# **INFORMATION**

Quality / Regulatory Affairs



EIP-1036-USA

Revision 2

Date of issue: 13.12.2023

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### **Nitrosamines**

EMA/369136/2020; FDA Guidance for Industry "Control of Nitrosamine Impurities in Human Drugs" MEGGLE USA Products:

- Lactose Monohydrate: GranuLac® 70, GranuLac® 140, GranuLac® 200
- 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 <a href="IPEC Questionnaire">IPEC Questionnaire</a> 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.

Whey does not contain relevant amounts of nitrates (as precursor of nitrites) and nitrites. Testing on nitrates and nitrites is conducted as part of incoming goods inspection. The acceptance limits are as follows: Nitrate < 50 ppm, Nitrite < 5 ppm.

The MEGGLE Products are not chemically synthesized. 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.

MEGGLE USA Products are tested on nitrites. Test results on nitrosamines in MEGGLE 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.

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#### **Nitrosamine Risk Evaluation**

1) Applicable category based on structure and origin of the excipient in support to evaluate nitrosamines in the excipient <sup>1</sup>	the risk o	f format	ion of			
Target Excipient:  Yes  Proteins, enzymes, products of fermentation or extraction of biologic sources,		ineral acids or bases, ents, polymers, inorganic organic N-free entities,				
Nitrogen containing?  Mined excipients, N-free products of fermentation or natural origin,	olvents, po					
No	Y	es				
including processes to introduce chemically synthe	Chemical Synthetic Manufacturing Process? including processes to introduce chemically synthesized fragments to biological products or substances of natural origin					
2) Is sodium nitrite (NaNO <sub>2</sub> ) or any other nitrite or nitrosating agent <sup>2</sup> :  - used in any steps in the manufacturing process <sup>3</sup> as reagents/catalyst?  - known to be used in the preparation of raw materials or intermediates used in the manufacturing process?	YES	NO	Information not available			
<ul> <li>known to be used in the preparation of reagents/catalysts/processing aids used in the manufacturing process?</li> <li>known or likely to be generated as impurities during the manufacturing process?</li> <li>deliberately added to the process, including components of cell culture media or for fermentation?</li> </ul>	he					
3) Have you analysed the excipient for: - nitrites? - nitrosamines? Nitrites: Method FIA; LoD 0.39 ppm / Nitrosamines NDMA, NDEA, NDPA, NDBA, NMOR, NPYR, NPIP: Method GC/TEA; LoQ 0.5 ppb / Tests conducted in a contracted laboratory.	YES	<b>NO</b>	Test result < LoD < LoQ			
4) Is water used in the manufacturing process? If "Yes": i. is purified water <sup>4</sup> used in the manufacturing process? ii. if potable water is used, where possible, please report the maximum level of nitrite.	YES	NO 	Not applicable			
Maximum levels of - Nitrites Note: Water is mainly prepared by reverse osmosis. Nevertheless, use of water which is n cannot be excluded. Requirements according EPA National Primary Drinking Water Regulations: Nitrite < 1 mg		•				
5) Are there any secondary and/or tertiary amines <sup>5</sup> present in the manufacturing process a raw material <sup>6</sup> ? - intermediate? - reagent? - processing aids? - catalyst? - solvent?	ss: YES	NO NO NO NO NO NO NO NO NO NO	Not			
If yes, are those amines present in the same - previous - subsequent step as any pitrosating agent mentioned in section 22			applicable			

<sup>1</sup> Nitrogen-free materials are considered to be of lower inherent risk for nitrosamine contamination as they are typically manufactured and do not contain nitrosatable 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.
 See Guidance 1 in Annex
 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.
 Prepared by distillation, ion exchange, reverse osmosis
 See Guidance 2 in Annex
 2020 IPEC General Glossary of Terms and Acronyms, <a href="https://www.ipec-europe.org/glossary.html">https://www.ipec-europe.org/glossary.html</a>
 This MEGGLE USA Information was electronically released and is valid without signature.

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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?		$\boxtimes$	
- Intermediate?		$\boxtimes$	
- Reagent?		$\boxtimes$	
- Processing aids?		$\boxtimes$	
- Catalyst?		$\boxtimes$	
- Solvent?		$\boxtimes$	
- Washing Fluid?		$\boxtimes$	
7) Recycled/recovered Solvents <sup>7</sup> :	YES	ОИ	
- Are recycled / recovered nitrogen containing solvents used in the manufacturing process?		$\boxtimes$	
			Not
8) Equipment:	YES	NO	applicable
- Is the substance produced in multipurpose equipment?		$\boxtimes$	
- 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			$\boxtimes$
nitrosamines?			
- Are chloramines used as part of cleaning procedures used for manufacturing equipment?		$\boxtimes$	
9) Additional comments, if any, not covered in the questionnaire			

#### Annex8:

#### 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. CINO, 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.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 guench and work-up as well as during reactive chemistry.

#### Guidance 2 (Sources of secondary and tertiary amines)<sup>10</sup>

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
- 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.

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