**REPORT ON THE RISK OF POTENTIAL PRESENCE**

**OF NITROSAMINE IMPURITIES**

**Document ID:**

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| ***ACTIVE PHARMACEUTICAL INGREDIENT (API)***  Name: …………………………………………………………………………………………………………………………............................................  Material code(s): ……………………………………………………………………………………………………………………………………………………….............. |

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| ***MANUFACTURER*** (refers to the manufacturing site)  Name: ……………………………………………………………………………………………………………………………………………………………………...  Address: …………………………………………………………………………………………………………………………………………………………………….. |

*(Optionally indicate name / function)* ***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 API*) was assessed with respect to the risk of the potential presence of Nitrosamine impurities in line with EMA guidelines (current versions of EMA/369136/2020, EMA/409815/2020) and other related regulations published by other Health Agencies.

All information contained in this report is based on current knowledge and is true and sincere to our actual knowledge considering available supplier information and likely chemical production processes where information from the supplier is not available.

The information in this document may be updated as more information becomes available.

**Date**

*(Optionally sign)* **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. *Remove the text referring to the internal instruction (blue), e.g. definition of Nitrosatable/vulnerable substances (amine, hydrazine, hydrazide or hydrazone) in Chapter 7.*
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. 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.*
5. *For table in section 6 (Table 2), fill one line per nitrosamine which has been identified as being possibly generated during the API manufacturing process.*
6. *Before finalization of the report, please check the references of currently valid Health Authorities' (HAs) guidelines. If an updated revision, without changes in identified risk factors is available, a revision of the Table 1 is not needed and only references in a foot note of the page 3 should be updated. However, if additional (new) root cause is identified in any future revision of the HAs guidelines, an update of the APIC template should be endorsed.*

**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 API.

**2 SCOPE**

The Risk Evaluation has evaluated the items as potential sources of nitrosamines or their precursors in line with root causes described in *Questions and answers for marketing authorisation holders*2.

Please note that listed root causes (Table 1) follow 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*.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, both are covered within questions related to combination of nitrosating agent and nitrosatable substances or compounds susceptible of degradation into nitrosatable as well as questions related to contamination of starting materials/intermediates/raw materials.

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

The risk evaluation covers all API manufacturing steps as presented below.

*(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Include route of synthesis and process description, if relevant.* *The process description can be replaced by a workflow with the relevant information for the evaluation or just to reference the filing applicable section.)*

1. **RISK EVALUATION METHODOLOGY**

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  
   (includes justification and risk evaluation outcome)**

*(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. 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 7. 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.*)

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| **Note:**  Please note that below Summary table (Table 1) is done based on CMDh/439/2022 (Template for nitrosamine RE)[[5]](#footnote-5) for convenience of drug product manufacturer and to transparently demonstrate that the risk evaluation has been performed based on the current version of the EMA Q&A document2 and all risk factors related to active substance are sufficiently addressed in the risk evaluation itself. |

Table 1: Summary of items reviewed for the risk evaluation, justification and risk outcome

|  |  |  |
| --- | --- | --- |
|  | **Currently identified risk factors for presence of nitrosamines (Q4 of EMA/409815/2020)** | **Risk for presence of nitrosamines identified?**  **(Yes / No / NA)** |
|  | | |
| ***Risk factors related to the manufacture of the active substance:*** | | |
| **1** | Use of nitrite salts and esters (e.g. NaNO2, alkyl nitrites), or other nitrosating agents (e.g. nitroso halides, nitrosonium salts, nitrogen oxides, nitro alkanes, halogenated nitro alkanes, Fremy’s salt, nitroso sulfonamides), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process. Sources for secondary or tertiary amines can also be starting materials, intermediates, reagents, solvents (e.g. DMF, DMAc and NMP) and catalysts, which contain amine functionality, amine impurities (e.g. quaternary ammonium salts) or which are susceptible to degradation to reveal amines. | YES  NO  **Justification:** |
| **2** | Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process (see 1). | YES  NO  **Justification:** |
| **3** | Use of disinfected water (chlorination, chloro-amination, ozonisation) in the presence secondary or tertiary amines within the same or different steps of the manufacturing process (see 1). | YES  NO  NA  **Justification:** |
| **4** | Oxidation of hydrazines, hydrazides and hydrazones by hypochlorite, air, oxygen, ozone and peroxides in the manufacturing process or during storage.  Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts). | YES  NO  NA  **Justification:** |
| **5** | Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts). | YES  NO  NA  **Justification:** |
| **6** | Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents. | YES  NO  **Justification:** |
| **7** | Carry-over of nitrosamines deliberately generated (e.g. as starting materials or intermediates) during the manufacturing process. | YES  NO  **Justification:** |
| ***Risk factors also related to the finished product:\**** | | |
| **8** | A particular risk of formation of nitrosamines should be noted for active substances that contain a nitrosatable amine functional group. Several examples have been reported where the amine functionality was shown to be vulnerable to nitrosation and formation of the corresponding *N*-nitroso impurity (i.e. NO-API). Secondary amines appear particularly vulnerable to this reaction, although some cases with tertiary amines have also been observed. For further information, please refer to the assessment report of the *CHMP’s Article 5(3) opinion on nitrosamine impurities in human medicinal products*. | |
| **8a** | Does the API, or one of its known impurities, have a nitrosatable nitrogen functionality? | YES  NO  **Justification:** Please refer to the Chapter 7. |
| **8b** | May nitrites be present in one of the used excipients? | NA |
| **9** | Degradation processes of active substances, including those induced by inherent reactivity (e.g. presence of nitro-alkyl, oxime, or other functionality) or by the presence of an exogenous nitrosating agent. This could potentially occur during both active substance and finished product manufacturing processes or during storage and could be influenced by crystal structure, crystal habit and storage conditions (temperature, humidity etc.). For more details, refer to page 6 of *Referral under Article 31 of Directive 2001/83/EC for ranitidine* and published literature. | YES  NO  NA  **Justification:** |
| **10** | Oxidation of hydrazine or other amine-containing functional groups present in active substances or their impurities/degradants (e.g. from hydrazones and hydrazides), either in active substance manufacturing processes or during storage. This root cause has also been observed during manufacture and storage of finished products containing such functional groups. Potential oxidants include oxygen and peroxides (common impurities in some excipients). | YES  NO  NA  **Justification:** Please refer to the root cause No. 4. |
| **11** | Use of certain packaging materials. | YES  NO  **Justification:** |
| **12** | Reaction of amines leaching from quaternary ammonium anion exchange resins (e.g. used for purification steps) with nitrosating agents present in the liquid phase. In addition, disinfection procedures such as e.g. chlorination, chloro-amination and ozonisation can lead to significant *N*-nitrosamine generation as by-products in case vulnerable amines are present. Given the source of contamination, risk is related to the concentration of the reactive agent(s) and thus, to the volume of water in or used to dilute a particular product. The same risks could be associated with active substances or finished products manufactured using water purified using similar resins. | YES  NO  NA  **Justification:** |
| ***Risk factors related to GMP aspects:*** | | |
| **13** | Cross-contamination due to different processes being run successively on the same manufacturing line. | YES  NO  NA  **Justification:** |
| **14** | 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. | YES  NO  NA  **Justification:** |
| **15** | Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts) where the recovery is outsourced to third parties who are not aware of the content of the materials they are processing. Recovery processes carried out in non-dedicated equipment should also be considered. | YES  NO  NA  **Justification:** |
| ***Any other risk factor identified:*** | | |
| **16** |  |  |
|  |  |  |

