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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



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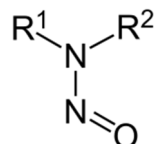
Introduction

The [assessment report](#) of the CHMP's Article 5(3) of Regulation (EC) No 726/2004 opinion on nitrosamine impurities in human medicinal products provides general guidance and recommendations on mitigating and preventing the presence of nitrosamines in human medicinal products. In this context all MAHs/Applicants of human medicinal products should work with the manufacturers of their Active Pharmaceutical Ingredients (APIs) and finished products (FPs) in order to ensure that the presence of nitrosamine impurities in their medicinal products is mitigated as much as possible and controlled at or below a limit defined based on ICH M7(R1) principles for substances of the "cohort of concern" reflected in this guideline and calculated considering a lifetime daily exposure and kept as low as possible and that appropriate risk mitigating measures are taken.

While the review by CHMP under Article 5(3) was ongoing, the regulatory authorities established in September 2019 a specific framework (hereinafter 'call for review')^{1,2} for medicinal products containing chemically synthesised APIs, to provide details on the reporting to the authorities by the MAHs and set expectations regarding risk evaluation (step 1), risk assessment/confirmatory testing (step 2) and risk mitigation measures (step 3) to be carried out. Following the CHMP's Article 5(3) opinion, a similar exercise is launched for medicinal products containing a biological API, as further explained in this document. Further details are provided in Q2 below.

The published CHMP Article 5(3) opinion, supplemented by the current Question and Answer document on its implementation, will replace the previous letter entitled 'Information on nitrosamines for marketing authorisation holders' (EMA/189634/2019, published on 19 September 2019).

The terms "nitrosamine" and "N-nitrosamine" are used interchangeably within this Q&A and related documents and should both be understood to refer to the following structure:



For the purpose of this Q&A please see definitions below:

Risk evaluation: all activities in step 1.

Risk assessment: all activities in step 2.

1. Should the risk of presence of nitrosamines be considered for all human medicinal products?

MAHs/Applicants of all human medicinal products should ensure that the presence of nitrosamines is controlled and kept as low as possible, irrespective of marketing status or the type of product (e.g. generics and over the counter (OTC) products).

¹ https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf

² https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf

For details on the approach required, please refer to Q10 on the limits for nitrosamines and Q12 on the measures to mitigate the risk of presence of nitrosamines.

MAHs/Applicants are reminded of their obligations to ensure that, in accordance with Article 23 and Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, their medicinal products are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress.

Therefore, MAH/ Applicants shall:

- design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of *N*-nitrosamines in their API and FP(s);
- assess the risk of presence nitrosamine impurities in their API(s) and FP(s) and introduce any resultant changes to the dossier as needed (e.g. changes to their manufacturing processes);
- ensure that active substances and excipients used in their FPs are manufactured in compliance with good manufacturing practices in line with Article 46(f) of Directive 2001/83/EC.

Compliance of the MAHs/Applicants with the above-mentioned obligations is subject to regular controls by competent authorities including during GMP inspections.

While the Article 5.3. recommendations on controlling nitrosamine impurities apply to all human medicinal products, the call for review applies only to human medicines containing chemically synthesised APIs or biological APIs, as further explained in Q2 below.

2. What is the 'call for review'?

In September 2019, a 'call for review' was launched for medicinal products containing chemically synthesised APIs to request MAHs to review their manufacturing processes in order to identify and, if necessary, mitigate the risk of presence of nitrosamine impurities and report the outcome back to authorities. This exercise was started while the review by CHMP under Article 5(3) for Nitrosamine impurities in human medicinal products was ongoing.

Following the conclusion of [the review](#) under Article 5(3), the CHMP considered that there is also a risk of presence of nitrosamines in biological medicinal products, in particular for the biological medicines with the following risk factors:

- biologicals containing chemically synthesised fragments, where risk factors similar to chemically synthesised active substances are present;
- biologicals using processes where nitrosating reagents are deliberately added;
- biologicals packaged in certain primary packaging material, such as blister packs containing nitrocellulose.

For the above reasons the current call for review has been extended to cover also all biological medicinal products for human use. For further reference on what is considered to be a biological medicinal product for the purpose of this exercise, please consult the [CMDh Questions & Answers on Biologicals](#).

The call for review consists of 3 steps:

- Step 1: MAHs to perform a risk evaluation to identify if APIs and/or FPs could be at risk of presence of nitrosamine;

- Step 2: if a risk is identified, MAHs to proceed with confirmatory testing in order to confirm or refute the presence of nitrosamines. MAHs should report outcomes as soon as possible;
- Step 3: if the presence of nitrosamine(s) is confirmed, MAHs should implement effective risk mitigating measures through submission of variation.

Please refer to Q3 for further details on the 'call for review' including the timelines for chemicals and the timelines for biologicals.

