



To whom it may concern

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Quality Unit

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Nitrosamines

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

MEGGLE Product: CombiLac®

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 product to support the marketing authorisation holders. This evaluation (page 2 and 3) is based on the [IPEC Questionnaire](#).

The product is a co-processed, directly compressible spray agglomerate comprising 70 % Lactose Monohydrate (Ph. Eur. / USP-NF / JP), 20 % Microcrystalline Cellulose and 10 % Maize Starch (Ph. Eur. / USP-NF / JP).

The compound lactose monohydrate produced at MEGGLE is 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, acidic conditions as necessary prerequisite for the formation of nitrosamines are not achieved during manufacturing process. Lactose monohydrate is isolated and purified from whey which is a by-product of cheese manufacturing. 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 compounds microcrystalline cellulose and maize starch are not chemically synthesized. They are of vegetable origin. Secondary and/or tertiary amines, amides, primary amines and ammonium salts are not used or present in the manufacturing processes. The suppliers certify that the substances are free from nitrosamines

The product CombiLac® is 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, acidic conditions as necessary prerequisite for the formation of nitrosamines are not achieved during manufacturing process. The product itself is tested on nitrates and nitrites. Furthermore, testing on nitrosamines was conducted (see page 2).

Strongly acidic conditions as necessary prerequisite for the formation of nitrosamines are not achieved during manufacturing process.

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 products.

Best regards

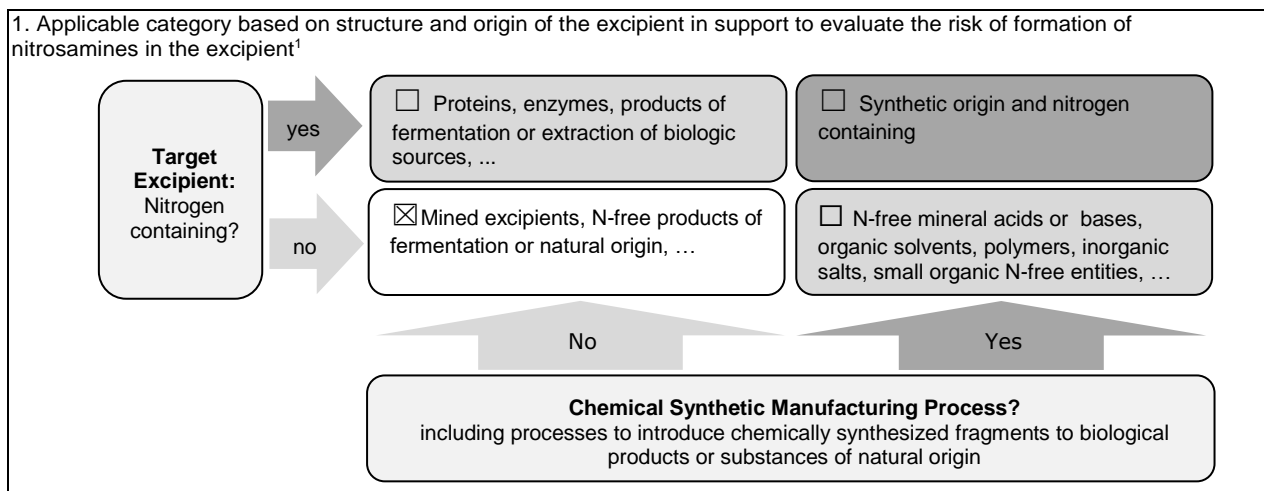
MEGGLE GmbH & Co. KG

A handwritten signature in blue ink that reads "i. V. Stefan Dreiheller".

Dr. Stefan Dreiheller

Regulatory Affairs / Specification Management

Nitrosamine Risk Evaluation



| | | | |
|--|---|---|---|
| 1) 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 to be generated as impurities during the manufacturing process? | YES <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"/> | Information not available <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> |
| 3) Have you analysed, and are the results available for the excipient for: - Nitrites? - Nitrates? - Nitrosamines? Tests conducted in a contracted laboratory. - Nitrites and Nitrates: Method FIA, for Nitrates with Cd reduction; LoD 0.2 ppm - Nitrosamines NDMA, NDEA, NDPA, NDBA, NMOR, NPYR, NPIP: Method GC/TEA; LoQ 0.5 ppb | YES <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> | NO <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> | Test result, if available < LoD 5 ppm < LoQ |
| 4) Where water is used in the manufacturing process, is it prepared by distillation, by ion exchange or by reverse osmosis? If "No", please inform about the maximum level of - Nitrites - Nitrates | YES <input checked="" type="checkbox"/> _____ | NO <input type="checkbox"/> Not specified <input type="checkbox"/> <input type="checkbox"/> | Not applicable <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> |
| 5) Is there any secondary and/or tertiary amine ⁴ present in the manufacturing process as: - Raw material ⁵ ? - Intermediate? - Reagent? - Processing aids? - Catalyst / Base? - Solvent? If yes, are those amines present in the - Same - Previous - Subsequent | YES <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <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"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> | Not applicable <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> |

step as any nitrosating agent mentioned in section 2?

¹ 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 according EMA 369136/2020
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 see Guidance 2 in Annex
⁵ 2020 IPEC General Glossary of Terms and Acronyms, <https://www.ipec-europe.org/glossary.html>



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? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| - Intermediate? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| - Reagent? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| - Processing aids? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| - Catalyst / Base? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| - Solvent? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| - Washing Fluid? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| 7) Recycled/recovered Solvents ⁶ : | YES | NO | |
| - Are recycled / recovered nitrogen containing solvents used in the manufacturing process? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| 8) Multipurpose Equipment: | YES | NO | <i>Not applicable</i> |
| - Is the substance produced in multipurpose equipment? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| 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? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| 9) 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 products. | | | |

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.