. raw materials, intermediate, reagent, solvent?
- Is there any amide, amine or ammonium salt present in the substance(s) e.g. raw materials, intermediate, reagent, solvent?
- Have utilities such as water been considered as a possible source of contamination?
- Have equipment been considered as a possible source of contamination, including efficiency of cleaning procedures?
- Are nitrites (NO2-), nitrous acid, nitrates (NO3-), nitric acid, or azides (N3-) or their sources present in any excipients (e.g., microcrystalline cellulose), processing aids (e.g., water, nitrogen)?
- Are peroxides present in any of the excipients, processing aids?
- Are nitrites (NO2-), nitrous acid, nitrates (NO3-), nitric acid, or azides (N3-) or their sources present in packaging components (including ink, and materials permeability factors)?
- Is there a risk that secondary or tertiary amine-contaminants may be present in any primary amines used in your manufacturing process?
- Are any components containing/potentially containing nitrites and amines present together in solution or in suspension during processing (e.g., during granulation, coating)?
- Are nitrites (NO2-), nitrous acid, nitrates (NO3-), nitric acid, or azides (N3-) or their sources present in chemically synthesized APIs?
- Based on the structure of drug substance and excipients, is there any possibility of formation of nitroso compounds by interaction of drug substance and excipients?
- Are any components containing/potentially containing nitrites and amines maintained together at elevated temperatures (e.g., during drying, coating stages, autoclaving)?

- Do solvents or any other process materials undergo recycling/recovery?
- In the manufacturing process of the drug product, are any of the solvents, spent solvents, or process materials treated prior to or during recovery (in-house or by a third party) such that the treatment could lead to formation of amines or nitrosonium ions that could be introduced back into the process through the recovered solvents?
- Are the recovered materials, if any, dedicated to the process?
- Is there a potential for nitrosamine impurity formation during the finished product manufacturing, through degradation and by-products (i.e., if certain excipients, APIs, or packaging components containing sources of amines and nitrite are used together)?
- Are "sartan" products manufactured in the same facility? Is there a risk of cross-contamination?
- Are manufacturing equipment material of construction of any concern?
- Are chemicals such as sodium azide or sodium nitrite, which are primary sources of nitrosamine impurity, used in the facility?
- Are cleaning procedures of equipment involved in manufacturing validated using worst-case product consideration (i.e., solubility, potency, toxicity and cleanability)?
- Are there amines and nitrosonium ions (degradation and by-products) likely to come into contact with each other either in the same processing step or through carryover into subsequent processing steps?
- Is there any potential of nitrosamine formation during storage throughout the finished product's shelf life?
- Is chloramine used as part of the water treatment process, for water used for cleaning, or as part of the production process?
- Have the cleaning solvents/cleaning agents used, been assessed for nitrosamine or nitrosamine precursor risk?
- Does any of the manufacturing processes contribute toward formation of N-Nitrosamines?
- Is there any risk of nitrosamine formation due to the use of nitrogen?

6.3. Examples of possible root causes are listed below. Appropriate controls should be identified and implemented to mitigate risks:

6.3.1. Amines and nitrite reaction

Formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines and nitrite salts under acidic reaction conditions. Under these conditions, nitrite salts may form nitrous acid, which can react with an amine to form a nitrosamine. Nitrites used as reagents in one step can carry over into subsequent steps, despite purification operations, and react with amines to generate nitrosamine impurities. Therefore, whenever nitrite salts are present, carryover into subsequent steps cannot be ruled out. In general, processes that use nitrites in the presence of secondary, tertiary, or quaternary amines are at risk of generating nitrosamine impurities *(1).*

6.3.2. Amine functional groups in processing

Amines are sometimes added as reagents or catalysts during a manufacturing process. Nitrosamine formation is possible when amines react with nitrous acid or other nitrosating agents. Another source of secondary amines is amide solvents. These are susceptible to degradation under certain reaction conditions. *(Note the degradation of N,N-dimethylformamide, N-methylpyrrolidone, N,N-dimethylacetamide, and N,N-diethylacetamide).*

6.3.3. Introduction of Nitrosamine impurities

Nitrosamine impurities can be introduced into materials and products when contaminated materials such as starting materials and raw materials, are incorporated into products. Starting materials and intermediates may be at risk through cross-contamination if they are manufactured at sites where nitrosamine impurities are formed during other processes. In addition, materials are sometimes contaminated during storage, shipment, distribution.

