IPEC Questionnaire on Nitrosamines

Questionnaire for Excipient Nitrosamines Risk Evaluation

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], 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.

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.

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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., 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.. 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,

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This information for nitrosamine risk evaluation is prepared for:

Supplier product number and name:	Pharmatose®, Respitose®, Lactochem®, Lactopress®, Lactohale®, SuperTab® (EU), Wynhale®, HMS, Lactose DT
Supplier:	DFE Pharma GmbH & Co. KG

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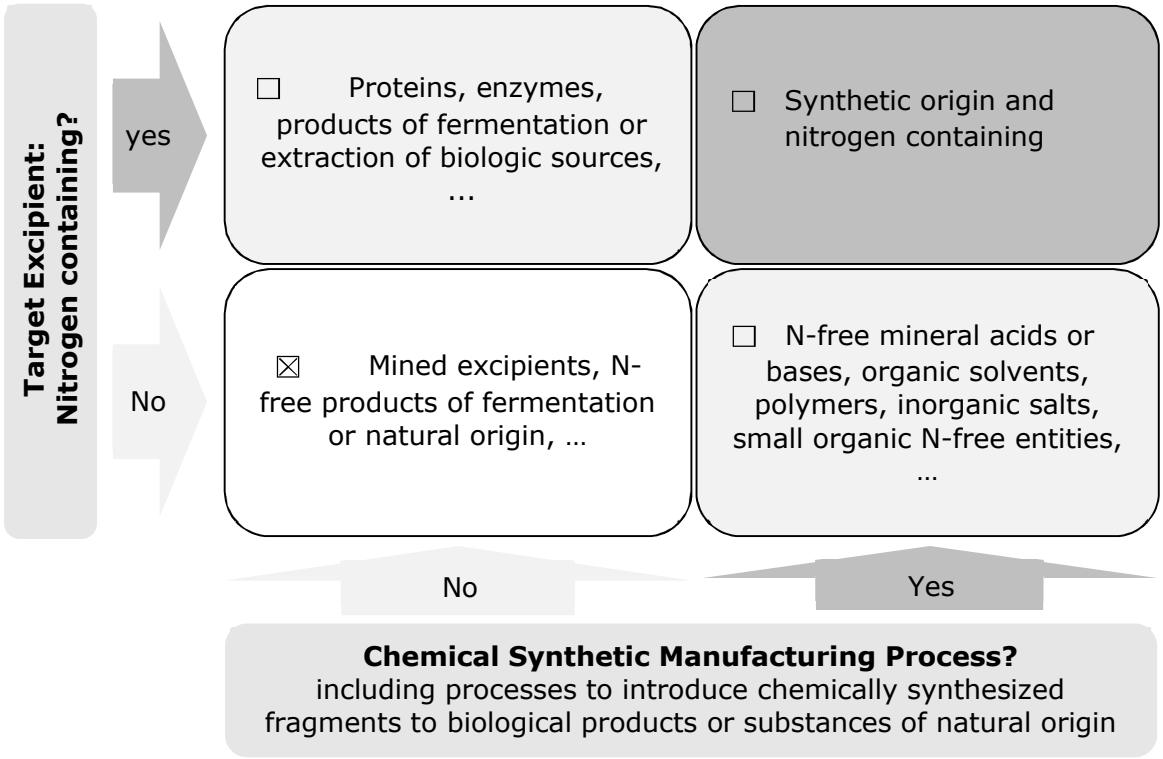
1) Please tick the applicable category based on structure and origin of the excipient in support to evaluate the risk of formation of nitrosamines[5].



2) Is sodium nitrite ($NaNO_2$) or any other nitrite or nitrosating agent[6]:			Not available/ applicable or unknown
- used in any steps in the manufacturing process[7] 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	**YES** ☐	**NO** ☒	☐

[5] 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. **Error! Bookmark not defined.**

[6] see Guidance 1 in Annex

[7] 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.

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** ☐	**NO** ☒ **NO** ☒	☐ ☐
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:** Analytical data for nitrosamines were collected to confirm findings of a Risk Assessment performed by DFE Pharma. Data obtained are used to validate our risk assessment (may be consulted on DFE Pharma sites) and are mentioned there. All data obtained for nitrosamines (NDMA; NMEA; NDEA; NDIBA; NDPA; NDBA; NPIP; NPYR; and NMOR) are below 2 ppb (= Limit of detection). Presented analytical data for nitrites are relative to measures on several commercial batches, as part of monitoring program. The test method used is ISO 14673-2:2004 | IDF 189-2:2004. *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** ☐	Test result ***Nitrite < 0.1 ppm (LOD)*** ***Nitrosamines < 2 ppb (LOD)***

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4) Is water used in the manufacturing process? If "Yes": i. Is purified water[8] used in the manufacturing process? ii. If potable water is used, where possible, please report the maximum level of nitrite. Note: In the production of DFE Pharma lactose products both: potable water (compliant with EU and local legislation) and RO water (derived from potable water) can be used. This information is included in the specific product PFS. Potable water used, complies with the current Directive (EU) 2020/2184 on drinking water (EU sites) or with the current Drinking-Water Standards for New Zealand (New Zealand site). Please inform of maximum levels of Nitrites **Maximum levels in accordance with Directive (EU) 2020/2184**	**YES** ☒ **YES** ☒ **YES** ☒ **0.5 ppm**	**NO** ☐ **NO** ☐ **NO** ☐ Not available ☐	Not applicable ☐

5) Are there any secondary and/or tertiary amines[9] present in the manufacturing process as: - Raw material[10]? - 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): **Not applicable**	**YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES**☐	**NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☐ **NO** ☐ **NO** ☐	Not applicable ☒ ☒ ☒

[8] Prepared by distillation, by ion exchange or by reverse osmosis.
[9] see Guidance 2 in Annex
[10] IPEC General Glossary of Terms and Acronyms: https://www.ipec-europe.org/guidelines.html

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6) Is there any amide, primary amine 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: **Not applicable**	 **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐ **YES** ☐	 **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒ **NO** ☒	
7) Recycled/recovered Solvents[11]: - 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 ☒

[11] see Guidance 3 in Annex

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9) Additional comments, if any, not covered in the questionnaire

Conclusion: ***The risk of presence of nitrosamine in the product is low and nitrite precursors are present only at trace levels (typically < 0.1 ppm).***

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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][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)[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-methyl morpholine) may contain 2ry amines as impurities.

Secondary Amines may also be introduced as impurities or degradants:

[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.

- 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 considered to be a lower cross contamination risk.