For the specific case of sartans with a tetrazole ring that have been subject to a review under Article 31 of Directive 2001/83/EC, further guidance will be published soon.

3. For the 'call for review' for chemically synthesised and biological medicinal products, when and how should MAHs report steps 1 and 2 to competent authorities?

Submission of step 1 outcome

Products that have been approved after September 26, 2019 but for which a risk evaluation was not assessed within the MAA procedure should comply with the call for review deadlines, if not already done so.

For product containing **chemically** synthesised APIs, the step 1 risk evaluation should be concluded and reported at the latest by **31st March 2021**.

For product containing **biological** APIs, step 1 risk evaluation should be concluded and reported at the latest by **01st July 2021**.

The risk assessment has to be performed for all products for which a potential risk has been identified in step 1, irrespective of the marketing status of the product or whether any registered manufacturers are actively used in supply. However, it is recognised that step 2 may not be possible for medicines that are not marketed, including the case of manufacturers not actively used in supply, since there may be no finished product batches available for confirmatory testing. In these cases, i.e. where no batches of finished products are available, it would be acceptable to submit a written commitment that step 2 confirmatory testing will be conducted once finished product has been manufactured and/or the product is launched. The outcome of step 2 testing as well as any necessary variation(s) as part of step 3 will therefore need to be submitted and approved before the product can be placed on the market or the manufacturer can be actively used in supply, even if this is after the step 2 and 3 deadlines. MAHs'/Applicants' compliance with the above-mentioned obligations is subject to regular controls by competent authorities including during inspections.

All MAHs should inform the concerned Competent Authorities of the outcome of their risk evaluation (step 1) using the [dedicated templates](#).

If a risk has been identified, the expected timeline for the testing activities should also be provided as foreseen in the [dedicated template](#). No additional documentation is required at this stage. However, the risk review should be adequately documented, and related documentation should be made available upon request.

Step 2 should be started as soon as a risk is identified in API and/or FP and in accordance with product prioritisation (see Q6).

If a risk has been identified for the API, the MAH is advised to report this outcome by using step 1 response template and to proceed directly to step 2 confirmatory testing of the FP. If no risk has been identified in the API, the MAH is advised to proceed with the risk evaluation of the FP and to present the result of Step 1 when a final conclusion has been reached on both the API and the FP. MAHs should inform the concerned Competent Authorities of the outcome of their risk evaluation (step 1) even if no risk has been identified in the API or FP.

It is acceptable for the submission of the outcome of step 1 to submit one email notification grouping products with identical outcome under the following provisions:

- For those Member States that have a dedicated portal, the MAH should submit the notification via this portal;
- If the outcome of step 1 is "risk identified", it is possible to provide a response by grouping these products. MAHs are still required to indicate the expected testing timeline on the related "Step 1 risk identified response template" excel file.

Submission of step 2 outcome

The step 2 confirmatory testing should be conducted in accordance with product prioritization (see Q6).

For product containing **chemically** synthesised APIs, confirmatory testing activities at Step 2 and submission of any changes required to Marketing Authorisations (Step 3, see Q13), are expected to be finalized at the latest by **26th September 2022**.

For product containing **biological** APIs, confirmatory testing activities at Step 2 and submission of any changes required to Marketing Authorisations (Step 3, see Q13), are expected to be finalized at the latest by **1st July 2023**.

In order to meet the above deadlines for submission of any changes required to Marketing Authorisations at Step 3 for products containing chemically synthesised or biological APIs, it would be expected that confirmatory testing activities at Step 2 are finalized in advance of these deadlines.

MAHs should forthwith inform the competent authorities if tests confirm the presence of nitrosamine, irrespective of the amount detected and by utilising the dedicated [reporting templates](#). The immediate risk to patients should be assessed based on the limits defined in Q10 and appropriate action proposed to avoid or minimise the exposure of patients to nitrosamines.

For the submission of the outcome of step 2 confirmatory testing several products can be combined when the outcome is "no nitrosamines detected". When the outcome is "nitrosamines detected" all strengths and pharmaceutical forms of one marketing authorisation can be combined in one response template when the supporting documentation is completely identical for all products concerned; if not the response has to be submitted separately.

In case one or more nitrosamines are identified that exceed the limit defined in Q10, the following supportive documentation is required at the time of reporting:

- testing results expressed in ng and ppm;
- interim investigation report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment.

For their responses, MAHs are required to use dedicated templates and contact points as outlined on the [EMA](#) and [CMDh](#) websites.