6.3.4. Solvents

Fresh solvents can be contaminated at different stages in the supply chain, as well as during transfer between storage vessels. Recovered materials such as solvents, reagents, and catalysts may also pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine). The use of recovered

solvents that are comingled from different processes or across manufacturing lines without control and monitoring can introduce nitrosamine impurities. Outsourcing of recovery of raw materials (e.g., solvents, reagents, and catalysts) can pose a risk of contamination.

6.3.5. Inadequate equipment cleaning

The suitability of use of equipment (and management of utilities), as well as their cleaning, should be assessed to ensure that the risk of introducing nitrosamine impurities through their use, is appropriately controlled.

Materials, intermediates and products can be contaminated if adequate cleaning of equipment between different materials, products or batches is not carried out, or is not validated as being capable of removing residue or impurities of concern.

Inadequate and unvalidated cleaning procedures can also lead to cross-contamination if precautions to avoid nitrosamine contamination are not in place before materials are combined for recovery.

The nature and composition of the cleaning solvents used for the cleaning of reactors used during API synthesis/purification and for the cleaning of finished dosage form equipment should be considered as cleaning solvents (e.g. amines) could react to form nitrosamines under certain conditions if the equipment is not perfectly dry prior to its used for subsequent manufacture and/or if there are residues remaining. The contaminants found in the cleaning solvents, could also react to form nitrosamines *(6)*.

6.3.6. Utilities

Utilities such as HVAC and water systems, may also be a source of contamination. Risk assessment should be done to consider the contaminants in air and water, as well as the treatment of air and water - as these contain nitrites and other contaminants.

Potable water is sometimes used in the production of materials such as excipients and APIs; or to clean equipment. Water may contain low levels of chloramine and or nitrites/nitrates, which are known to potentially react with secondary amines to form nitrosamine impurities, depending on specific conditions. The source, quality and purification of water may impact on the absence, presence or formation of nitrosamine impurities. For example, chlorination may contribute to the formation of nitrosamine impurities. Chloramine, nitrite/nitrate and nitrosamine levels in water should thus be determined.

Where required, water should be purified to remove unacceptable impurities before use.

6.3.7. Nitrosamines from environmental contamination.

Atmospheric NO2 is a nitrosating agent for various secondary amines, such as DMA. It has been shown that there is a correlation between the concentration of atmospheric NO2 and the NDMA content in certain products. The following examples are controls that could be considered:

- Inlet air to equipment, such as fluidized bed friers, should be appropriately controlled as it may be contaminated;
- APIs with low DMA content should be used where possible;
- Risks associated with process parameters such as granulation drying time and temperatures should be controlled.

6.3.8. Quenching Process as a Source of Nitrosamine Contamination

The risk of nitrosamine formation when a quenching step is performed directly in the main reaction mixture should be avoided or controlled.

Inadequate removal of impurities, or operations which are not optimized for removing specific impurities of concern, may increase the risk of nitrosamine impurities carried over to subsequent steps.

6.3.9. Poorly controlled reaction conditions

The manufacturing process for APIs should be optimized. Reaction conditions such as temperature, pH, or the sequence of adding reagents including catalysts, intermediates, or solvents should be appropriate and controlled to prevent the formation of impurities.