**NA – not applicable**

**\*Risk factors are assessed for API.**

1. **RISK OUTCOME**

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

*negligible (no risk identified)*

*potentially present (risk identified):*

Table 2: List of all potentially present *N*-nitrosamine impurities identified in the API risk evaluation

*(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Please list all N-nitrosamine impurities for which risk is identified in evaluation following root causes indicated in Table 1.*

*Indicate if mitigation measures/control strategy is in place.)*

|  |  |  |  |
| --- | --- | --- | --- |
| **Possible *N*-nitrosamine**  **(Chem. Name / Code Name and Chem. Structure)** | **Origin of possible *N*- nitrosamine / Root cause**  **(specify nitrosating agent and nitrosatable substance)** | **Mitigation measures / Control strategy** | **Test results available?** |
|  |  |  | YES\*  NO |

\* Analytical test results:

*(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Include analytical results or provide reference to the appropriate attachment.)*

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 the following nitrosating agents in the final API is identified (Table 3).

**Table 3**: 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/vulnerable substances:**

* Nitrosatable/vulnerable substances are not likely to be present in the final API.
* A risk for potential presence of the following nitrosatable/vulnerable substances in the final API or as integral part of the API is identified (Table 4)

**Table 4:** Nitrosatable/vulnerable substances in API

|  |  |  |  |
| --- | --- | --- | --- |
| **Nitrosatable/vulnerable substance** | **Structure** | **By-products** | **(Potentially) present in final API / Levels in 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) |  |  |  |
| *(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. Justification on vulnerability or non-vulnerability of amine, hydrazine, hydrazide or hydrazone function should be added here. Decision should be supported by literature data.)* | | | |

*(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. The term “vulnerable amines” corresponds to an amine function having extractable α-proton and that form an alkylating diazonium salt as described in below scheme.*



*It corresponds to (but not limited to): Secondary amines (cyclic, acyclic), tertiary amines (cyclic, acyclic), secondary/tertiary amine precursors such as (but not limited to) quaternary ammonium salts, N,N-dialkylamines (e.g. N-methyl-2-pyrrolidone, dimethylformamide, dimethylacetamide), N-chloroalkylamines, N,N-dialkyl carbamates or N,N-dialkylhydrazines.)*

*(INTERNAL INSTRUCTION ONLY. SHOULD BE DELETED. The term “vulnerable hydrazine, hydrazide or hydrazone” corresponds to a hydrazine, hydrazide or hydrazone function that can lead to N-nitrosamine derivative by mean of an oxidation step. This nitrosamine should as well be able to lead to an alkylating diazonium salt as described in below scheme.)*



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.12, 10 October 2022. [Nitrosamines EMEA-H-A5(3)-1490 - QA Art. 5(3) Implementation\_ for July CHMP CMDh - (QA3)\_ADOPTED (europa.eu)](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: Guidance on nitrosamine impurities in medications, date adopted 1 September 2022, [Nitrosamine impurities in medications: Guidance - Canada.ca](https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities/medications-guidance.html). [↑](#footnote-ref-4)
5. CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines, CMDh/412/2019, Rev.16, May 2022 and The template for nitrosamine risk evaluation, CMDh/439/2022, May 2022

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