Nitrosamines

EMA/369136/2020; FDA Guidance for Industry „Control of Nitrosamine Impurities in Human Drugs“
MEGGLE USA Products:
- Lactose Monohydrate: GranuLac® 70 US, GranuLac® 140 US, GranuLac® 200 US
- Anhydrous Lactose: DuraLac® H

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 risk evaluation reflects the whole manufacturing process at Agropur inc. as subcontracted production site of MEGGLE USA starting with whey independent from the defined starting material as regard of GMP requirements.

The MEGGLE USA Products are isolated and purified from whey which is a by-product of cheese manufacturing. Therefore, nitrite traces might come from the raw material whey and water. Testing on nitrates and nitrites is conducted as part of incoming goods inspection of whey. The acceptance limits are as follows: Nitrate < 50 ppm, Nitrite < 5 ppm.
The process water is regularly tested on nitrites. Results are given in the risk evaluation.

The MEGGLE USA Products are natural materials and are not chemically synthesised. The chemical structure does not contain nitrogen. 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. The manufacturing includes several washing steps as well as double crystallisation and refining. These steps are leading to a highly purified product. The manufacturing process does not create the highly acidic conditions necessary for the formation of nitrosamines and for drying only indirect heating is used. There is no potential NO_x generation from combustion.

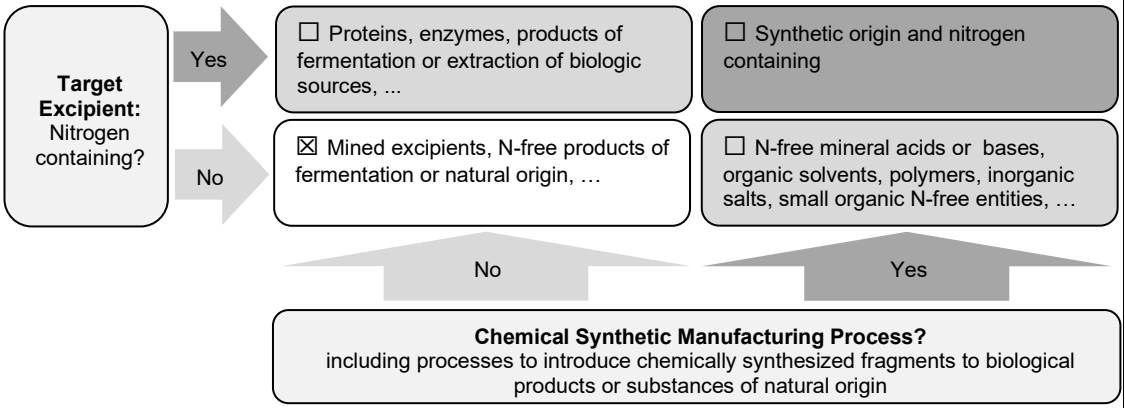
MEGGLE USA Products are tested on nitrites. Test results on nitrosamines in MEGGLE USA Products are available. Results are given in the risk evaluation.

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

MEGGLE USA Inc., 592 Route 22, Suite 2B, Pawling, NY 12564, USA
Telephone +1 845 289 0264, customer.service@meggle.com
www.meggle-pharma.com

Nitrosamine Risk Evaluation

1) Applicable category based on structure and origin of the excipient in support to evaluate the risk of formation of nitrosamines in the excipient[1]



	YES	NO	*Information not available*
2) Is sodium nitrite ($NaNO_2$) or any other nitrite or nitrosating agent[2]:			
- used in any steps in the manufacturing process[3] 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 as impurities during the manufacturing process?	☐	☒	☐
- deliberately added to the process, including components of cell culture media or for fermentation?	☐	☒	☐

	YES	NO	*Test result*
3) Have you analysed the excipient for:			
- nitrites?	☒	☐	≤ 0.1 ppm
- nitrosamines?	☒	☐	< LoQ
Nitrites: Method IC; LoD 0.01 ppm, LoQ 0.03 ppm / Nitrosamines NDMA, NDEA, NDPA, NDBA, NMOR, NPYR, NPIP: Method GC/TEA; LoQ 0.5 ppb / Tests conducted in a contracted laboratory. Test results are "typical" and are not part of Specification.			

	YES	NO	*Not applicable*
4) Is water used in the manufacturing process? If "Yes":	☒	☐	
i. is purified water[4] used in the manufacturing process?	☒	☐	☐
ii. if potable water is used, where possible, please report the maximum level of nitrite.	☒	☐	☐
Maximum levels of			*Not available*
- Nitrites	< LoD		☐
Note: Water is mainly prepared by reverse osmosis. Nevertheless, use of water which is not prepared by reverse osmosis cannot be excluded.			
Requirements according EPA National Primary Drinking Water Regulations: Nitrite < 1 mg/l, calculated as N.			

	YES	NO	
5) Are there any secondary and/or tertiary amines[5] present in the manufacturing process as:			
- raw material[6]?	☐	☒	
- intermediate?	☐	☒	
- reagent?	☐	☒	
- processing aids?	☐	☒	
- catalyst?	☐	☒	
- solvent?	☐	☒	
If yes, are those amines present in the …			*Not applicable*
- same	☐	☐	☒
- previous	☐	☐	☒
- subsequent	☐	☐	☒

[1] Nitrogen-free materials are considered to be of lower inherent risk for nitrosamine contamination as they are typically manufactured 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.
[2] See Guidance 1 in Annex
[3] 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.
[4] Prepared by distillation, ion exchange, reverse osmosis
[5] See Guidance 2 in Annex
[6] 2020 IPEC General Glossary of Terms and Acronyms, https://www.ipec-europe.org/glossary.html

Nitrosamine Risk Evaluation

step as any nitrosating agent mentioned in section 2?			

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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:	**YES**	**NO**	
- Raw material?	☐	☒	
- Intermediate?	☐	☒	
- Reagent?	☐	☒	
- Processing aids?	☐	☒	
- Catalyst?	☐	☒	
- Solvent?	☐	☒	
- Washing Fluid?	☐	☒	
7) Recycled/recovered Solvents[7]:	**YES**	**NO**	
- Are recycled / recovered nitrogen containing solvents used in the manufacturing process?	☐	☒	
8) Equipment:	**YES**	**NO**	*Not applicable*
- 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?	☐	☒	
9) Additional comments, if any, not covered in the questionnaire			

Annex[8]:

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.[9]
- 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)[10]

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-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.

[7] See Guidance 3 in Annex
[8] This information is partly transferred from the EFPIA decision tree for drug substances, published 1 Nov 2019
[9] Nawrocki, J et al. Nitrosamines and Water, J. Hazard. Mater. 2011, 189, 1-18.
[10] SCCS (Scientific Committee on Consumer Safety), Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, 27 March 2012.

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