

REPORT ON THE RISK OF POTENTIAL PRESENCE OF NITROSAMINE IMPURITIES

Document ID:

ACTIVE PHARMACEUTICAL INGREDIENT (API) (/or other (specify), e.g. in case risk assessment is requested for API intermediates)

Name:

Material code(s):

MANUFACTURER (refers to the manufacturing site)

Name:

Address:

(Optionally)

CEP/ASMF/DMF reference:

(Optionally, if manufacturer is different than DMF holder):

DMF holder

Name:

Address:

(Optionally indicate name / function) **This report was completed by [person / central service]:**

▪ Name and position:

▪ E-mail address:

▪ Postal address:

Declaration:

The current manufacturing process of (*API name*) was assessed with respect to the risk of the potential presence of Nitrosamine impurities in line with EMA guidelines (current versions of EMA/369136/2020, EMA/409815/2020) and similar related regulations published by other Health Agencies.

All information contained in this report is based on current knowledge and is true and sincere to our actual knowledge considering available supplier information and likely chemical production processes where information from the supplier is not available.

The information in this document may be updated as more information becomes available.

Date

(Optionally sign) **Signature and Company stamp**

Delete this page when issuing the letter.

Instructions when using this template:

- 1. Replace APIC logo by your company logo.*
- 2. In the footer, replace CEFIC logo by “This document was prepared based on APIC template”.*
- 3. Remove the text referring to the internal instruction (blue), e.g. definition of Nitrosatable/vulnerable substances (amine, hydrazine, hydrazide or hydrazone) in Chapter 7.*
- 4. In the section 3, the detail would depend on the customer (or Health Authorities) with whom the report will be shared. The process description can be replaced by a workflow with the relevant information for the evaluation or just to reference the filing applicable section. A description of the process step where the risk evaluation was initiated, e.g. from starting material or from intermediate, should be provided with a rationale for the selection.*
- 5. In the table in the section 5 (Table 2), fill one line per nitrosamine which has been identified as being possibly generated during the API manufacturing process.*
- 6. Before finalization of the report, please check the references of currently valid Health Authorities' (HAs) guidelines. If an updated revision, without changes in identified root causes is available, a revision of the Table 1 is not needed and only references in a foot note of the page 4 should be updated. However, if additional (new) root cause is identified in any future revision of the HAs guidelines, an update of the APIC template should be endorsed.*
- 7. If justification for risk evaluation of the root cause in the Table 1 is supported by any other document/literature reference, please provide any additional information/document or reference within this table, as appropriate.*

1 INTRODUCTION

This document reports the outcome of the risk evaluation on the above mentioned API based on the requirements defined in the EMA/369136/2020 assessment report “*Nitrosamine impurities in human medicinal products*”¹, the EMA/409815/2020 “*Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products*”², the US FDA Guidance for Industry “*Control of Nitrosamine Impurities in Human Drugs*”³ and other related regulations published by other Health Agencies, such as Health Canada.⁴

Such evaluation on the risk of presence of nitrosamine impurities in the APIs was performed using quality risk management principles, as per current ICH Q9 guideline (*ICH guideline Q9 on quality risk management*) and ICH M7 (*Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*). Manufacturing processes are being reviewed to identify and, if found, to mitigate risk of presence of *N*-nitrosamine impurities during manufacture and storage of the API.

2 SCOPE

The Risk Evaluation has evaluated the items as potential sources of nitrosamines or their precursors in line with root causes described in the EMA/409815/2020 guideline².

Please note that listed root causes (Table 1) follow the EMA/409815/2020 guideline.² In addition, the root causes, such as “*Quenching Process as a Source of Nitrosamine Contamination*” and “*Lack of Process Optimization and Control*” as described in FDA Guidance for Industry³ are addressed within the present EMA’s root causes. Namely, both are covered within questions related to combination of nitrosating agent and nitrosatable substances or compounds susceptible for degradation into nitrosatable substances, as well as questions related to contamination of starting materials/intermediates/raw materials.

