

Active Pharmaceutical Ingredients Committee (APIC)

**Additional guidance on the assessment on the risk assessment
for presence of N-nitrosamines in APIs**

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Foreword

This guidance document was prepared in 2020 by the APIC Nitrosamines Task Force on behalf of the Active Pharmaceutical Ingredient Committee (APIC)

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1. Introduction

The EMA and other Health authorities have published requirements (EMA/189634/2019 [1] and Health Canada Letter [3] for the API industry and the MAH for drug products to expand the scope of potential sources of nitrosamines beyond that of ICH M7 [2]. This requirement is based on the fact that, as the Industry and the authorities are gathering more information about the potential ingress / formation of such impurities in APIs, there is need to expand the evaluation of risk assessments that are needed to ensure APIs are fit for their intended use and do not pose a patient safety risk for such impurities. These requirements are new to the industry and as such APIC had devised this document to aid industry generating risk assessments as well as assistance on the level of information that is needed to be sent to the MAH for their overall drug product risk assessments.

As indicated, this is a recent requirement for the Industry and authorities, and as such the level of knowledge and understanding on it may evolve with time. Therefore, in certain areas that need to be assessed detailed specific information is not practically possible to add to this guidance document, plus it may be amended with time as new information become available.

2. Risk Assessment guidance

The request from health authorities is to perform the assessment to all market products.

Due to the large numbers of products involved, EMA document [1] suggests the use of a risk-based approach to prioritize the evaluations and later the confirmatory testing (if the risk evaluation would indicate that testing would be required). The factors suggested are daily dose taken, duration of treatment, therapeutic indication and number of patients treated. However, this data is not always available at the API manufacturers side, who might use other criteria such as the ones suggested below to perform the requested risk evaluations.

2.1. Prioritization of the risk assessment

The following criteria might be used for prioritization (“>” meaning “higher priority than”) depending on the information available:

- Higher daily dose taken
- Long duration of treatment
- therapeutic indication
- Higher number of patients treated
- Commercial APIs > APIs used for clinical trials
- API manufactured in multipurpose equipment > dedicated equipment
- API manufactured in multipurpose equipment exposed to nitrosating agents
- API > Intermediate > RSM (for companies manufacturing the three categories)
- APIs still manufactured > APIs no longer manufactured but still on the market
- APIs sold to markets where risk assessment have already been requested by authorities > APIs sold to other markets
- Knowledge of the likelihood of a risk based on the chemistry of the process (presence of amine, nitro functionalities, nitrosating agents)

2.2. Management of raw materials in the risk assessment

The need and type of information to be obtained from suppliers depends on the type of material and on its use in the manufacturing process. Following factors are helpful to assess the impact of the raw materials on the risk to have nitrosamines in the API.

- Regulatory status of the raw material in the associated regulatory file (RSM, processing aid...)
- Chemistry of the raw material such as:
 - complex process
 - use of nitrosating agents and amines
 - type of solvents used (e.g. recovered in house or by 3rd party)
- Number and type of chemical steps between introduction of raw material and final API stages. The evaluation should take in consideration:
 - if the raw material is used in early or late steps of the API synthesis
 - If the next step(s) can purge the impurities or not, and if yes at which level the impurity can be purged
 - type of chemical process(es) is involved and process conditions
 - if the next step(s) can purge the impurities or not and if yes at which level
 - if the raw material is used in later stages of the API synthesis and no further crystallization is performed

The information from raw material suppliers can be also obtained through questionnaires, which cover chemical process and risk of contamination at the raw material supplier's facility. The scope of the questionnaire can be very narrow and composed by just the 2 questions below to perform an efficient screening, or more complex covering all applicable potential sources of nitrosamines as described in EMA [1]. The first option does not prevent from receiving later the results of the full evaluation to confirm the conclusions achieved. If required the API risk evaluation should be revised.

