REPORT ON THE RISK OF POTENTIAL PRESENCE OF NITROSAMINE IMPURITIES

Document ID:

MATERIAL

Name : ……

Material code(s) :……

MANUFACTURER (refers to the manufacturing site)

Name :……

Address :……

This report was completed by [person / central service]:

- Name and position: ……
- E-mail address: ……
- Postal address: ……

Declaration:

The current manufacturing process of (**the name of the substance**) was assessed with respect to the risk of the presence of Nitrosamine impurities.

The signatory expressly recognizes that all information contained in this report is based on current knowledge and is true and sincere to his / her actual knowledge considering available supplier information and likely chemical production processes where information from the supplier is not available. The signatory further confirms that he / she has the authority to act on behalf of the company they represent.
The information in this document may be updated as more information becomes available.

Date, Signature and Company stamp

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4. In section 3, the detail would depend on the customer with whom the report will be shared. The process description can be replaced by a workflow with the relevant information for the assessment or just to reference the filing applicable section.

5. In section 3, a description of the process step where the risk assessment was initiated, e.g. from starting material or from intermediate, should be provided with a rationale for the selection.

6. For table in section 6, fill one line per nitrosamine which has been identified as being possibly generated during the API manufacturing process.

1 INTRODUCTION

This document reports the outcome of the Risk Assessment on the above mentioned API based on the requirements defined in the EMA notices *Information on nitrosamines for marketing authorisation holders* EMA/189634/2019 and *Questions and answers on "Information on nitrosamines for marketing authorisation holders"* EMA/428592/2019 and following revisions and other similar published by other Health Agencies.

Such evaluation on the potential risk of presence of nitrosamine impurities in the APIs was performed using quality risk management principles, as per ICH Q9 guideline and ICH M7. Manufacturing processes are being reviewed to identify and, if found, to mitigate risk of presence of N-nitrosamine impurities during manufacture and storage of the drug substance.

2 SCOPE

The Risk Assessment has evaluated the following items as potential sources of nitrosamines or their precursors in line with root causes described in *Questions and answers on Information on nitrosamines for marketing authorisation holders* EMA/428592/2019:

1. Use of sodium nitrite or other nitrosating agents in presence of secondary, or tertiary amines, or quaternary ammonium salts within the API manufacturing process either within the same or at different process steps.
2. Use of sodium nitrite or other nitrosating agents in combination with reagents, solvents, and catalysts, which are susceptible to degradation to secondary or tertiary amines, within the same or different process steps.
3. Use of contaminated raw materials (e.g. solvents, reagents, catalysts)
4. Use of recovered materials (e.g. solvents, reagents, catalysts)
5. Use of contaminated starting materials and intermediates supplied by vendors.
6. Potential contamination due to risk for cross-contamination or carry over in multipurpose plants
7. Degradation processes of starting materials, intermediates, or drug substances.
8. Primary packaging materials.

3 MANUFACTURING / PROCESS STEPS COVERED BY RISK ASSESSEMENT

The Manufacturing Process described below may not contain some process details due to Intellectual Property Protection as per Company Policy.

4 RISK ASSESSMENT METHODOLOGY

The Risk Assessment methodology used has been *[FMEA / Questionnaire / other]*. The risk assessment for potential presence of nitrosamines has been conducted taking into account the following dimensions *[severity, probability, detectability]*.

5 SUMMARY OF ITEMS REVIEWED FOR THE RISK ASSESSMENT

For each of the following items, indicate whether a risk for potential presence of nitrosamines has been identified or not. As applicable, comment on the response provided whether the response is yes or no.

5.1 Use of sodium nitrite or other nitrosating agents in presence of secondary, or tertiary amines, or quaternary ammonium salts within the API manufacturing process either within the same or at different process steps.

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

5.2 Use of sodium nitrite or other nitrosating agents in combination with reagents, solvents, and catalysts, which are susceptible to degradation to secondary or tertiary amines, within the same or different process steps.