4. What are the currently identified root causes for presence of nitrosamines?

Currently identified sources of nitrosamine impurities are listed below:

1. Use of sodium nitrite (NaNO_2), 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 (NaNO_2), 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 in the API manufacturing process (e.g. solvents, reagents and catalysts).
4. Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts), including recovery outsourced to third parties who are not aware of the content of the materials they are processing and recovery processes carried out in non-dedicated equipment.
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 and active 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. This could potentially occur also during finished product formulation or 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.³
10. Use of certain packaging materials. Nitrosamine contamination has been observed in finished products stored in blister packs with lidding foil containing nitrocellulose. Nitrosamines have been shown to form from nitrocellulose degradation products and low molecular weight amines present either in printing ink or in the FP during the blister heat-sealing process and to transfer to the product within the blister.
11. Reaction of nitrosatable nitrogen functionality in APIs or their impurities with nitrosating agents present in components of the FP during formulation or storage.

For further information, please refer to the [assessment report](#) of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

1. ³ e.g. *Org. Process Res. Dev.* 2020, 24, 12, 2915–2926.

5. What to do if after completing step 1 and /or step 2 new information (e.g. related to a new potential root causes) is identified?

In line with their control strategy, once steps 1 and 2 are completed, MAHs together with API and FP manufacturers are expected to maintain the quality of their product throughout its lifecycle and therefore to review the outcome of the risk evaluation and testing as and when new information (e.g. on potential root causes for nitrosamine formation or contamination) becomes available. Appropriate timelines for conducting the risk evaluation and testing for the newly identified risks should be implemented depending on the level and impact of the risk identified. The same approach is also valid in case, after finalisation of a MAA, a new potential risk for nitrosamines is identified.

EMA and CMDh will continue to publish any newly identified sources of nitrosamine impurities on their websites.

6. What factors should be considered in prioritising the risk evaluation?

When conducting the risk evaluation and risk assessment, MAHs should use a risk-based approach to prioritise products for evaluations and confirmatory testing. MAHs may consider factors such as the maximum daily dose taken for the concerned medicinal product, duration of treatment, therapeutic indication and number of patients treated. For example, medicinal products with higher daily dose and those for chronic use may take priority.

In order to undertake the analysis of the identified medicinal products at risk, MAHs can also use tools such as Failure Mode Effects Analysis (FMEA) and Failure Mode, Effects and Criticality Analysis (FMECA) as outlined in the [ICH Q9 guideline](#) on quality risk management.

7. How should the risk evaluation be performed?

MAHs/Applicants in collaboration with API, FP manufacturers and their raw material suppliers are required to perform risk evaluations using quality risk management principles, as outlined in ICH Q9 guideline. The principles described in ICH M7 guideline and in the [Assessment report](#) of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products in relation to the toxicology assessment, control strategy and changes to the manufacturing processes for active substances should also apply.

Manufacturers of active substances and FP and their raw material suppliers should provide MAHs/applicants with all information necessary for a comprehensive risk evaluation. If the risk of nitrosamine impurity formation was assessed during the development phase of the API/FP manufacturing processes, the information from this assessment can be used to support the risk evaluation.

MAHs/Applicants and manufacturers should consider as part of the risk evaluation all potential sources of contamination or formation of nitrosamine, notably the root causes listed under Q4.

As MAHs/Applicants and manufacturers for products containing biological APIs should consider the following aspects that may increase the risks of nitrosamine presence in their products:

- biologicals containing chemically synthesised fragments, where risk factors similar to chemically synthesised active substances are present;

- biologicals using processes where nitrosating reagents are deliberately added;
- biologicals packaged in certain primary packaging material, such as blister packs containing nitrocellulose.

For further information on root causes, please refer also to the [assessment report](#) of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

If, after completion of the risk evaluation, a risk is identified in the API and/or the FP, MAHs/applicants must notify the competent authorities of the identified risk, proceed without further delay with confirmatory tests (see Q8) and introduce any necessary changes to the dossier.

All MAHs should inform the concerned Competent Authorities of the outcome of their risk evaluation (step 1) even if a risk has not been identified, please see Q3 for further details.

8. How should confirmatory tests be conducted by MAHs and manufacturers?

For the purpose of confirmatory testing as part of step 2 of the call for review to MAHs, testing should be carried out on the FP. Testing of the API or its intermediates is also recommended if the risk evaluation indicates that the API or its intermediates are a potential source of nitrosamine impurities in the FP. In such cases, the results of API or intermediate testing may be used to support root cause investigations and the development of a justified control strategy for nitrosamine impurities.

The number of batches to be tested should be commensurate with the risk. MAHs and manufacturers should test a representative number of batches of FP and the relevant starting materials, intermediates, API or raw materials as applicable. If the source of risk has been identified and is well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch, testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. This includes testing not only of newly produced batches but also retained samples of batches still within expiry date. If fewer than 3 batches are manufactured annually, then all batches should be tested.

If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, (or were used historically for batches still within expiry date), then testing of additional batches would be necessary to cover these risk factors.

