**Questionnaire for Excipient Nitrosamines Risk Evaluation**

Version 1 - February 2023

Notice

This Questionnaire has been converted from the latest version (version 4.2, January 2023). of the IPEC Europe document to extend its applicability globally. This updated version becomes the official IPEC Questionnaire for this topic.
However, pre-existing completed questionnaires do not need to be updated.

Introduction

Several authorities issued guidance and information on nitrosamine impurities within which are requests for Marketing Authorization Holders (MAHs) to conduct a risk evaluation with regards to nitrosamine formation in their drug products. Excipients can contribute to the formation or content of nitrosamines in drug products through precursor substances present in the excipient (e.g., nitrites, amines, or other nitrogen containing compounds). This questionnaire aims to provide information about excipients to assist the MAH in their evaluation of the risk of the presence of nitrosamine impurities in the final drug product. It is not the requirement of the excipient manufacturer to conduct a nitrosamine risk assessment, indeed this is not possible without specific knowledge of the actual and specific drug product formulation and properties of the active.

This questionnaire reflects the guidance from the EMA assessment report “Nitrosamine impurities in human medicinal products”[[1]](#footnote-1), the related EMA guidance[[2]](#footnote-2) including the “Questions and answers for marketing authorization holders”[[3]](#footnote-3), the US FDA Guidance for Industry “Control of Nitrosamine Impurities in Human Drugs”[[4]](#footnote-4) and how they may be adapted for pharmaceutical excipients.

The information generated should also assist companies to address similar requests from other regulatory authorities, based on our current understanding of global activities on this subject.

The questionnaire includes a matrix to consider the structure and the origin of the excipient as a first risk indication. In addition, excipient suppliers are encouraged to share their conclusion.

The use of a standard format will facilitate data collection from excipient suppliers and thus enable a more efficient process of conducting the required risk assessments by drug product manufacturers / Marketing Authorisation Holders.

With this form, excipient suppliers can provide information for nitrosamine risk evaluation to the best of their knowledge, considering available supplier information and likely chemical production processes where information from the supplier is not available.

***Based on emerging information this form may be adapted accordingly.***[[5]](#footnote-5)

This information for nitrosamine risk evaluation is prepared for:

|  |  |
| --- | --- |
| Supplier product number and name: |  |
| Supplier: |  |

|  |  |
| --- | --- |
| Created by / Date |  |
| Approved by |  |
| Job title |  |
| Signature |  |

IPEC Federation Questionnaire

|  |
| --- |
| 1) Please tick the applicable category based on structure and origin of the excipient in support to evaluate the risk of formation of nitrosamines[[6]](#footnote-6). [ ]  Mined excipients, N-free products of fermentation or natural origin, … [ ]  Synthetic origin and nitrogen containing [ ]  Proteins, enzymes, products of fermentation or extraction of biologic sources, ... [ ]  N-free mineral acids or bases, organic solvents, polymers, inorganic salts, small organic N-free entities, …yesYesNoNo**Target Excipient: Nitrogen containing?****Chemical Synthetic Manufacturing Process?** including processes to introduce chemically synthesized fragments to biological products or substances of natural origin |
| 2) Is sodium nitrite (NaNO2) or any other nitrite or nitrosating agent[[7]](#footnote-7): * used in any steps in the manufacturing process[[8]](#footnote-8) as reagents/catalyst?
* known to be used in the preparation of raw materials or intermediates used in the manufacturing process?
* known to be used in the preparation of reagents/catalysts/processing aids used in the manufacturing process?
* known or likely to be generated during the manufacturing process?
* deliberately added to the process, including components of cell culture media or for fermentation?
 | **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ]  | **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ]  | Not available/ applicable or unknown[ ] [ ] [ ] [ ]  |
| 3) Have you analysed the excipient for\*:* Nitrites?
* Nitrosamines?