3 MANUFACTURING / PROCESS STEPS COVERED BY RISK EVALUATION

The risk evaluation covers all API manufacturing steps as presented below.

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Include route of synthesis and process description, if relevant. The process description can be replaced by a workflow with the relevant information for the evaluation or just to reference the filing applicable section.)

¹ European Medicines Agency (EMA): Assessment report, Procedure under Article 5(3) of Regulation EC (No) 726/2004, Nitrosamine impurities in human medicinal products. EMA/369136/2020, 25 June 2020, [Nitrosamines EMEA-H-A5\(3\)-1490 - Assessment Report](#).

² European Medicines Agency (EMA): Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. EMA/409815/2020, Rev.23, 10 October 2025. [Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5\(3\) of Regulation \(EC\) No 726/2004 referral on nitrosamine impurities in human medicinal products](#) and corresponding Appendices: Appendix 1 (EMA/42261/2025), Appendix 2 (EMA/451665/2023) and Appendix 3 (EMA/120337/2024).

³ U.S. Food & Drug Administration, Control of Nitrosamine Impurities in Human Drugs, Revision 2, September 2024, [Nitrosamine final guidance, Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities \(NDSRIs\) Guidance for Industry, August 2023 Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities \(NDSRIs\) Guidance for Industry](#) and Updated Information | Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) – published on website [CDER Nitrosamine Impurity Acceptable Intake Limits | FDA](#)

⁴ Health Canada: Guidance on nitrosamine impurities in medications, date adopted 1 August 2025, [Guidance on nitrosamine impurities in medications](#)

In the footnote on page 4, please update accordingly applicable and current guideline version. Please add also other guidelines, for other scopes and reported by other National Competent Authorities, if applicable.

4 RISK EVALUATION METHODOLOGY

The risk evaluation for potential presence of nitrosamines has been conducted taking into account quality risk management principles, as per current ICH Q9 guideline (*ICH guideline Q9 on quality risk management*).

5 SUMMARY OF ITEMS REVIEWED FOR THE RISK EVALUATION (includes justification and risk evaluation outcome)

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. For each of the following items, indicate whether a risk for presence of nitrosamines has been identified or not. In each case consider the item's potential as a direct source of nitrosamines and/or source of nitrosamine precursors, which could subsequently pose a risk of nitrosamine formation. Please consider presence of nitrosating agents and nitrosatable substances for the risk evaluation results in Chapter 7. Provide justification as to why the response is yes / no / na. For additional information regarding presence of nitrosating agents and nitrosatable substances in the API, please refer to Chapter 7.)

Note:

Please note that below Summary table (Table 1) is done based on CMDh/439/2022 (Template for nitrosamine RE)⁵ for convenience of drug product manufacturer and to transparently demonstrate that the risk evaluation has been performed based on the current version of the EMA/409815/2020 document² and all risk factors related to active substance are sufficiently addressed in the risk evaluation itself.

By assessing the risk factors related to the manufacture of API, also the potential risks arising in finished product formulation due to active substance are addressed and the MAH is supported with relevant information to perform further comprehensive risk evaluation for medicinal product.

Table 1: Summary of items reviewed for the risk evaluation, justification and risk outcome

	Currently identified risk factors for presence of nitrosamines (Q4 of EMA/409815/2020)	Risk for presence of nitrosamines identified? (Yes / No / NA)
<i>Risk factors related to the manufacture of the active substance:</i>		
1	Use of nitrite salts and esters (e.g. NaNO ₂ , alkyl nitrites), or other nitrosating agents (e.g. nitroso halides, nitrosonium salts, nitrogen oxides, nitro alkanes, halogenated nitro alkanes, Fremy's salt,	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:

⁵ CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines, CMDh/412/2019, Rev.21, July 2023 [CMDh_412_2019_Rev.21_2023_07_clean - PG to MAHs on nitrosamines](#) and The template for nitrosamine risk evaluation, CMDh/439/2022, May 2022 [CMDh_439_2022_Rev.0_03_2022_clean - Template for nitrosamine risk evaluation.docx](#)

	nitroso sulfonamides), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process. Sources for secondary or tertiary amines can also be starting materials, intermediates, reagents, solvents (e.g. DMF, DMAc and NMP) and catalysts, which contain amine functionality, amine impurities (e.g. quaternary ammonium salts) or which are susceptible to degradation to reveal amines.	
2	Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
3	Use of disinfected water (chlorination, chloro-amination, ozonisation) in the presence secondary or tertiary amines within the same or different steps of the manufacturing process.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
4	Oxidation of hydrazines, hydrazides and hydrazones by hypochlorite, air, oxygen, ozone and peroxides in the manufacturing process or during storage.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
5	Use of contaminated raw, recovered or recycled materials (e.g. solvents, reagents and catalysts) in the API manufacturing process.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
6	Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
7	Carry-over of nitrosamines deliberately generated (e.g. as starting materials or intermediates) during the manufacturing process.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
Risk factors also related to the finished product:*		
8	A particular risk of formation of nitrosamines should be noted for active substances that contain a nitrosatable amine functional group. Several examples have been reported where the amine functionality was shown to be vulnerable to nitrosation and formation of the corresponding <i>N</i> -nitroso impurity (i.e. NO-API). Secondary amines appear particularly vulnerable to this reaction, although some cases with tertiary amines have also been observed.	
8a	Does the API, or one of its known impurities, have a nitrosatable nitrogen functionality?	YES <input type="checkbox"/> NO <input type="checkbox"/> Justification: Please refer to the Chapter 7.
8b	May nitrites be present in one of the used excipients?	NA
9	Degradation processes of active substances, including those induced by inherent reactivity (e.g. presence of nitro-alkyl, oxime, or other functionality) or by the presence of an exogenous nitrosating agent.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
10	Oxidation of hydrazine or other amine-containing functional groups present in active substances or their impurities/degradants (e.g. from hydrazones and hydrazides), either in active substance manufacturing processes or during storage.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification: Please refer to the root cause No. 4.
11	Use of certain packaging materials.	YES <input type="checkbox"/> NO <input type="checkbox"/> Justification:
12	Reaction of amines leaching from quaternary ammonium anion exchange resins (e.g. used for purification steps) with nitrosating agents present in the liquid phase. In addition, disinfection procedures such as e.g. chlorination, chloro-amination and ozonisation can lead to significant <i>N</i> -nitrosamine generation as by-products in case vulnerable amines	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:

	are present. Given the source of contamination, risk is related to the concentration of the reactive agent(s) and thus, to the volume of water in or used to dilute a particular product. The same risks could be associated with active substances or finished products manufactured using water purified using similar resins.	
Risk factors related to GMP aspects:		
13	Cross-contamination due to different processes being run successively on the same manufacturing line.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
14	Carry-over of impurities between process steps due to operator-related errors or insufficiently detailed batch records such as inadequate phase separations during work-up procedures.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
15	Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts) where the recovery is outsourced to third parties who are not aware of the content of the materials they are processing. Recovery processes carried out in non-dedicated equipment should also be considered.	YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Justification:
Any other risk factor identified:		
16		

NA – not applicable

*Risk factors are assessed for API.

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED.

In case no risk identified evaluating root causes, no further action is expected by API manufacturer and risk outcome is concluded with no risk (section 6).

In case risk is identified evaluating root causes, list all N-nitrosamine impurities for which risk is identified and complete the Table 2.

Indicate if mitigation measures/control strategy is in place. In case the risk is identified and further mitigation/control strategy, including testing, is developed, maximum daily dose (MDD) of active substance used for acceptable limit determination for N-nitrosamine impurities is recommended to be included. Indicate also acceptable limit with a reference to the corresponding nitrosamine guideline, e.g. CPCA categorization, ICH Q3A limit for nitrosamines reported as non-mutagenic impurities or APIs indicated for advanced cancer treatment.)