If a product is available in multiple strengths of the same dosage form with the same risk factors applicable to each, then testing could be rationalised by testing only the worst-case scenario strength. The worst-case approach should be justified by the MAH on a case by case basis. The justification should be documented in the risk assessment in the MAH's pharmaceutical quality system.

During development of an analytical method, a reference standard of the relevant nitrosamine impurity is generally needed. If, despite extensive efforts, it becomes apparent that the relevant nitrosamine impurity cannot be synthesized, then this could be an indication that the nitrosamine either does not exist or that there is no risk of it being formed. In such cases, it may not be necessary to conduct confirmatory testing. This should be justified thoroughly on a case by case basis according to appropriate scientific principles. The justification could include relevant literature, information on structural/stereo-electronic features and reactivity of the parent amine, stability of the nitrosamine and experimental data to illustrate the efforts made to synthesize and to analyse the impurity. The justification should be documented in the risk assessment in the MAH's pharmaceutical quality system.

Methods for determination of various nitrosamines in sartans with a tetrazole ring, metformin and ranitidine have already been developed by the Official Medicines Control Laboratories and are available for reference on the [European Directorate for the Quality of Medicines & HealthCare \(EDQM\)](#) website. These may serve as a starting point for the development and validation of analytical methods for testing other APIs/FPs.

Appropriately sensitive analytical methods for determination of specific nitrosamines in other medicinal products should be developed and validated accordingly before testing. The limit of quantification (LoQ) should be at or below the acceptable limit for the respective nitrosamine impurity. If the same analytical method is used to test for multiple nitrosamines, then the selectivity of the method should be demonstrated at the LoQ for each nitrosamine.

Given the trace levels of nitrosamines to be measured, the following technical aspects should be considered when developing analytical methods:

- Interference caused by presence of trace amounts of nitrosamines in testing materials utilised (e.g. water, airborne sources, plastics products and rubber/elastomeric products);
- Contamination during sample preparation (avoiding cross contaminations from gloves, membranes, solvents etc.) which could lead to false positive results;
- *In situ* formation of nitrosamines during analysis;
- Use of accurate mass techniques are required (MS/MS or high-resolution accurate mass systems) in order to overcome interference in the identification of the specific peak of a certain nitrosamine (e.g. false positives have been observed from DMF co-eluting with NDMA).

As a result of the above considerations, control experiments should be conducted such as analysing samples by orthogonal analytical methods.

Further details in relation to analytical methodology can be found on [EDQM website](#) and in the CHMP [assessment report](#) of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

9. What are the requirements of the analytical method(s)?

The analytical methods need to be sufficiently sensitive in order to adequately detect and quantify trace levels of nitrosamine impurities. The following principles apply:

- The limit of quantification (LoQ) provides the minimum level at which an analyte can be quantified with acceptable accuracy and precision and should thus be used for impurity testing and decision-making;
- If quantitative testing is performed as a routine control, the LoQ should be $\leq$ of the acceptable limit based on the relevant acceptable intake (AI) for the respective nitrosamine impurity;
- If quantitative testing is performed to justify skip testing, the LoQ of the analytical procedure employed should be $\leq$ 30% of the acceptable limit based on the AI;
- If quantitative testing is performed to justify omission of specification, the LoQ of the analytical method employed should be $\leq$ 10% of the acceptable limit based on the AI;

- Exceptions are anticipated for medicinal products used at high daily doses (AI may be below technical feasibility of the method), or in case more than one nitrosamine is anticipated or identified in a given medicinal product.

Different analytical methods may be used for determination of multiple nitrosamines. If the same analytical method is used for multiple nitrosamines, the selectivity of the method should be demonstrated for each nitrosamine.

10. Which limits apply for nitrosamines in medicinal products? (UPDATED)

ICH M7 (R1) guideline defines N-nitrosamines as substances of the “cohort of concern” for which limits in medicinal products refer to the so-called substance-specific acceptable intake (AI) (the Threshold of Toxicological Concern, TTC, value of 1.5 ug/day cannot be applied) which is associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure). The calculation of AI assumes a lifelong daily administration of the maximum daily dose of the medicinal product and is based on the approach outlined in the ICH M7 (R1) guideline as well as the principles described in relation to the toxicological evaluation in the [assessment report](#) of the CHMP’s Article 5(3) opinion on nitrosamine impurities in human medicinal products.

The ‘less than lifetime’ (LTL) approach should not be applied in calculating the limits as described above but can only be considered after consultation with competent authorities as a temporary measure until further measures can be implemented to reduce the contaminant at or below the limits defined above.

For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, N-nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines, as specified in the Q&A document to ICH S9 guideline. If the active substance itself is mutagenic or clastogenic at therapeutic concentrations, N-nitrosamine impurities should be controlled at limits for non-mutagenic impurities according to ICH M7(R1).