- Do you manufacture nitrosamines, amines or sources of amines in the same equipment as those used to manufacture the raw material?
- Do you use or is there a potential presence of nitrosating agents and/or amines (secondary or tertiary amines) in your manufacturing process?

Examples of nitrosating agents can be found in EFPIA decision-tree for N-nitrosamine risk assessment [4] or IPEC questionnaire [5].

Information obtained from suppliers on the quality of water (especially nitrite and chloramines content) used in their process can be useful.

API manufacturers have observed that it is difficult to obtain feedback in due time as suppliers are learning on how to proceed. The API risk analysis should be clear on the depth of raw material information to be taken into account in the risk assessment.

When the supplier's data is not available, possible actions are:

- Quote this raw material as high risk in the API risk assessment due to the absence of response, which should be later confirmed either during the EMA process Step 2 [1] (confirmatory testing) or with the information received from supplier. The API risk assessment should be reviewed and updated as applicable.
- Use scientific knowledge or literature to obtain information (synthesis pathway, etc.)
- Use alternative source of information (website, audit report...)

2.3. Risk assessment

EFPIA decision tree [4] is a helpful tool to undertake the risk assessment.

2.3.1 Content of the risk assessment

The risk assessment should consider the following possible sources:

- **Raw materials:** attention should be paid to recovered solvents, nitrosating agents, nitric acid, nitrites, dimethylformamide and/or other materials as per [1]. Some raw materials can be considered as low risk due to their chemical nature (e.g.: heptane due to its polarity, methanol...) Such low risk classification should be justified based on scientific literature.
- **Manufacturing process and reaction conditions:** conditions forming or suppressing nitrosamines must be assessed such as temperature, pH, carbon treatment [6], chemical reduction [6] or excess of alcohol [7]. Purging factors, if known, can be useful to review the risk level [5].
- **Structural study and potential subsequent degradation of the structural fragments:** amine, nitro... The degradation pathway depends on the process.
- **Water:**
 - Well-water and tap-water can contain nitrites and nitrates. Nitrite content is limited on a country by country basis. In EU the limits are typically between 0.1 and 0.5 ppm for well-water and tap water, as other global countries. If in house treatment (e.g. addition of chloramines) is used the impact on the level of nitrosamines formation should be assessed. For APIs manufactured in countries outside Europe, specific analysis of the nitrite or nitrate content in water might be considered.¹
 - It is generally agreed that the level of nitrite in purified water is typically low, therefore purified water is considered as a low risk. In particular, steps of water carbon treatment are known to lower the nitrosamine content. On the contrary, ozonation of the water (containing traces of secondary amines) can theoretically lead to formation of nitrosamines.
 - Some suppliers are not controlling nitrite content in their water system, therefore in such cases nitrite or Nitrosamine presence (if amines involved) should be assessed, considering that in general no nitrite limit is established for tap-water.
- **Cross contamination and cleaning of equipment:**
 - The question to be addressed is whether the equipment (used for synthesis/storage/transport) is dedicated or multipurpose. In case of multipurpose equipment, the potential carryover (nitrites, nitrosating agents, amines, etc.) should be assessed and if there is a risk, it should be mitigated by setting appropriate cleaning limits and (e.g. by a corresponding control strategy).
 - Some cleaning solvents (such as dimethylformamide) should also be expressly considered in the risk assessment.
- **Steam, cleaning agents other than solvents, and consumables (gaskets...)** should also be considered as applicable, depending on the chemical processes involved.

¹ Purified water according Ph. Eur. complies with a nitrates level of maximum 0.2 ppm

- **Nitrogen** should be considered in the risk assessment because of the presence of NO_x (nitric oxides) which might be considered as nitrosating agents, alternatively the demonstration of a proper control of nitrogen to prevent the presence of NO_x can be relevant.
- **Primary packaging:** The most used material is polyethylene. Particular attention might be paid to the ones with additives such as antistatic packaging (which might contain specific additives) or packaging for liquid APIs by assessing potential interactions between packaging and API.