Table 2: List of all potentially present N-nitrosamine impurities identified in the API risk evaluation

Possible N-nitrosamine (Chem. Name / Code Name and Chem. Structure)	Origin of possible N-nitrosamine / Root cause (specify nitrosating agent and nitrosatable substance)	Acceptable limit (Acceptable intake, MDD)	Mitigation measures / Control strategy	Test results available?
				YES* <input type="checkbox"/> NO <input type="checkbox"/>

* Analytical test results

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Include analytical results or provide reference to the appropriate attachment.)

6 RISK OUTCOME

Based on the risk evaluation conducted and mitigation measures, the risk for presence of nitrosamines is evaluated as:

- negligible (no risk identified)*
- potentially present (risk identified)*

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Please select appropriate conclusion based on the applicable option. Example text:

Option 1:

The risk evaluation indicates that there is no risk for N-nitrosamine impurities in API (name). No further actions is needed.

Option 2

The risk evaluation indicates that there is a potential presence of N-nitrosamine impurity (name) in API (name). However, according to the analytical testing results it is demonstrated that the levels of N-nitrosamine impurity (name) are below 10% of acceptable limit. Therefore, there is no risk for the presence of N-nitrosamine impurity in drug substance (API name) from the manufacturer (API manufacturer name).

Option 3:

The risk evaluation indicates that there is a potential presence of N-nitrosamine impurity (name) in API (name). According to the analytical testing results it is demonstrated that the levels of N-nitrosamine impurity (name) are above 10% of acceptable limit. Therefore, N-nitrosamine impurity is controlled in final API specification (API name) with limit of xy ppm (indicate the value)).

7 ADDITIONAL INFORMATION TO SUPPORT THE RISK EVALUATION BY THE DRUG PRODUCT MANUFACTURER / MARKETING AUTHORIZATION HOLDER (MAH)

Based on the manufacturing process reviewed and on its related risk evaluation for potential presence of nitrosamines, the API manufacturer declares that:

7.1 For nitrosating agents:

- Nitrosating agents are **not likely** to be present in the final API.
- A risk for **potential presence** of the following nitrosating agents in the final API is identified (Table 3).

Table 3: Nitrosating agents

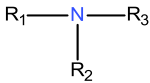

Nitrosating agent	Structure	Potentially present in final API / Levels in API, if applicable
Nitrite salts	MNO ₂	
Nitrate salts	MNO ₃	
Nitrous acid	HNO ₂	
Nitrous acidium ion	H ₂ O ⁺ -NO	
Nitric acid (contains N ₂ O ₄)	HNO ₃	
Alkyl nitrites	R-ONO	
Peroxyxynitrite	ONOO(-)	
Nitrosonium ion	NO ⁺	
Nitro compounds	R-NO ₂	
Nitrous anhydride	N ₂ O ₃	
Dinitrogen tetroxide	N ₂ O ₄	
Nitrosyl halides	Halide-NO	
Nitrosyl thiocyanate	ONSCN	
Nitrosophenol	Phenol-NO	
Nitrosothiol	SH-NO	
Aqua regia	HCl + HNO ₃	
Nitryl chloride	NO ₂ Cl	
Other (specify)		

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. The term “nitrosating agent” corresponds to (but not limited to): nitric acid, nitrite salts, organic nitrites, nitrosonium salts, nitrogen oxides and nitro compounds).