The same risk approach is applicable to all routes of administration. Corrections to limits are generally not acceptable unless route-specific differences are justified by data.

Calculation of the limit when a single known nitrosamine is identified

Table 1: The following limits have been established for some specific N-nitrosamines and should be applied:

N-Nitrosamine (CAS number)	ng/day*
N-Nitrosodimethylamine, NDMA ¹ (62-75-9)	96.0
N-Nitrosodiethylamine, NDEA ¹ (55-18-5)	26.5
N-Nitrosoethylisopropylamine, EIPNA ² (16339-04-1)	26.5
N-Nitrosodiisopropylamine, DIPNA ² (601-77-4)	26.5
N-Nitroso-N-methyl-4-aminobutyric acid, NMBA ³ (61445-55-4)	96.0
1-Methyl-4-nitrosopiperazine, MeNP ² (16339-07-4)	26.5
N-Nitroso-di-n-butylamine, NDBA ² (924-16-3)	26.5

N-Nitrosamine (CAS number)	ng/day*
N-Nitroso-N-methylaniline, NMPA ¹ (614-00-6)	34.3
N-nitrosomorpholine, NMOR ⁴ (59-89-2)	127
N-nitroso-varenicline, NNV ⁵	37.0
N-nitrosodipropylamine, NDPA (621-64-7) ²	26.5

These limits are applicable only if a FP contains a single N-nitrosamine.

¹Limit based on the harmonic mean TD50 database included on the carcinogenic potency database (CPDB)

²Limit derived using structure-activity-relationship (SAR) /read-across approach using the TD50 of NDEA as point of departure

³Limit derived using structure-activity-relationship (SAR) /read-across approach using the TD50 of NDMA as point of departure

⁴Limit based on the most sensitive TD50 derived from the most robust TD50 dataset from carcinogenic potency database (CPDB)

⁵Limit derived using structure-activity-relationship (SAR) /read-across approach using the TD50 of N-nitroso-1,2,3,6-tetrahydropyridine as point of departure

*The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective above limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC.

Calculation of the limit when a new nitrosamine is identified

Two scenarios are foreseen for detections of new nitrosamines:

- If N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data, TD50 should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R1) guideline.
- If N-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R1) guideline,
 - a class specific TTC for nitrosamines of 18 ng/day (derived from the Lhasa carcinogenic potency database) can be used as default option.
 - an approach based on SAR considerations to derive an acceptable intake limit is acceptable, if appropriately justified.

The approach taken needs to be duly justified by the MAH/Applicant.

The risk approach is applicable to all routes of administration. Corrections to limits are generally not acceptable unless data justify route-specific differences.

In all above cases, the MAH/Applicant is required to liaise with the relevant competent authorities in order to verify acceptability of the approach taken.

Calculation of limit when more than one nitrosamine is identified in the same product

Please also refer to the decision tree in Annex 1 for further guidance.

For determining limits in the case of presence of more than one nitrosamine, two approaches are considered acceptable in order not to exceed the acceptable risk level of 1:100,000 as outlined in ICH M7(R1) guideline:

1. The total daily intake of all identified *N*-nitrosamines not to exceed the AI of the most potent *N*-nitrosamine identified, or
2. Total risk level calculated for all identified *N*-nitrosamines not to exceed 1 in 100,000.

The approach chosen needs to be duly justified by the MAH/Applicant.

Specifications for individual *N*-nitrosamines should generally include an AI limit expressed in ppm or ppb. The conversion to an AI limit in ppm/ppb for a particular medicinal product is calculated by dividing the respective above AI (in ng/d) by the maximum daily dose (in mg) of a given product as reflected in the SmPC. The calculation of the specification limit does not take into account the molecular weight of the *N*-nitrosamine.

It is considered that the presence of one or more *N*-nitrosamines at <10% of their respective AI constitutes a negligible toxicological risk, and as such, they do not need to be specified. *N*-Nitrosamines present below 10% of their respective AI do not need to be factored into the calculation of limits for individual or total *N*-nitrosamine(s).

However, the overall principle of the Article 5(3) referral should still be considered, notably that *“the presence of N-nitrosamines in human medicinal products shall be mitigated as much as possible.”* Therefore, manufacturers are encouraged to improve their processes, even if they result in only very small amounts (<10% AI) of multiple nitrosamines, as processes and controls should be designed to prevent if possible or mitigate as much as possible the presence of *N*-nitrosamines in APIs and FPs (see Q1).