 \*Default testing is **NOT** mandatory but may be performed if considered relevant for a specific excipient.Test results:Note: Presently, nitrite testing of excipients is not harmonized, and results may vary depending on the method used by different manufacturers of the same excipient. Users are encouraged to test themselves when comparing suppliers.  | **YES** [ ] **YES** [ ]  | **NO** [ ] **NO** [ ] **NO**[ ]  | Test result, if available- report below or provide separately  |
| 4) Is water used in the manufacturing process[[9]](#footnote-9)? If “Yes”:1. Is the water used prepared by distillation, by ion exchange or by reverse osmosis?
2. If ‘no’ and potable water is used, where possible, please report the maximum level of nitrite.

(Note: Nitrite is a controlled impurity in potable water with a WHO guideline limit of 3 mg/L and a European limit of 0.5 mg/L.)[[10]](#footnote-10) | **YES** [ ] **YES** [ ] \_\_\_\_ ppm | **NO** [ ] **NO** [ ] Not available [ ]  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| 5) Are there any secondary and/or tertiary amines[[11]](#footnote-11) present in the manufacturing process as8: * Raw material[[12]](#footnote-12)?
* Intermediate?
* Reagent?
* Processing aids?
* Catalyst?
* Solvent?

If yes, are those amines present in the * Same
* Previous
* Subsequent

step as any nitrosating agent mentioned in question 2? Please provide any relevant information about the chemical name / structure of amine(s):……………………………………………………………………………………………………………………………………………………………… | **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ]  | **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ]  | Not applicable[ ] [ ] [ ]  |
| 6) Is there any amide, primary amine[[13]](#footnote-13) or ammonium salt used or present in the excipient manufacturing process as:* Raw material
* Intermediate
* Reagent / Base
* Processing aid
* Catalyst
* Solvent
* Washing Fluid

Information about the chemical name / structure:……………………………………………………………………………………………………………………………………………………………… | **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ] **YES** [ ]  | **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ] **NO** [ ]  |  |
| 7) Recycled/recovered Solvents[[14]](#footnote-14): * Are recycled / recovered nitrogen containing solvents used in the manufacturing process?
 | **YES** [ ]  | **NO** [ ]  |  |
| 8) Equipment:* Is the excipient produced in multipurpose equipment?
* In case of multipurpose equipment, is the equipment used for manufacturing of any material involving nitrites, nitrosating agents or material with identified risk of formation of nitrosamines?
* Are chloramines used as part of cleaning procedures used for manufacturing equipment?
 | **YES** ☐**YES** ☐**YES** ☐ | **NO** ☐**NO** ☐**NO** ☐ | Not applicable☐ |
| 9) Additional comments, if any, not covered in the questionnaire*If “information is not available” has been ticked to any option in question 2), please include any additional comments here.*  |

Annex[[15]](#footnote-15):

## Guidance 1 (Sources of nitrosating agents)

Nitrosating agents to be considered include nitrites (e.g., sodium nitrite, NaNO2) and nitrous acid (HNO2), nitric oxide (NO), nitrosyl halides (e.g., ClNO, BrNO), dinitrogen trioxide (N2O3), dinitrogen tetroxide (N2O4) and organic nitrites (e.g., t-BuONO).

Other potential nitrosation risks:

* Side reaction in nitration reactions. Nitric acid typically contains nitric oxide as an impurity, additional nitrous acid may also be produced, leading to nitrosation, if any reducing agents are present.
* Hydroxylamine under oxidative conditions.
* Chloramines are known to generate N-nitrosamines under certain conditions and so should also be considered.[[16]](#footnote-16)
* Ozone may lead to the formation of N-nitrosamines by initial oxidation of amines to nitrite.13
* Use of azide salts and azide compounds is commonly followed by quenching with nitrous acid or nitrites and may lead to nitrite residues.14
* Nitric acid and nitrates under reducing conditions may result in by-products with nitrosating activity.14

This evaluation must include the use of all chemicals within a process, including those used during the quench and work-up as well as during reactive chemistry.

## Guidance 2 (Sources of secondary and tertiary amines)[[17]](#footnote-17)

Secondary amines are of greatest concern, however tertiary amines can also undergo nitrosation via more complex pathways. All secondary and tertiary aliphatic and aromatic amines should therefore be considered including those present as part of the starting material, intermediate or final structure as well as those introduced as reagents, catalysts, solvents or as impurities.

Tertiary amine bases (i.e., triethylamine, diisopropylethylamine and N-methyl morpholine) may contain secondary amines as impurities.

