**REPORT ON THE RISK OF POTENTIAL PRESENCE**

**OF NITROSAMINE IMPURITIES**

**Document ID:**

|  |
| --- |
| ***DRUG SUBSTANCE***  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 drug substance**) was assessed with respect to the risk of the potential presence of Nitrosamine impurities in line with EMA guidelines (EMA/369136/2020, EMA/409815/2020) and other related regulations published by other Health Agencies.

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**

**Delete this page when issuing the letter.**

Instructions when using this template.

1. Replace APIC logo by your company logo.
2. In the footer, replace CEFIC logo by “This document was prepared based on APIC template”.
3. In various places in the template, text appears in italics in square brackets, e.g. *[Option 1, Option 2, Option3]*. Keep the text that applies and remove the text that don’t apply to the situation which is being described.
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 evaluation or just to reference the filing applicable section.
5. In section 3, a description of the process step where the risk evaluation 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 evaluation on the above mentioned API based on the requirements defined in the EMA assessment report “Nitrosamine impurities in human medicinal products”[[1]](#footnote-1), the EMA “*Questions and answers for marketing authorisation holders”*[[2]](#footnote-2) , the US FDA Guidance for Industry *“Control of Nitrosamine Impurities in Human Drugs”*[[3]](#footnote-3) and other related regulations published by other Health Agencies, such as by Health Canada.[[4]](#footnote-4)

Such evaluation on the risk of presence of nitrosamine impurities in the APIs was performed using quality risk management principles, as per current 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 Evaluation has evaluated the following items as potential sources of nitrosamines or their precursors in line with root causes described in *Questions and answers for marketing authorisation holders*2:

1. Use of sodium nitrite (NaNO2), or other nitrosating agents, in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process.
2. Use of sodium nitrite (NaNO2), or other nitrosating agents, in combination with reagents, solvents (e.g. DMF, DMAc and NMP) 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) and water.
4. Use of contaminated recovered or recycled materials (e.g. solvents, reagents, catalysts).
5. Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents.
6. Carry-over of nitrosamines deliberately generated (e.g. as intermediates) during the manufacturing process.
7. Cross-contamination due to different processes being run successively on the same manufacturing line.
8. Carry-over of impurities between process steps due to operator-related errors or insufficiently detailed batch records such as inadequate phase separations during work-up procedures.
9. Degradation processes of starting materials, intermediates, or drug substances including those induced by inherent reactivity (e.g. presence of nitro, oxime, or other functionality) or by the presence of an exogenous nitrosating agent.
10. Primary packaging materials.
11. Presence of nitrosatable nitrogen functionality in APIs or their impurities.

Please note that above listed root causes follow EMA *Questions and answers for marketing authorization holders*.2 In addition, the root causes, such as “*Quenching Process as a Source of Nitrosamine Contamination*” and “*Lack of Process Optimization and Control*” as described in FDA Guidance for Industry3 are addressed within the present EMA’s root causes. Namely, “*Quenching Process as a Source of Nitrosamine Contamination*” is covered under root causes 1 and 2, meanwhile “*Lack of Process Optimization and Control*” is covered under root causes 3-8.

1. **MANUFACTURING / PROCESS STEPS COVERED BY RISK EVALUATION**

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

1. **RISK EVALUATION METHODOLOGY**

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

1. **SUMMARY OF ITEMS REVIEWED FOR THE RISK EVALUATION**

For each of the following items, indicate whether a risk for presence of nitrosamines has been identified or not. In each case consider the item’s potential as a direct source of nitrosamines and/or source of nitrosamine precursors which could subsequently pose a risk of nitrosamine formation. Please consider presence of nitrosating agents and nitrosatable substances for the risk evaluation results in Chapter 6. Provide justification as to why the response is yes or no. For additional information regarding presence of nitrosating agents and nitrosatable substances in the API please refer to Chapter 7.

* 1. Use of sodium nitrite (NaNO2), or other nitrosating agents, in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process.

Risk for presence of nitrosamines identified: YES  NO

Justification:

* 1. Use of sodium nitrite (NaNO2), or other nitrosating agents, in combination with reagents, solvents (e.g. DMF, DMAc and NMP) 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

Justification:

* 1. Use of contaminated raw materials (e.g. solvents, reagents, catalysts) and water.

Risk for presence of nitrosamines identified: YES  NO

Justification:

* 1. Use of contaminated recovered or recycled materials (e.g. solvents, reagents, catalysts).

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

Justification:

* 1. Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents.

Risk for presence of nitrosamines identified: YES  NO

Justification:

* 1. Carry-over of nitrosamines deliberately generated (e.g. as intermediates) during the manufacturing process.

