

INFORMATION

Quality / Regulatory Affairs



EIP-4036

Revision 10

Date of issue: 27.05.2025

1/3

Nitrosamines

EMA/369136/2020 / FDA Guidance for Industry „Control of Nitrosamine Impurities in Human Drugs“

MEGGLE Product:

Co-processed Excipients: StarLac®

The formation of potent genotoxic nitrosamines as impurities is possible in the presence of secondary, tertiary, or quaternary amines and nitrite salts under acidic reaction conditions.

Regarding the requests of EMA-CHMP and FDA-CDER that marketing authorisation holders for human medicines containing chemically synthesised active substances have to evaluate the risk for the possible presence of nitrosamines (e.g. NDMA, NDEA, NMBA, NMPA, NIPEA, NDIPA), a risk evaluation was conducted for the MEGGLE Products used as excipients to support the marketing authorisation holders. This evaluation is based on the [IPEC Questionnaire](#) and attached.

The MEGGLE Product is a co-processed, directly compressible spray agglomerate containing

- 85 % Lactose Monohydrate (Ph. Eur. / USP-NF / JP) and
- 15 % Maize Starch (Ph. Eur. / USP-NF / JP).

The risk evaluation reflects the whole manufacturing process at MEGGLE independent from the defined starting material as regard of GMP requirements.

The component Lactose Monohydrate is not chemically synthesised. It is isolated and purified from whey at MEGGLE. Secondary and/or tertiary amines, amides, primary amines and ammonium salts are not used or present in the manufacturing process. Due to the knowledge of the raw material, production process and equipment the risk for a contamination with nitrosamines is excluded.

The component is tested on nitrite with typical results ≤ 0.1 ppm.

The component Maize Starch is not chemically synthesised. It is of vegetable origin. Secondary and/or tertiary amines, amides, primary amines and ammonium salts are not used or present in the manufacturing process. The supplier states that due to the knowledge of the raw material, production process and equipment the risk for a contamination with nitrosamines is excluded.

The component is tested on nitrite with typical results ≤ 0.47 ppm.

The MEGGLE Product StarLac® is not chemically synthesised. Organic solvents, catalysts and other reagents which might be a reason for the presence of secondary, tertiary, or quaternary amines and nitrite salts are not used. Furthermore, strongly acidic conditions as necessary prerequisite for the formation of nitrosamines are not achieved during manufacturing process.

Test results on nitrites and nitrosamines are available. Results are given in the risk evaluation.

Conclusion: Neither the chemical composition nor the processing conditions indicate any possibility for nitrosamine contamination and formation in the process or storage of the MEGGLE Product.

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Nitrosamine Risk Evaluation

6) Is there any amide, primary amine or ammonium salt used or present in the substance manufacturing process as: - Raw material? - Intermediate? - Reagent? - Processing aids? - Catalyst? - Solvent? - Washing Fluid?	YES <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	NO <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	
7) Recycled/recovered Solvents ⁶ : - Are recycled / recovered nitrogen containing solvents used in the manufacturing process?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	
8) Equipment: - Is the substance 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 <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	NO <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<i>Not applicable</i> <input type="checkbox"/>
9) Additional comments, if any, not covered in the questionnaire			

Annex⁷:

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.⁸
- Ozone may lead to the formation of N-nitrosamines by initial oxidation of amines to nitrite.
- Use of azide salts and azide compounds is commonly followed by quenching with nitrous acid or nitrites and may lead to nitrite residues.
- Nitric acid and nitrates under reducing conditions may result in by-products with nitrosating activity.

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)⁹

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.

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-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.

⁶ See Guidance 3 in Annex

⁷ This information is partly transferred from the EFPIA decision tree for drug substances, published 1 Nov 2019

⁸ Nawrocki, J et al. Nitrosamines and Water, J. Hazard. Mater. 2011, 189, 1-18.

⁹ SCCS (Scientific Committee on Consumer Safety), Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, 27 March 2012.

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