Secondary Amines may also be introduced as impurities or degradants:

* Of common amide containing solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and N-methyl pyrrolidinone (NMP)
* Of quaternary ammonium salts such as tetrabutylammonium bromide (TBAB)
* Of primary amines such as methylamine
* Of starting materials, intermediates, or the product itself

This evaluation must include the use of all chemicals within a process, including those used during the quench and work-up as well as during reactive chemistry.

## Guidance 3 (Potential contamination risks)

Consider all potential sources of contamination in input materials.

Use of recovered materials (solvents, reagents, catalysts) is of particular concern if appropriate controls are not put in place. The materials DMF, ortho-xylene and tributyltin chloride were highlighted by the EMA as materials at risk of cross contamination by N-nitrosamines. Sodium azide was highlighted by Health Canada for risk of cross contamination with nitrite.

Cross contamination from other processes using shared equipment should be considered. Steps performed under GMP (using solvents/reagents with appropriate controls, and controls on their recovery and reuse) are a lower cross contamination risk.

1. European Medicines Agency (EMA): Assessment report, procedure under Article 5(3) of Regulation EC (No) 726/2004, Nitrosamine impurities in human medicinal products: <https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf> [↑](#footnote-ref-1)
2. European Medicines Agency (EMA): Nitrosamine impurities, Guidance for marketing authorization holders: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities#guidance-for-marketing-authorisation-holders-section>. [↑](#footnote-ref-2)
3. European Medicines Agency (EMA): Questions and answers for marketing authorization holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human products: <https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf> [↑](#footnote-ref-3)
4. U.S. Food & Drug Administration, Control of Nitrosamine Impurities in Human Drugs. [↑](#footnote-ref-4)
5. Text in italics is to aid completion of the template. These instructions should be removed prior to signature. [↑](#footnote-ref-5)
6. Nitrogen-free materials are considered to be of lower inherent risk for nitrosamine contamination as they are typically manufactured and do not contain without nitrosatable structures. Nitrosamines have been observed in medicinal products with N-containing APIs of chemical synthetic origin. EMA concludes that there is a very low risk of nitrosamines being present as impurities in biological medicinal products, although it can’t be completely ruled out.1 [↑](#footnote-ref-6)
7. see Guidance 1 in Annex. [↑](#footnote-ref-7)
8. in this document, “manufacturing process” refers to the manufacturing steps that are outlined in the flow chart of the manufacturing procedure for the mentioned product. [↑](#footnote-ref-8)
9. EMA Guideline on the quality of water for pharmaceutical use: <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-water-pharmaceutical-use_en.pdf> [↑](#footnote-ref-9)
10. Ian W. Ashworth, Olivier Dirat, Andrew Teasdale, and Matthew Whiting. Potential for the Formation of N-Nitrosamines During the Manufacture of Active Pharmaceutical Ingredients: An Assessment of the Risk Posed by Trace Nitrite in Water, Org. Process Res. Dev. 2020, 24 (9), 1629-1646: <https://www.sciencedirect.com/org/science/article/abs/pii/S1083616021021551> [↑](#footnote-ref-10)
11. see Guidance 2 in Annex [↑](#footnote-ref-11)
12. IPEC General Glossary of Terms and Acronyms: <https://www.ipec-europe.org/guidelines.html> [↑](#footnote-ref-12)
13. Primary amines may reduce the risk of nitrosamines formation. See KK Nanda et al., J Pharm Sci 2021 (12), 3773; DOI: <https://doi.org/10.1016/j.xphs.2021.08.010>; M Homsak, Processes 2022 (10), 2428; <https://doi.org/10.3390/pr10112428> [↑](#footnote-ref-13)
14. see Guidance 3 in Annex. [↑](#footnote-ref-14)
15. This information is partly transferred from the EFPIA decision tree for drug substances, published 1 Nov 2019. [↑](#footnote-ref-15)
16. Nawrocki, J et al. Nitrosamines and Water, J. Hazard. Mater. 2011, 189, 1-18. [↑](#footnote-ref-16)
17. SCCS (Scientific Committee on Consumer Safety), Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, 27 March 2012. [↑](#footnote-ref-17)