Risk for presence of nitrosamines identified: YES  NO

Comment:

* 1. Cross-contamination due to different processes being run successively on the same manufacturing line.

Risk for presence of nitrosamines identified: YES  NO

Justification:

* 1. Carry-over of impurities between process steps due to operator-related errors or insufficiently detailed batch records such as inadequate phase separations during work-up procedures.

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

Justification:

* 1. Degradation processes of starting materials, intermediates, or drug substances including those induced by inherent reactivity (e.g. presence of nitro, oxime, or other functionality) or by the presence of an exogenous nitrosating agent.

Risk for presence of nitrosamines identified: YES  NO

Justification:

* 1. Primary packaging materials

Risk for presence of nitrosamines identified: YES  NO

Justification:

* 1. Presence of nitrosatable nitrogen functionality in APIs or their impurities

Presence identified: YES  NO

Justification:

1. **RISK EVALUATION RESULT**

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

*negligible (no risk identified)*

*potentially present (risk identified)*

If the risk for potential presence of nitrosamines was identified, indicate the possible nitrosamine impurity, the origin of its presence and proposed mitigation measures:

|  |  |  |  |
| --- | --- | --- | --- |
| Possible Nitrosamine  (Name and Structure) | Origin of possible nitrosamine  (specify nitrosating agents and nitrosatable substances) | Mitigation measures | Test results available? |
|  |  |  | YES  NO |

\*Available analytical test results are given here / included in the attachment (please choose the applicable option).

1. **ADDITIONAL INFORMATION TO SUPPORT THE RISK EVALUATION BY THE DRUG PRODUCT MANUFACTURER / MARKETING AUTHORIZATION HOLDER (MAH)**

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

**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 | MNO2 |  |
| Nitrate salts | MNO3 |  |
| Nitrous acid | HNO2 |  |
| Nitrous acidium ion | H2O+-NO |  |
| Nitric acid (contains N2O4) | HNO3 |  |
| Alkyl nitrites | R-ONO |  |
| Peroxynitrite | ONOO(-) |  |
| Nitrosonium ion | NO+ |  |
| Nitro compounds | R-NO2 |  |
| Nitrous anhydride | N2O3 |  |
| Dinitrogen tetroxide | N2O4 |  |
| Nitrosyl halides | Halide-NO |  |
| Nitrosyl thiocyanate | ONSCN |  |
| Nitrosophenol | Phenol-NO |  |
| Nitrosothiol | SH-NO |  |
| Aqua regia | HCl + HNO3 |  |
| Nitryl chloride | NO2Cl |  |
| Other (specify) |  |  |

**7.2 For Nitrosatable substances:**

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

**Table 2**. Nitrosatable substances

|  |  |  |  |
| --- | --- | --- | --- |
| **Nitrosatable substance** | **Structure** | **By-products** | **(Potentially) present in final API** |
| Secondary amines (cyclic and acyclic) | R1-NH-R2 | - |  |
| Tertiary amines (cyclic and acyclic) |  | NHR1R2,  NHR1R3, or/and  NHR2R3 |  |
| Hydrazine derivatives | NH2-NR1R2 | NHR1R2 |  |
| N-methyl-2-pyrrolidinone | N-Methylpyrrolidone Structural Formulae.png | N-methyl-4-aminobutyric acid |  |
| Tertiary amides | R1CONR2R3 | NHR2R3 |  |
| N-Chloroalkylamines | R1R2N-Cl | NHR1R2 |  |
| N-alkylcarbamates | R1O-CO-NR2R3 | NHR2R3 |  |
| Other (specify) |  |  |  |

1. **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 document, we will evaluate the impact, revise this document when necessary and inform our customers in case of any changes in the outcome.

1. European Medicines Agency (EMA): Assessment report, Procedure under Article 5(3) of Regulation EC (No) 726/2004, Nitrosamine impurities in human medicinal products. EMA/369136/2020, 25 June 2020, <https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf> [↑](#footnote-ref-1)
2. European Medicines Agency (EMA): Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. EMA/409815/2020, Rev.2, 26 February 2021. <https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf> [↑](#footnote-ref-2)
3. U.S. Food & Drug Administration, Control of Nitrosamine Impurities in Human Drugs, Revision 1 February 2021, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs> [↑](#footnote-ref-3)
4. Health Canada: Questions and Answers. Request to evaluate the risk of the presence of N-nitrosamine impurities in human pharmaceutical, biological and radiopharmaceutical products. Dated 2020-12-15 (update 2). <https://www.cosmeticsalliance.ca/wp-content/uploads/2020/12/HC-QnA-Document-on-Nitrosamines-Update-2-ver.-2020-12-15-final.pdf> [↑](#footnote-ref-4)