Guidance on Submission of Nitrosamine Risk Assessment where a Risk is Identified

This guidance outlines the minimum data required in a nitrosamine risk assessment report if a risk of nitrosamine formation has been identified. The requirements listed in this guidance is not exhaustive, and HSA may request for additional information as and when needed.

Minimum data requirements

1. The nitrosamine identity (i.e., name and structure)

2. A detailed assessment of the risk factors and root causes for the nitrosamine

(a) Due to carry-over of the nitrosamine precursors

Nitrosamines may be formed in late stages of the drug substance synthetic process when nitrosamine precursors are carried forward through subsequent process steps. Nitrosation of these precursors can occur with nitrites from different process steps.

(b) Due to formation of nitrosamine drug substance related impurities

Nitrosamine drug substance related impurities (NDSRI) may be formed in the drug product when secondary or tertiary amine groups present in the drug substance (DS) structure or DS intermediates/degradants react with nitrosating agents found in many common excipients. Hence, the risk of NDSRI formation should be assessed with consideration for the following:

- Type of excipient used
  Assess the risk of residual nitrites in excipients, including water.

- Conditions during the drug product (DP) manufacturing process
  Some conditions are known to influence the nitrosation reaction of amines (e.g., temperature, pH, presence of antioxidants).

(c) Due to any other risk factors

Please refer to the scientific paper 'Regulatory Experiences with Root Causes and Risk Factors for Nitrosamine Impurities in Pharmaceuticals' that provides an insight on the current scientific information from a quality perspective on risk factors and potential root causes for nitrosamine impurities. Please refer to the publication to better understand the risk factors and the recommendations for risk mitigation and control strategies. A significant amount of information on this topic has also been published by other regulatory agencies such as the EMA, Health Canada, Swissmedic, TGA, UK MHRA and US FDA. Please refer to Question 33 of the Question-and-answer (Q&A) document.

3. The acceptable intake for the nitrosamine

The acceptable intake (AI) of the nitrosamine should be determined according to Appendix 1 - HSA recommended acceptable intake for certain known nitrosamines. For nitrosamines that are not identified in Appendix 1, an AI based on the approaches mentioned in Question 19 of the Q&A document should be proposed. Alternatively, the AI published by HSA's reference agencies (Australia TGA, EMA, Health Canada, Swissmedic, UK MHRA, US FDA) can be proposed for evaluation.

4. A detailed assessment on whether the nitrosamine level increases with time when stored under the locally registered conditions

Some nitrosamines (e.g., degradation impurities) level may increase with shelf life if the nitrosation reaction continues during storage. An assessment on whether the nitrosamine level is expected to increase over time when stored under the proposed/registered long-term storage conditions should be provided. The possibility of the nitrosamine being a degradation impurity based on the degradation pathway of the DS should also be assessed.

5. The analytical method and method validation report for the nitrosamine

Please refer to Section C: Product Testing, Root Cause Analysis and CAPA Development of the Q&A document for the testing requirements.

6. The test results

Testing for nitrosamines is usually conducted on the DP. However, if the root cause identified the source of the nitrosamine to be the DS manufacturing process, other control strategies such as those stated in the ICH M7 guideline could be used. Data should be provided to show that the nitrosamine will not be present above the AI in the drug product. Justification based on scientific principles alone (i.e., use of Option 4 outlined in the ICH M7 guideline) to conclude that nitrosamine is not formed is generally considered inadequate. Such cases will be evaluated on a case-by-case basis and needs to be supported by actual experimental data (e.g., spiking/purging data).

The test results of the at-risk nitrosamine performed on at least 6 pilot batches, or 3 commercial-scale batches should be submitted to HSA. Test results of the nitrosamine in a DS intermediate at a later stage may be accepted as an alternative, where applicable, with relevant justification provided.

If the nitrosamine level is expected to increase over time, the test results of the nitrosamine under the following conditions should be provided:

(a) At release;

(b) Stress testing as per ICH Q1 guideline; and

(c) Near the end of the shelf life of the DP. If the data is not available, extrapolation of nitrosamine levels is acceptable based on the principles of ICH Q1 guideline.

7. Corrective action and preventive action (CAPA), where needed, to ensure that the nitrosamine level remains at or below the AI throughout the product's registered shelf life

If nitrosamine formation has been identified, the company must submit to HSA their interim and final CAPAs to minimise the risk of nitrosamine formation and to control the nitrosamine level at or below the AI throughout the product's registered shelf life. CAPAs may include:

(a) Change of manufacturing process

(b) Change of raw material quality

(c) Testing of the nitrosamine in S.4.1 and/or P.5.1 (both release and shelf-life specifications, where required). In cases where the nitrosamine is observed to increase during long-term storage or stressed testing, additional data based on the stability/stress testing data (where appropriate) may be required to justify the limit of the nitrosamine used at release and at the end of shelf life, considering the rate of increase in the nitrosamine over time.

(d) Introduction of control of nitrosamine precursors at DS intermediate stage with relevant justifications. For example:
   - Control of residual nitrite in DS starting materials before amines are introduced later in the process
   - Control of specified impurity with amine (possible precursor)

(e) Introduction of control of residual nitrites in excipients with relevant scientific justifications

Please refer to Section C: Product Testing, Root Cause Analysis and CAPA Development of the Q&A document for more information on the controls that can be taken.