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

5.3 Use of contaminated raw materials (e.g. solvents, reagents, catalysts)

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

5.4 Use of recovered materials (e.g. solvents, reagents, catalysts)

Risk for presence of nitrosamines identified: YES ☐ NO ☐ N/A ☐

Comment:

5.5 Use of contaminated starting materials and intermediates supplied by vendors.

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

5.6 Potential contamination due to risk for cross-contamination or carry over in multipurpose plants

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

5.7 Degradation processes of starting materials, intermediates, or drug substances.

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

5.8 Packaging materials

Risk for presence of nitrosamines identified: YES ☐ NO ☐

Comment:

6 RISK ASSESSMENT RESULT

Based on the risk assessment conducted, the risk for presence of nitrosamines is evaluated as:

- ☐ *negligible*
- ☐ *potentially present*

If the risk for contamination by nitrosamines is potentially present, indicate the possible nitrosamine impurity, the origin of contamination and proposed mitigation measures:

Possible Nitrosamine (Name and Structure)	Origin of contamination (specify nitrosating and nitrosable agents)	Mitigation measures

7 ADDITIONAL INFORMATION TO SUPPORT THE RISK ASSESSMENT BY THE DRUG PRODUCT MANUFACTURER / MARKETING AUTHORIZATION HOLDER (MAH)

As the drug product manufacturer is responsible to evaluate whether any residual nitrosating or nitrosable substances from the API may lead to potential formation of nitrosamines in the Drug Product, the following information is provided.

Based on the manufacturing process reviewed and on its related risk assessment for potential presence of nitrosamines, the API manufacturer declares that there is

7.1 For nitrosating agents:

- ☐ Nitrosating agents are not likely to be present in the final API.
- ☐ A risk for potential presence of nitrosating agents in the final API (see table below for details).

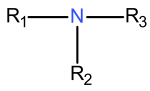
Table 1. Nitrosating agents

Nitrosating agent (NO)*	Structure	Potentially present in final API
Nitrite salts	MNO_2	
Nitrate salts	MNO_3	
Nitrous acid	HNO_2	
Nitrous acidium ion	H_2O^+-NO	
Nitric acid (contains N_2O_4)	HNO_3	
Alkyl nitrites	R-ONO	
Peroxynitrite	ONOO(-)	
Nitrosonium ion	NO+	
Nitro compounds	R-NO_2	
Nitrous anhydride	N_2O_3	
Dinitrogen tetroxide	N_2O_4	
Nitrosyl halides	Halide-NO	
Nitrosyl thiocyanate	ONSCN	
Nitrosophenol	Phenol-NO	
Nitrosothiol	SH-NO	
Aqua regia	HCl + HNO3	
Nitryl chloride	NO_2Cl	
Other (specify)		

7.2 For Nitrosable substances:

- ☐ Nitrosable substances are not likely to be present in the final API.
- ☐ A risk for potential presence of nitrosable substances in the final API or as integral part of the API (see table below for details).

Table 2. Nitrosable substances

Nitrosatable substance	Structure	byproducts	(Potentially) present in final API
Secondary amines (cyclic and acyclic)	R_1-NH-R_2	-	
Tertiary amines (cyclic and acyclic)		NHR_1R_2, NHR_1R_3, or/and NHR_2R_3	
Hydrazine derivatives	NH_2-NR_1R_2	NHR_1R_2	
N-methyl-2-pyrrolidinone		N-methyl-4-aminobutyric acid	
Tertiary amides	$R_1CONR_2R_3$	NHR_2R_3	
N-Chloroalkylamines	R_1R_2N-Cl	NHR_1R_2	
N-alkylcarbamates	R_1O-CO-NR_2R_3	NHR_2R_3	
Other (specify)			

8 CHANGES IN MANUFACTURING PROCESS WITH POTENTIAL IMPACT ON NITROSAMINE IMPURITY FORMATION

In case of changes in the manufacturing process, starting materials, suppliers etc. that may affect this risk assessment, we will evaluate the impact, revise this assessment when necessary and inform our customers of the outcome.