7. Excipients and packaging material

7.1. Excipients should be manufactured in compliance with WHO GMP for excipients used in pharmaceutical products *(2).*

7.2. Impurities, such as nitrite/nitrate, can be found in a range of commonly used excipients. This may lead to nitrosamine impurities forming in pharmaceutical products during production and storage of the product. The supplier qualification program should cover the verification of controls over the possibility of nitrite impurities.

7.3. Packaging materials may be a source of contamination. Nitrocellulose in PTP aluminium printing ink is commonly known as a nitrosating agent.

7.4. Where the excipient is identified as a probable cause for formation of nitrosamine impurities, appropriate controls should be implemented. This may include consideration to change the supplier of the excipient or the change of the excipient to reduce the risk of nitrosamine impurities formation.

Note: See reference to water, under the section "utilities"

8. Active Pharmaceutical Ingredients (APIs)

8.1. APIs should be manufactured in compliance with WHO GMP for APIs.

8.2. API manufacturers should carefully design route of synthesis (ROS) to minimize or prevent the formation of nitrosamine impurities. *(3, 7-9).*

8.3. Reaction conditions that may produce nitrosamines should be avoided as far as possible, starting from the process development stage. Where this is not possible, the process should

be adequately controlled and should be capable of consistently reducing nitrosamine impurities.

8.4. Bases other than secondary, tertiary, or quaternary amines (when possible) should be used if ROS conditions may form nitrosamines.

8.5. Caution should be used when the ROS involves the use of amide solvents (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, and N-methylpyrrolidone).

8.6. Where possible, nitrites should be replaced with other quenching agents for azide decomposition processes.

8.7. Sequences of reactions, processes, and reaction conditions (such as pH, temperature, and reaction time) should be optimized and consistently controlled for avoiding the formation of nitrosamine impurities.

8.8. Manufacturing process should be designed to facilitate the purge of nitrosamine impurities in the subsequent processing steps

8.9. Supply chains should be audited and monitored for any at-risk raw materials, starting materials, and intermediates.

8.10. Records including the name of the raw material manufacturer and its supplier, roles of the actual manufacturers of such materials, and any re-packers and distributors who handle the materials before API manufacture, should be maintained.

8.11. When appropriate, controls and additional specifications should be considered for at-risk materials to prevent nitrosamine contamination.

8.12. API manufacturers should verify with their suppliers whether the purchased materials used in their processes are recovered.

8.13. Recovered materials such as solvents, reagents, and catalysts should be used only in the same step or in an earlier step (if there is sufficient purification) of the same process from which it was collected.

8.14. The recovered materials should meet appropriate standards before reuse. If the recovery of materials is outsourced to third-party contractors, the API manufacturer should audit the contractors' validation of procedures, including cleaning procedures.

8.15. Potable water may contain low levels of nitrite and even nitrosamines from environmental contamination. Nitrite and nitrosamine levels in water should be determined. Where required, water should be purified to remove unacceptable impurities before use.

8.16. API batches containing nitrosamine impurities may be reprocessed or reworked under oversight of the quality unit. Records should be kept.

8.17. Batches of API containing levels of nitrosamine impurities above the recommended limits should not be released for sale or distribution.

8.18. Batches of API with unacceptable levels of nitrosamine impurities already in distribution, should be reported to the national medicine regulatory authority. A batch or product recall should be considered.

9. Finished Pharmaceutical Product (FPP) manufacturers

9.1. Products should be manufactured in compliance with WHO GMP for pharmaceutical products *(4).*

9.2. Risk assessments should be conducted to determine the potential for nitrosamine impurities in FPPs.

9.3. A control strategy should be defined to prevent or mitigate the risk of nitrosamine contamination of FPPs.

9.4. The risk assessment should include evaluation of the supply chain, any excipient, API processing, utilities, as well as storage, re-packaging, distribution pathway and degradation that may introduce nitrosamines during production or storage. Consideration should be given to establish whether nitrosamines could form in an FPP, over the product's shelf life.

9.5. If a risk of nitrosamine presence is identified, confirmatory testing of batches should be conducted using sensitive, appropriately validated, analytical methods.

