Questionnaire for Excipient Nitrosamines Risk Evaluation

Several authorities issued guidance and information on nitrosamine impurities and request 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 either directly or through precursor substances present in the excipient (e.g., nitrites, nitrates, 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.

In December 2019 IPEC Europe published a questionnaire assisting excipient manufacturers to collect data that MAH would need to perform their nitrosamine risk assessment. This questionnaire has been used successfully and the information collected herewith was well received by MAHs.

This questionnaire is revised to reflect the 2020 regulatory updates, with reference to the EMA assessment report "Nitrosamine impurities in human medicinal products"[1], the related EMA guidance[2] including the "Questions and answers for marketing authorization holders"[3], the US FDA Guidance for Industry "Control of Nitrosamine Impurities in Human Drugs"[4] and how they may be adapted for pharmaceutical excipients. However, 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 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.

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[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, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

[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.

[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. EMA/409815/2020 Rev.1, 29 January 2021. 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

[4] U.S. Food & Drug Administration, Control of Nitrosamine Impurities in Human Drugs, Revision 1, February 2021, https://www.fda.gov/media/141720/download

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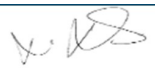
Based on emerging information this form may be adapted accordingly.[5]

This information for nitrosamine risk evaluation is prepared for:

Supplier product number and name:	Zephex®134a
Supplier:	Mexichem UK Ltd

Created by / Date	Richard Greenhough 17 March 2021
Approved by	Helen Harris
Job title	Team Leader - Medical Products Quality Assurance
Signature	

[5] Text in italics is to aid completion of the template. These instructions should be removed prior to signature.

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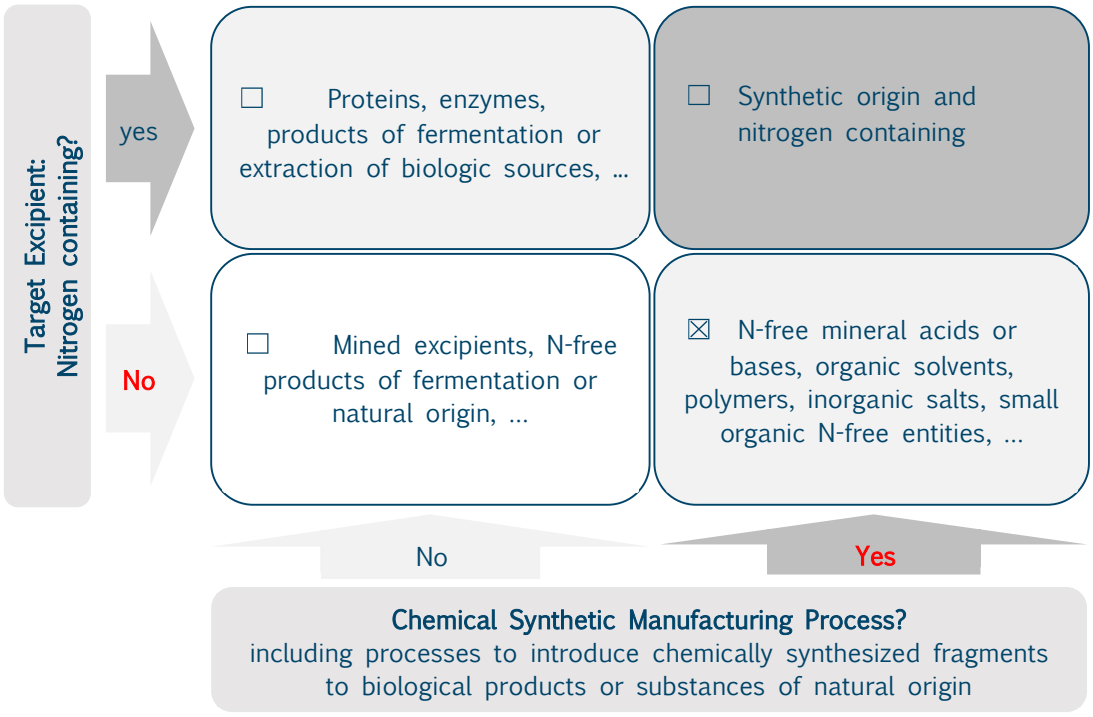
1) Please tick the applicable category based on structure and origin of the excipient in support to evaluate the risk of formation of nitrosamines in the excipient[6].