7.2 For Nitrosatable/vulnerable substances:

- Nitrosatable/vulnerable substances are **not likely** to be present in the final API.
- A risk for **potential presence** of the following nitrosatable/vulnerable substances in the final API or as integral part of the API is identified (Table 4)

Table 4: Nitrosatable/vulnerable substances in API

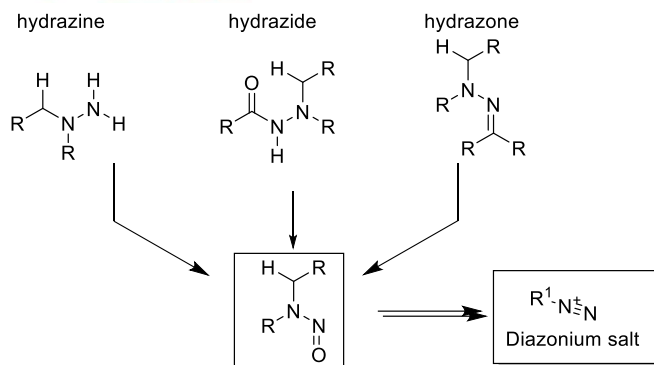
Nitrosatable/vulnerable substance	Structure	By-products	(Potentially) present in final API / Levels in API
Secondary amines (cyclic and acyclic)	R_1-NH-R_2	-	
Tertiary amines (cyclic and acyclic)		NHR ₁ R ₂ , NHR ₁ R ₃ , or/and NHR ₂ R ₃	
N,N-Dialkylamides	$R_1CONR_2R_3$	NHR ₂ R ₃	
N-Methyl-2-pyrrolidinone		N-methyl-4-aminobutyric acid	
N-Chloroalkylamines	R_1R_2N-Cl	NHR ₁ R ₂	
N,N-Dialkylcarbamates	$R_1O-CO-NR_2R_3$	NHR ₂ R ₃	
Hydrazine derivatives	$NH_2-NR_1R_2$	NHR ₁ R ₂	
Other (specify)			
<i>(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Justification on vulnerability or non-vulnerability of amine, hydrazine, hydrazide or hydrazone function should be added here. Decision should be supported by literature data.)</i>			

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. The term nitrosatable/vulnerable substances consider amines, hydrazines, hydrazides or hydrazones.

The term “nitrosatable /vulnerable amines” corresponds to an amine function that have potential to react with nitrosating agents. According to EMA “nitrosatable” and “vulnerable” are used interchangeably.

It corresponds to (but not limited to): Secondary amines (cyclic, acyclic), tertiary amines (cyclic, acyclic), secondary/tertiary amine precursors, such as (but not limited to) quaternary ammonium salts, N,N-dialkylamides (e.g. N-methyl-2-pyrrolidone, dimethylformamide, dimethylacetamide), N-chloroalkylamines, and N,N-dialkyl carbamates that may be converted to corresponding vulnerable amines.

(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. The term “vulnerable hydrazine, hydrazide or hydrazone” corresponds to a hydrazine, hydrazide or hydrazone function that can lead to N-nitrosamine derivative by means of an oxidation step. This nitrosamine should as well be able to lead to an alkylating diazonium salt as described in below scheme.)



(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED.)

The risk assessment does not concern nitroso compounds other than N-Nitrosamines. Currently, the EMA and FDA Guidelines are applicable to N-Nitrosamines, compounds that have a carbon atom on both sides of the amino nitrogen, where the carbon is not directly double bonded to a heteroatom.

Nitrosated impurities of other compounds such as nitroso-ureas, nitroso-guanidines, nitroso-amides, nitroso-carbamates, etc. could be under certain conditions theoretically possible. These classes of compounds are unstable compared to N-nitrosamines and have a different metabolism. These structures are not included in the scope of the EMA, FDA and other countries nitrosamine guidelines, and therefore are outside the scope of the nitrosamine risk assessment.

8 CHANGES IN MANUFACTURING PROCESS WITH POTENTIAL IMPACT ON NITROSAMINE IMPURITY FORMATION

In case of changes in the manufacturing process, starting materials, suppliers etc. that may affect this risk evaluation document, we will evaluate the impact, revise this document when necessary and inform our customers in case of any changes in the outcome.