For option 1, the AI limit for total *N*-nitrosamines should be set in ppm/ppb according to the most potent *N*-nitrosamine present at ≥10% of its AI. The most potent nitrosamine is the one with the lowest AI (see table 1). Limits for individual *N*-nitrosamines can be defined but are not necessarily needed. However, it should be clearly stated which *N*-nitrosamines are included in the calculation of total *N*-nitrosamines.

For option 2, the limits for *N*-nitrosamines should ensure an overall risk of not more than 1 in 100,000. Different approaches can be employed to achieve this risk requirement:

Fixed approach: fixed AI limits (in ppm/ppb) are set for individual nitrosamines and no limit for total *N*-nitrosamines is needed. The limit for each *N*-nitrosamine should be set at a percentage of its AI limit such that the sum of the % AI limits for each specified nitrosamine does not exceed 100%.

Flexible approach: each *N*-nitrosamine should be specified at its AI limit in ppm/ppb and an additional limit for total *N*-nitrosamines is required. The calculation for total *N*-nitrosamines could be written as:

$$\sum_{i=2}^n \frac{X_i}{AI_i} \times 100\% \leq 100\%$$

Where X_i is the amount of each single *N*-nitrosamine i in ppm and AI_i is the AI limit of each *N*-nitrosamine i in ppm.

For each batch, to determine whether the limit for total *N*-nitrosamines is met, the amount of each *N*-nitrosamine present (in ppm/ppb) should be converted to a percentage of its respective AI limit. The sum of %AI limits of specified *N*-nitrosamines should not exceed 100%.

Example of control options and specifications for multiple nitrosamines in the same finished product:

The case of two NAs:

Two NAs both at or above 10% of their respective AI

Example:

NDMA and NDEA are both detected at or above 10% of their respective AI) in a finished product with maximum daily dose of 300 mg.

AI limit

NDEA: 26.5 ng/day / 300 mg/day= 0.088 ppm or 88 ppb = most potent *N*-nitrosamine

NDMA: 96.0 ng/day / 300 mg/day= 0.32 ppm or 320 ppb

Specification possibilities for different control options:

Nitrosamine	Option 1	Option 2 - Fixed Example 20:80 ratio ²	Option 2 - Flexible
NDMA	Not needed	NMT 64 ppb (320 ppb x 0.2)	NMT 320 ppb
NDEA	Not needed	NMT 70 ppb (88 ppb x 0.8)	NMT 88 ppb
Total Nitrosamines	NMT 88 ppb	Not needed	NMT 100% ¹

$$1. \left(\frac{[NDMA] \text{ ppb}}{320 \text{ ppb}} + \frac{[NDEA] \text{ ppb}}{88 \text{ ppb}} \right) \times 100\% \leq 100\%$$

NMT 100% = 1:100,000 theoretical excess cancer risk.

2. For option 2 fixed approach, a ratio of 20% NDMA to 80% NDEA (20:80) is used as an example only. Different ratios could be used in different situations dependent on relative amounts present, provided that the sum of the % AI limits for each specified nitrosamine does not exceed 100%.

Example of presentation of acceptable batch results for each control option:

Model data from 1 batch:

NMDA found at 38 ppb

NDEA found at 44 ppb

	Option 1		Option 2 - Fixed Example 20-80 ratio		Option 2 - Flexible	
	Limit	Results	Limit	Results	Limit	Results
NDMA	Not needed	-	NMT 64 ppb	38 ppb	NMT 320 ppb	38 ppb (12% of AI)
NDEA	Not needed	-	NMT 70 ppb	44 ppb	NMT 88 ppb	44 ppb (50% of AI)
Total NA	NMT 88 ppb	82 ppb	Not needed	-	NMT 100%	62%

11. What should I do if a nitrosamine is detected in my medicinal product?

If one or several nitrosamine(s) is detected for the first time in my medicinal product:

The MAH/Applicant should forthwith inform the competent authorities, irrespective of the amount detected as described in Q3 for medicinal products subject to the call for review.

The levels should be reported in ng and ppm, together with the corresponding calculations used to describe the potential exposure to the detected nitrosamine based on the maximum daily dosage recommended in the SmPC. If SmPCs differ between Member States, the calculations should be provided for each different maximum exposure. Sufficient details should be provided to enable the calculations to be reviewed and verified.

The calculated exposure(s) should then be compared to the limit defined in Q10:

- If the limit is not exceeded for the detected nitrosamine or, in case of presence of multiple nitrosamines, if the total risk remains below a theoretical lifetime excess risk of $\leq 1:100,000$, the MAH/Applicant shall control the nitrosamine(s) in the FP at or below this limit (see Q10) and should take measures to mitigate the risk of nitrosamine formation or contamination in the medicinal product as much as possible (see Q12).
- Where the limit defined in Q10 for single or multiple nitrosamines is exceeded, the MAH/Applicant should submit forthwith an (interim) investigation report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment. The competent authorities will then assess the impact on the benefit/risk balance and the consequent need for any action to be taken.