9.6. If a nitrosamine impurity is detected, the root cause should be determined. Where appropriate, changes in the manufacturing process to mitigate or reduce the nitrosamine impurities should be made.

9.7. The risk of nitrosamine impurity formation during the manufacture and packaging of the finished pharmaceutical product (such as when certain containers, API or packaging components come into contact with amines or nitrites, e.g. reaction of secondary amines in printing inks with certain nitrocellulose lacquers or coating materials when heated) should be considered in the risk assessment.

9.8. Processing steps such as granulation or drying may increase the risk of nitrosamine impurity formation. Where appropriate, changes in the manufacturing process to mitigate or reduce the nitrosamine impurities should be made.

Note: *Purification steps during the production of an API may assist in mitigating risks of the presence of nitrosamine impurity in the API. This may not be the case with the production steps of a finished pharmaceutical product.*

10. Acceptable Intake (AI) limits

10.1. The low levels at which the nitrosamine impurities occur create challenges for testing.

10.2. Appropriate procedures should be developed and validated. (See also methods recommended by SRAs). Note: Higher temperature conditions of some test methods may cause the sample to generate NDMA.

10.3. Generally, sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb) should be used. The LOQ and limit of detection (LOD) should be as low as reasonably practical for products for which the maximum daily dose is high (e.g., greater than 1 g).

10.4. Where more than one nitrosamine listed in appendix 1 is detected, the analytical procedure should be validated for LOQs below 0.03 ppm to accurately quantify a total nitrosamine level of not more than 26.5 ng/day. *(For example, if the MDD is 1200 mg, the LOQ should be below 0.02 ppm. FDA's public webpage includes validated analytical test methods recommended for detecting nitrosamine impurities in several different APIs and products) (1).*

10.5. Only limited impurity-specific toxicity data is available for NDMA and NDEA. Based on this information interim acceptable intakes for these specific impurities have been adopted by most major regulators.

Acceptable Intake (AI) limits for nitrosamines in FPPs (10)

10.6. AI limits should be established. (Note: Different approaches are described in the literature and guidelines as those published by ICH, Health Canada, and the US FDA). For example:

10.6.1. If N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data, the TD50 should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7 guideline *(9);*

10.6.2. If N-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as described above, the Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines should be used to establish the AI, unless other robust data are available that would override this AI;

10.6.3. A negative result in an GLP-compliant Enhanced Ames Test (EAT) allows control of the N-nitrosamine at 1.5 µg/day. For substances testing positive, the AI should be established using options 1 or 3;

10.6.4. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the TD50 from the surrogate substance can serve as a point of departure for derivation of AI by SAR and read across.

10.7. A negative result in a relevant well-conducted in vivo mutagenicity study can allow control of the N-nitrosamine as a non-mutagenic impurity, i.e., according to Q3A/B limits, irrespective of the limit calculated through option 1, 2 or 3. For substances testing positive, the AI should be established using options 1 or 3.

10.8. In setting AI limits for nitrosamines, consideration should be given to:

- the Enhanced Ames Test (EAT) conditions and the Carcinogenic Potency Categorization Approach (CPCA);
- the threshold below which a nitrosamine impurity is not expected to be included in routine testing specifications;
- testing approaches where more than one strength of a dosage form is concerned, and
- expectations when a nitrosamine impurity cannot be synthesized or isolated and purified.

10.9. Recommended AI limits are presented in literature. (The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. See ICH M7 *(9)* and USA FDA regulatory information note[1])

10.10. Examples of Interim allowable daily intake limits for a selection of N-nitrosamine impurities are presented in Annex 1. For a nitrosamine impurity that is not included in the appendix, the principles as outlined in ICH's M7 guideline are recommended to be used to determine an acceptable Intake *(9)*.