2.3.2. Boundaries of the risk assessment

As the risk assessment has to address routine and accidental presence of nitrosamines in APIs, the definition of the boundaries of the risk assessment should be justified. A difference should be made between “possibility” to have nitrosamine and “likelihood” to have nitrosamines.

Some potential helpful criteria are listed below:

- Number of synthesis steps where critical components are used (e.g. sodium nitrite and secondary amines) by calculating the theoretical value, assuming that all nitrites and amines are converted in nitrosamines
- Number of synthesis steps after potential nitrosamine formation and if they are able to purge the potential impurities formed

While the number of N-nitrosamines listed by regulators is limited, a useful reference on nitrosamine, some of their properties and toxicological data can be found on the National Institutes of Health website [8].

2.3.3. Methodology and outcome of the risk assessment

The risk assessment can be performed:

- Through a FMEA-type tool with different scores assigned to various risk levels
- Through a yes/no questionnaire which has the benefit of better orienting the result. An example of such a questionnaire can be found in the IPEC questionnaire [5].

The outcome of the risk assessment can be:

- A high/medium/low risk to further establish planning and priority of next steps (in particular analytical testing), so that the API producer can prioritize further mitigation measures
- A negligible/potentially present outcome for external use to provide a clear position to the MAH (see next paragraph).

The decision to proceed to analytical testing should be taken, only when a risk is confirmed, and the associated testing strategy can be unambiguously established. An ICH M7 assessment is also a useful step to undertaken before proceeding to any analytical testing.

2.3.4. Collaboration with customers

The collaboration with the customer depends on the type of contract and product.

Generic API manufacturers will mostly establish themselves a methodology for risk assessment and inform the customer about the outcome. A Letter template to formalize the results of the risk assessment to be shared with customers is in Appendix 1.

Contract API manufacturers may receive risk assessment methodology of their customers. The decision on which risk assessment to perform depends on the company policy and on its contractual and quality agreements with the customer.

Examples of authorities' expectations regarding the information to be supplied by our customers to their authorities can be found on [1], [3] and [9], (no risk identified response template and risk identified response template) websites.

2.3.5. Lifecycle of the risk assessment

The risk assessment is a living document which will be updated whenever additional knowledge is obtained on the API or process change is conducted (when risk assessment may need repeated). Mitigation actions should be defined if a risk is identified.

If new information is obtained, such as late supplier information, and such information increases the risk level versus the previous version of the risk assessment, such new information will have to be communicated to the customers accordingly.

The results of analytical testing change control and investigation systems should also feed the risk assessment. The analytical testing lifecycle is described below.

3. Analytical Testing and Lifecycle Control Strategy

3.1. Analytical Testing

The outcome of the risk assessment performed for the API manufacturing process will determine the need for analytical testing to confirm the presence and content of any potential Nitrosamine impurity(ies). The confirmatory testing is defined as Step 2 on the EMA document [1].

In the European Directorate for the Quality of Medicines & HealthCare (EDQM) website several analytical methods to determine Nitrosamines namely *NDMA - N-nitrosodimethylamine* and *NDEA - N-nitrosodiethylamine* in Sartans are provided, which may be suitable for other APIs potentially classified as "at risk". The likelihood that other nitrosamines impurities may be formed depending on the API manufacturing process should be taken in consideration during the risk assessment (see section 2). This may require introducing adjustments in the available analytical methods, or even to develop new analytical methods and to validate them as appropriate following *ICH Q2(R1) - Validation of Analytical Procedures: Text and Methodology* guideline for Limit Testing.

Theoretical values should be determined, if technically possible, during the risk assessment and compared with the interim limits defined in *EMA/351053/2019 - Temporary interim limits for NMBA, DIPNA and EIPNA impurities in sartan blood pressure medicines, rev 1, August 2019*.

During the confirmatory testing - step 2 on the EMA [1], priority should be provided to the APIs with a theoretical value classified as "potentially present" and "at risk" as per the following table.