Please refer to the [Assessment report](#) of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products for further information.

Changes to the marketing authorisation related to measures to prevent or minimize the risk should be introduced without delay and in accordance with the guideline on classification of variation (please refer to Q13).

If the presence of specific nitrosamine(s) in a medicinal product has already been reported to the authorities by the MAH and is below the limit defined in Q10 or a limit approved by the authorities, there is no need for a further notification to the authorities.

Batch records are subject to inspection by competent authorities.

12. Which are the measures to mitigate the risk of presence of nitrosamines?

The presence of N-nitrosamines in the FP shall be mitigated as much as possible and shall be at or below a limit defined in Q10.

MAHs shall design or adapt the manufacturing process of their medicinal products to prevent formation of and contamination with nitrosamines whenever possible.

MAHs should implement a control strategy regarding N-nitrosamines, which should include current and prospective measures to minimise the risk of generation of/contamination with nitrosamines (e.g. change

of manufacturing process, change of raw material quality, introduction of appropriate specifications and development of appropriate methods, and measures on the premise and equipment such as cleaning procedures and environmental monitoring). MAHs should control nitrosamine levels in accordance with the limits defined in Q10 and any future changes that may impact on the risk (e.g. change of supplier, change of manufacturing process and change of packaging).

MAHs shall also ensure that active substances and excipients used in their FPs are manufactured in compliance with good manufacturing practices in line with Article 46(f) of Directive 2001/83/EC.

Please refer to the [Assessment report](#) of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products for further information.

13. Which changes would be required for Marketing Authorisations?

MAHs should introduce changes to their API and/or FP (e.g. manufacturing process, controls and specification, product formulation, raw materials and packaging), through the timely submission of appropriate variation(s) in accordance with the guideline on classification of variations.

When nitrosamine(s) is (are) identified, the corresponding limit(s) as defined in Q10 should be introduced in the specifications of the FP. Please refer to Q15 for information on the test modalities.

The application for a variation should contain information on amendments to the marketing authorisation – i.e. in module 3 (3.2.S and 3.2.P), the active substance master files (ASMF) or the Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) that is necessary to control nitrosamine impurities in the active substance and/or FP. Variations should be submitted according to the existing variations classification guideline:

https://ec.europa.eu/health/sites/health/files/files/betterreg/pharmacos/classification_guideline_adopted.pdf.

Depending on the root cause identified and extent of changes to be made, grouping of variations or use of work-sharing procedures might be applicable: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers>.

14. What is the approach for new and ongoing marketing authorisation applications (MAA)?

Applicants shall design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of *N*-nitrosamines in their API and FPs (please refer to Q12).

The potential presence of nitrosamines must be evaluated as part of the MAA as follows:

- **At the submission stage:**
 - For the risk evaluation, Applicants are required to follow the principles for step 1 *as per* Q2. The risk evaluation should be submitted as an attachment to Module 1 with a corresponding reference in Module 3.2 of the marketing authorisation dossier.
 - If a risk of presence of nitrosamines in the medicinal product is identified, applicants are required to provide the risk assessment outlining the impact on the benefit-risk balance of the product and a risk mitigation strategy. Applicants should also submit confirmatory testing plans or confirmatory testing data as mentioned in step 2 (see Q2).

- In case applicants have not submitted a risk evaluation and, if applicable, confirmatory testing plans with their MAA, these should be submitted during the marketing authorisation review procedure.
- **During the Marketing Authorisation (MA) evaluation procedure:**
 - If the risk evaluation was not submitted as part of the MAA, it will be requested during the MA review process. Risk evaluation will have to be adequately documented and, if applicable, supported by confirmatory testing in case a possible risk of presence of nitrosamines has been identified. This information should be submitted as part of the responses to the list of questions.
 - If the applicant is not able to provide satisfactory information and justification of a favourable benefit-risk profile of the product at this stage, a request to further assess the risk of presence of nitrosamine will be part of the further list of questions / outstanding issues depending on the stage of the MA procedure.
 - Any outstanding issues related to the quality requirements of the product would have to be addressed before the final opinion on the granting of the MA.

For new and on-going marketing authorisation applications, the number of batches to be tested as part of any confirmatory testing should be commensurate with the risk in line with ICH M7(R1) guideline. The source of risk has to be well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch. Test results from a minimum of 6 pilot scale batches or 3 production scale batches may be sufficient. Depending on the risk factors for nitrosamine presence, e.g. with risk factors being closer to the FP, more batches may need to be tested. If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, (or were used historically during development), then testing of additional batches would be necessary to cover these risk factors.

If a product is available in multiple strengths of the same dosage form with the same risk factors applicable to each, then testing could be rationalised by testing only the worst-case scenario strength. The worst-case approach should be justified by the MAH on a case by case basis.