10.11. The conversion of AI limit into ppm varies by product and is calculated based on a product's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)). These limits are applicable only if a drug product contains a single nitrosamine *(1)*.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

11. Analytical procedures

11.1. Validated analytical procedures should be used when testing for the presence of nitrosamines. The procedure should be sensitive for the determination of the specific nitrosamine(s) in the product.

11.2. Where the presence of a nitrosamine is confirmed, it should not exceed the acceptable limits. Where it exceeds the acceptable limit, appropriate corrective action should be taken. If the manufacturing procedure needs to be changed, the change management procedure should be followed for the relevant variation. In this case, where relevant, the NMRA should be informed.

11.3. Where appropriate, analytical methodology to separate thermally labile nitrosamine impurities using gas chromatography (GC) coupled with detection by thermal energy analysis (TEA) or mass spectrometry (MS), should be used.

11.4. Liquid chromatography (LC) coupled with detection by TEA, MS, or ultraviolet light (UV) may be an alternative analytical methodology applicable to both volatile and non-volatile nitrosamines.

11.5. High performance liquid chromatography (HPLC) with UV detection has low sensitivity and may only be adequate for analysis of low dose drugs with lower limits.

11.6. Examples of analytical procedures are presented in table 1.

Table 1. Examples of analytical procedures*

Methodology	Detector	Limit of Detection
Gas chromatography	TEA	< 0.1 to 5 ppb
	MS	1 to 5 ppb
Liquid chromatography	TEA	1 to 50 ppb
	MS	1 to 5 ppb
	UV	1 to 200 ppb

* used for detection of nitrosamine in e.g. water and food products

12. Recommendations

12.1. Excipient, API and FPP manufacturers should take steps to mitigate the risk of nitrosamine impurities in their products.

12.2. Risk assessment of nitrosamine impurities should be conducted in a timely manner, as early as during product development as well as thereafter during the manufacturing of excipients, APIs and FPPs.

12.3. It should be noted that:

- average nitrosamines and potential nitrosamine precursors content and batch to batch variance differ among excipients;
- for solid dosage forms, the nitrosamine and potential nitrosamine precursors contribution is dominated by the highest formula % excipients, e.g., the fillers (diluents), which are typically used in larger proportion, and are characterized by low nitrite levels and low variability, leading to an average value of 1 µg/g nitrite in a typical formulation;
- substantial differences may occur in average nitrosamine and potential nitrosamine precursor content in batches from different excipient vendors potentially reflecting differences in source materials or processing methods for excipient manufacturing;
- selection of raw materials or processing by excipient manufacturers may help reduce nitrite levels in finished drug product formulations, and thus the overall risk of nitrosamine formation in cases where the product contains vulnerable amines *(11).*

12.4. The benefit and the risks of products with levels of nitrosamines exceeding acceptable limits or more than one nitrosamine should be reviewed by the NMRA. When considering the withdrawal, the NMRA should balance the impact on the patient if the product will no longer be available. This should involve determining the availability of alternative products or treatments on their own market and the clinical impact of stopping or switching to a different treatment.

12.5. Where manufacturers identify contamination of nitrosamines above acceptable limits, appropriate action should be taken. Risk and impact assessment should be done with root cause determination. Thorough investigations should be done to identify whether shared

facilities, shared equipment or other batches may be impacted, whether common excipients, starting materials or solvents were used which may be the potential source of contamination. The investigation should be extended to other batches which may have been impacted.

References

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Appendix 1: Examples of Interim allowable daily intake limits for a selection of N-nitrosamine impurities.

Impurity (Abbreviation)	Chemical name	Allowable daily intake
NDMA	N-nitrosodimethylamine	96.0 ng/day
NDEA	N-nitrosodiethylamine	26.5 ng/day
NMBA	N-nitroso-N-methyl-4-aminobutryric-acid	96.0 ng/day
DIPNA	N-nitroso-diisopropylamine	26.5 ng/day
EIPNA	N-nitroso-ethylisopropylamine	26.5 ng/day