Theoretical value	Priority	Risk Classification
< 30%	No confirmatory testing	Negligible
> 30% < Interim limit	2	Potentially present
≥ Interim limit	1	At risk

At least 3 consecutive commercial batches of API should be tested to confirm the level of nitrosamines in the API. Whenever values above 30% of the interim limit are confirmed, Marketing Authorization Holder should be informed. API Manufacturer should clearly identify the sources of the concerned impurities, to define actions to reduce the values determined and to update the control strategy document accordingly.

3.2. Control Strategy Lifecycle

As per *ICH Q10 - Pharmaceutical Quality System*, and the summary in *ICH M7 [2]*, a set of controls based on process understanding and risk management principles (*ICH Q9 - Quality Risk Management*) should be defined to assure process performance and product quality is defined as Control Strategy.

From the risk assessment and the evaluation of the level of the nitrosamine(s) impurity(ies) a specific testing frequency or any other control should be defined to assure that the level of the impurity(ies) will be kept under control and below of the acceptance limit, across the product lifecycle.

The four (4) possible control options described in *ICH M7 [2]* should be evaluated based on the process understanding, the impurity(ies) level and type and manufacturing step where it is formed.

The option chosen should be fully justified based on scientific principles, analytical data, the knowledge on the downstream process and impact on the impurity level.

The control strategy effectiveness and process performance should be assessed periodically. The knowledge gained from the commercial manufacturing should be used to promote the continuous improvement and adjustment of the control strategy. Manufacturing continuous improvement may include manufacturing process changes.

Any proposed process changes independently of the type of change (raw materials, suppliers, analytical methods, manufacturing step, etc.) and based on the understanding of the manufacturing process, should include the impact assessment on several areas such as, but not limited to:

1. impurities level and the possibility of new impurities be formed either due to side reactions or due to new solvents, reagents, water, etc. In the case of new impurities being formed, *ICH M7 guideline [2]* should be followed;
2. cleaning process: if it is still valid or needs to be adjusted, including composition assessment of cleaning agents
3. new solvent/reagent/catalyst used and respective supplier qualification with focus on the product origin (recovered or not)
4. internal use of recovered materials

The result of the impact assessment exercise may originate adjustments in the control strategy to assure process performance and product quality.

All changes should be handled through the change management process in place as part of the organization quality management system.

4. References

- 1 EMA/189634/2019 - *Information on Nitrosamines for Marketing Authorization Holders*
- 2 ICH M7 (R1) - Assessment and Control of the DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- 3 Health Canada - Information to Marketing Authorization Holders (MAH).of Human Pharmaceutical Products Regarding Nitrosamines Impurities, letter from October 2, 2019
- 4 EFPIA decision tree “Drug substance manufacturing process risk assessment for presence of N-nitrosamines”
- 5 IPEC Europe. Questionnaire for Excipient Nitrosamines Risk Evaluation. Guidance 5. Conducting purge assessments
- 6 Nawrock, J.; Andrzejewski, P. Nitrosamines and water. *Journal of Hazardous Materials* **2011**, *189*, 1-18. “Water treatment processes have shown that both a decrease and an increase in NDMA FP are possible. Filtration through biologically active carbon consistently lower nitrosamine concentration.”
- 7 Litsuka, M.; Hoshino, T.; Kato, T.; Kikugawa, K.; Formation of Nitrosamines in Organic Solvents and Aqueous Systems Containing Organic Solvents. *Chem. Pharm. Bull.* **1985**, *33*, 2516-2521.
- 8 <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/nitrosamines.pdf>
- 9 <https://www.swissmedic.ch/dam/swissmedic/en/dokumente/marktueberwachung/mu/Checkliste%20Risikoabkl%C3%A4rung%20N-Nitrosaminverunreinigung.pdf.download.pdf/Muster-Checkliste-Evaluation-Verunreinigung-mit-Nitrosaminen.pdf>
- 10 <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities-overview>

5. Appendix 1 - Letter Report Template