2) Is sodium nitrite ($NaNO_2$) or any other nitrite or nitrosating agent[7]:			Information not available
- used in any steps in the manufacturing process[8] as reagents/catalyst?	YES ☐	NO ☒	
- known to be used in the preparation of raw materials or intermediates used in the manufacturing process?	YES ☐	NO ☒	☐
- known to be used in the preparation of reagents/catalysts/processing aids used in the manufacturing process?	YES ☐	NO ☒	☐
- known or likely to be generated during the			

[6] Nitrogen-free materials are considered to be of lower inherent risk for nitrosamine contamination as they are typically manufactured without and do not contain 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.Error! Bookmark not defined.

[7] see Guidance 1 in Annex

[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 excipient.

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manufacturing process? - deliberately added to the process, including components of cell culture media or for fermentation?	YES ☐ YES ☐	NO ☒ NO ☒	☐ ☐
3) Have you analysed, and are the results available for the excipient for: - Nitrites? - Nitrates? - Nitrosamines? If yes, please provide test results for the tested analyte and a general indication of the applied test method and indicate if testing was performed in-house or contracted out.	YES ☐ YES ☐ YES ☐	NO ☒ NO ☒ NO ☒	Test result, if available
4) Where water is used in the manufacturing process[8], is it prepared by distillation, by ion exchange or by reverse osmosis? If "No", please inform about the maximum level of - Nitrites - Nitrates	YES ☐ ____ ppm ____ ppm	NO ☐ Not specified ☐ ☐	Not applicable ☒

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5) Is there any secondary and/or tertiary amine[9] present in the manufacturing process as[8]: - Raw material[10]? - Intermediate? - Reagent? - Processing aids? - Catalyst / Base? - Solvent? If yes, are those amines present in the - Same - Previous - Subsequent step as any nitrosating agent mentioned in section 2? 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 or ammonium salt used or present in the excipient manufacturing process as: - Raw material - Intermediate - Reagent - Processing aid - Catalyst / Base - Solvent - Washing Fluid Information about the chemical name / structure: ……	 YES ☐ YES ☐ YES ☐ YES ☐ YES ☐ YES ☐ YES ☐	 NO ☒ NO ☒ NO ☒ NO ☒ NO ☒ NO ☒ NO ☒	

[9] see Guidance 2 in Annex
[10] 2020 IPEC General Glossary of Terms and Acronyms, https://www.ipec-europe.org/glossary.html

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7) Recycled/recovered Solvents[11]: - Are recycled / recovered nitrogen containing solvents used in the manufacturing process?	YES ☐	NO ☒	
8) Multipurpose 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?	YES ☐ YES ☐	NO ☒ NO ☐	Not applicable ☒
9) Conclusion *Please use this field to draw a conclusion about the overall likelihood of the presence of nitrosamines and nitrosating agents.* *If "information not available" has been ticked to any option in question 2), please include any additional comments here.* Zephex® 134a does not contain any nitrogen within the structure of the molecule and is determined as 99.99% purity by specification. Additionally, no nitrogen containing substance, as defined in Q6, is used in the production of Zephex® 134a.			

[11] see Guidance 3 in Annex

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Annex[12]:

Guidance 1 (Sources of nitrosating agents)

Nitrosating agents to be considered 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).

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.[13]
- 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.[13]
- 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)[14]

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-methylmorpholine) are known to degrade to secondary amines and have been implicated in N-nitrosamine formation.

[12] This information is partly transferred from the EFPIA decision tree for drug substances, published 1 Nov 2019
[13] Nawrocki, J et al. Nitrosamines and Water, J. Hazard. Mater. 2011, 189, 1-18.
[14] SCCS (Scientific Committee on Consumer Safety), Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, 27 March 2012.

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Amines may also be introduced as impurities or degradants:

- Of common amide containing solvents such as N,N-dimethylformamide (DMF), N,N-dimethyacetamide (DMAC) and N-methylpyrrolidinone (NMP)
- Of quaternary ammonium salts such as tetrabutylammonium bromide (TBAB)
- Of primary amines such as monoethylamine
- 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 considered to be a lower cross contamination risk.

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