To whom it may concern

Dr. Stefan Dreiheller
Quality Unit / Regulatory Affairs

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Nitrosamines

EMA/369136/2020; FDA Guidance for Industry „Control of Nitrosamine Impurities in Human Drugs“
MEGGLE Product: Reta M®

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 50 % Mannitol (Ph. Eur. / USP-NF / JP) and 50 % Hypromellose (Ph. Eur. / USP-NF / JP).

The compound mannitol is not chemically synthesized. 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 certifies that the substance is free from nitrosamines. The supplier certifies that the substance is free from nitrosamines.

The compound hypromellose is synthesized without the use of nitrites and other nitrosating agents. Secondary and/or tertiary amines, amides, primary amines and ammonium salts are not used or present in the manufacturing process. The supplier certifies that the substance is free from nitrosamines.

The product Reta M® 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 (see page 2).

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.

Best regards

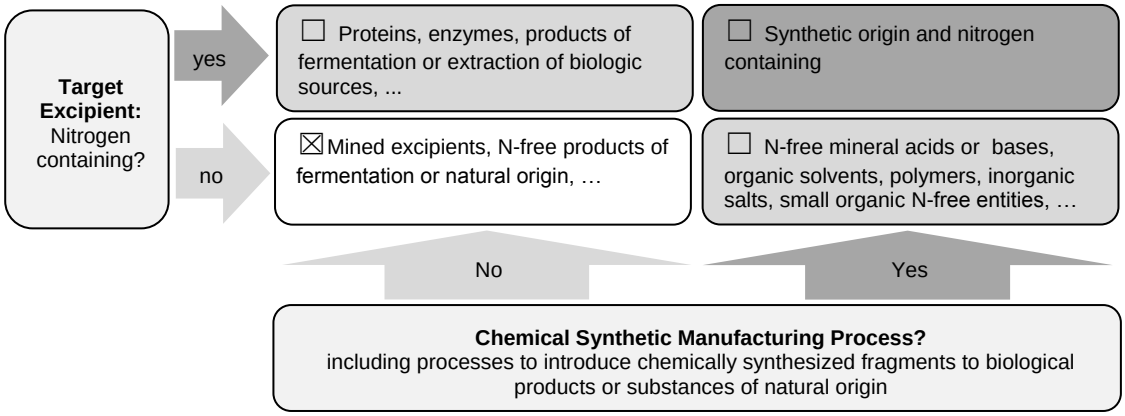
MEGGLE GmbH & Co. KG
represented by MEGGLE Verwaltungs GmbH

i. V. Stefan Dreiheller

Dr. Stefan Dreiheller

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 to be generated as impurities during the manufacturing process?	☐	☒	☐

	YES	NO	*Test result, if available*
3) Have you analysed, and are the results available for the excipient for:			
- Nitrites?	☒	☐	2.0 – 3.6 ppm
- Nitrates?	☒	☐	26.4 – 54.5 ppm
- Nitrosamines?	☐	☒	

Method: FIA, for Nitrates with Cd reduction; in contracted laboratory; LOD 0.2 ppm; LOQ: 0.5 ppm

	YES	NO	*Not applicable*
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		*Not specified*	
- Nitrites	____ ppm	☐	☒
- Nitrates	____ ppm	☐	☒

	YES	NO	
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			*Not applicable*
- Same	☐	☐	☒
- Previous	☐	☐	☒
- Subsequent	☐	☐	☒
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?	☐	☒	
- Intermediate?	☐	☒	
- Reagent?	☐	☒	
- Processing aids?	☐	☒	
- Catalyst / Base?	☐	☒	
- Solvent?	☐	☒	
- Washing Fluid?	☐	☒	
7) Recycled/recovered Solvents[6]:	**YES**	**NO**	
- Are recycled / recovered nitrogen containing solvents used in the manufacturing process?	☐	☒	
	YES	**NO**	*Not applicable*
8) Multipurpose 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?	☐	☒	☐
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 product.			

Annex[7]:

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.[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-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.

[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.