During development of an analytical method, a reference standard of the relevant nitrosamine impurity is generally needed. If, despite extensive efforts, it becomes apparent that the relevant nitrosamine impurity cannot be synthesized, then this could be an indication that the nitrosamine either does not exist or that there is no risk of it being formed. In such cases, it may not be necessary to conduct confirmatory testing. This should be justified thoroughly on a case by case basis according to appropriate scientific principles. The justification could include relevant literature, information on structural/stereo-electronic features and reactivity of the parent amine, stability of the nitrosamine and experimental data to illustrate the efforts made to synthesize and to analyse the impurity. The justification should be included in the submitted risk assessment.

15. When should a test for nitrosamines be included in the MA dossier?

When a nitrosamine is identified after Step 2 confirmatory testing, a limit will usually need to be included in the specifications of the finished product and the product must comply if tested. If the root cause has been identified in the finished product manufacturing process or nitrosamines have been detected in the finished product but the actual source of contamination remains unclear, routine testing of the finished product is required by default.

The control point (finished product, API or an intermediate) for nitrosamines should be selected in such a way that it will give assurance of presence of the impurity below the acceptable limit based on acceptable intake (AI) in the finished product. Testing is usually expected to be carried out in the finished product, however if the source of a nitrosamine impurity is identified in the active substance manufacturing process, control options 1 to 3 as stated in ICH M7(R1) guideline could be used to demonstrate that the nitrosamine will not be present above the acceptable limit based on AI in the finished product. Even if the control point for the nitrosamine is not at finished product level, a limit has to be included in the finished product specification and batches should comply if tested. Testing of raw materials (e.g. excipients) should also be considered if these are potential sources of nitrosamine impurities.

Exceptions from routine testing may be possible, if the root cause of contamination is demonstrated to be well-understood:

- Only if the amount of nitrosamine present is consistently below 10% of the acceptable limit based on AI in the finished product, then testing could be omitted.
- Only if nitrosamine levels are consistently below 30% of the acceptable limit based on AI in the API or the finished product, skip-testing according to the ICH Q6A definition could be acceptable.

16. What are the responsibilities of MAHs for APIs with CEPs or ASMFs?

MAHs/Applicants, manufacturing authorisation holders and API manufacturers should work together and take precautionary measures to mitigate the risk of presence of nitrosamines during the manufacture and storage of all medicinal products containing chemically synthesised APIs.

MAHs/Applicants must ensure that appropriate and robust risk evaluations are carried out by the relevant manufacturing authorisation holders and API manufacturers (including ASMF or CEP holders) in accordance with Article 46 of Directive 2001/83/EC.

17. How does the lessons learnt exercise from presence of nitrosamines in sartans relate to the Article 5(3) Referral Outcome?

The lessons learnt exercise was conducted by experts from the EU Regulatory Network to determine which lessons can be learnt from the handling of the cases of sartans with nitrosamine impurities. The objective is to make recommendations on how to reduce the risk of such impurities in medicines and to ensure that regulators are better prepared to manage cases of unexpected impurities in the future. Although the exercise focussed on lessons learnt from the assessment conducted for the sartans with a tetrazole ring, the recommendations apply to all human medicines.

The recommendations set forward include new or additional guidance on areas such as the control of impurities (including cohort of concern compounds), Good Manufacturing Practice, the roles and responsibilities of manufacturers and MAHs/Applicants but also proposals for improvement of communication with patients and healthcare professionals and cooperation with international partners. The [full recommendations](#) are available on [EMA's website](#). The European medicines regulatory network will develop an implementation plan and then work with the parties that will implement each action.

It should be noted that the lessons learnt exercise outcome has been taken into account in the [Article 5\(3\) procedure](#). The implementation of recommendations of the lessons learnt exercise will strengthen

the regulatory framework and complement the outcome of this Article 5(3) procedure which provides the scientific opinion on the presence of nitrosamine impurities in human medicines.

18. What about regulatory requirements in other regions?

Regulatory authorities in the EU have been cooperating with international partners in the United States, Canada, Japan, Singapore, Switzerland, Australia and other countries to mitigate presence of nitrosamines in medicinal products and to align requirements. For questions about regulatory requirements outside the EU, please contact the relevant authorities.

19. What is the approach for line extensions and variations applications not linked to changes required as part of article 5 (3) recommendation?

No risk evaluation is generally necessary when submitting line extension or variation application. The risk evaluation is only required to be submitted for products in scope of the call for review as reported in Q&A 3.

Nevertheless, in some exceptional cases questions on the presence of nitrosamines in the product may be raised if a potential risk is identified during the assessment.

Annex 1: Decision tree with control options for products containing multiple *N*-nitrosamines: (New)

