EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

20 December 2019
EMA/CHMP/428592/2019 Rev. 2

Questions and answers on "Information on nitrosamines for marketing authorisation holders"

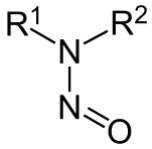
Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Introduction

MAHs of all human medicinal products containing chemically synthesised active pharmaceutical ingredients (APIs) should work with the manufacturers of their APIs and finished products in order to evaluate the risk of nitrosamines being present in their products, and take appropriate risk mitigating measures. The evaluations are necessary in light of the detection of nitrosamines in some sartan medicines and the subsequent Article 31 referral which concluded in April 2019, as well as phase 1 of CHMP's review under Article 5 (3) of Regulation (EC) No. 726/2004 of the presence of nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients.

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:



This questions and answers document should be read in conjunction with the document *Information on nitrosamines for marketing authorisation holders.*

1. Are all products to be reviewed? *(UPDATED)*

All authorised human medicinal products containing chemically synthesized APIs are to be reviewed, including generics and over-the counter (OTC) products. However, in view of the large number of authorised products, MAHs should use a risk-based approach and prioritize their evaluations and confirmatory testing.

MAHs of sartans with a tetrazole ring (i.e. those covered by the respective Art.31 referral procedure) should comply with the conditions from the referral. However, considering that additional root causes have emerged, subsequent to conclusion of that referral these additional risk factors should also be considered for products containing sartans with a tetrazole ring.

2. What factors should be considered in prioritizing the risk evaluation?

MAHs should prioritise products in order to establish the sequence in which their products are to be evaluated. For the purposes of this prioritisation, MAHs may consider factors such as the maximum daily dose taken, 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.

3. How should the risk evaluation be implemented?

MAHs together with API and finished product manufacturers are required to perform risk evaluations using quality risk management principles, as outlined in ICH Q9 guideline. The principles described in ICH M7 guideline in relation to toxicology assessment, control strategy and changes to the manufacturing processes for active substances should be applied.

The information necessary for risk evaluation should be made available to the MAHs by the API and finished product manufacturers. If the risk of nitrosamine impurity formation had been assessed during the development phase of the API/finished product manufacturing processes, the information from the assessment can be used to support this evaluation.

MAHs and manufacturers should consider the following:

- Is there a risk of nitrosamines forming in the API synthetic process taking into consideration the combination of reagents, solvents, catalysts and starting materials used, intermediates formed, impurities and degradants? (Refer to *Information on nitrosamines for marketing authorisation holders*)
- Is there a potential risk of nitrosamine contamination (e.g. from recovered materials such as solvents, reagents and catalysts, equipment, degradation, starting materials or intermediates)?
- Is there any potential of nitrosamine formation during the manufacture of the finished product and/or during storage throughout its shelf life?

MAHs and Manufacturers should verify by testing a representative number of samples of the relevant starting material, intermediate, API or finished product. The number of batches/samples tested should be scientifically justified.

4. How should tests be conducted by MAHs and manufacturers?

Methods for determination of NDMA and NDEA in sartans 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 appropriate for other APIs.

Depending on the manufacturing process used, other nitrosamines could potentially be present in medicinal products. During the Article 31 referral, some of these nitrosamines (e.g. N-nitrosoethylisopropylamine – EIPNA, N-nitrosodiisopropylamine – DIPNA and 4-(methyl)(nitroso)amino)butanoic acid - NMBA) were identified in sartan APIs; others (e.g. N-nitrosodibutylamine - NDBA, N-nitrosomethylphenylamine - NMPA)) were hypothesised based on the sartan manufacturing process.

Appropriately sensitive analytical methods for determination of the specific nitrosamines in other medicinal products containing APIs other than sartans should be developed and validated accordingly before testing.

5. When should MAHs report to competent authorities?

The risk evaluation of all products should be concluded at the latest within 6 months of the publication of "*Information on nitrosamines for marketing authorisation holders*" and MAHs should inform the concerned Competent Authorities when the risk evaluation is concluded.

Risk evaluation documents do not need to be submitted but should be made available upon request. If a risk of presence of nitrosamines is identified as a result of the evaluation, the MAH should proceed to Step 2 (see "*Information on nitrosamines for marketing authorisation holders*").

In addition, MAHs should inform the competent authorities as soon as possible if tests confirm the presence of nitrosamine, irrespective of the amount detected. The immediate risk to patients should be assessed and appropriate action taken to avoid or minimise the exposure of patients to nitrosamines.

For their responses MAHs are required to use dedicated templates and contact points as outlined on the EMA and CMDh websites.

Further questions should be addressed directly to the licensing authorities.

6. What limits will apply for nitrosamines detected in any products? *(See Q&A 16 for updated instructions)*

Given the substantial number of APIs and finished products involved, long-term acceptable limits of nitrosamines for non-sartan products are still under consideration.

For the conduct of the requested evaluations, MAHs are advised, as a temporary measure, to use the approach outlined in ICH M7 guideline as well as the principles described in relation to toxicology assessment in the published report for the Article 31 review of sartans, in addition to considering the prioritisation factors outlined in question 2. Acceptable intake (AIs), on which temporary limits should be based have been defined for NDMA and NDEA impurities in the Article 31 referral assessment report. Furthermore, for NMBA, DIPNA and EIPNA impurities additional AIs calculated by the Safety Working Party (SWP) are available for reference at the following ink:

https://www.ema.europa.eu/en/documents/other/temporary-interim-limits-nmba-dipna-eipna-impurities-sartan-blood-pressure-medicines_en.pdf

In any case, MAHs should inform competent authorities if a nitrosamine is present in a product, irrespective of the amount detected.

7. What are the deadlines for the evaluations?

Risk evaluation for all products should be concluded at the latest within 6 months of the publication of this notification.

Confirmatory testing activities should start as soon as the risk of presence of nitrosamine is identified from the risk evaluation exercise and should begin immediately for products considered at high risk. Confirmatory testing of all concerned medicinal products and submission of required changes in the manufacturing authorisations should be concluded at the latest within 3 years of the publication of this notification or at an earlier time if otherwise justified.

All the above timelines should be shortened and immediate communication to authorities should be ensured in case of findings indicating an immediate risk to public health.

8. Which changes would be required to Marketing Authorisations?

If MAHs identify that changes are necessary in their production process and/or product formulation, they should liaise with competent authorities in order to evaluate the type of variation needed and submit one as required in a timely manner. The application for a variation should contain information

on amendments to the marketing authorisation – i.e. module 3 (3.2.S and 3.2.P), the active substance master files (ASMF) or certificates of suitability (CEP) – that are necessary to amend the method of manufacture or control of the active substance and/or finished product. A non-exhaustive list of variations required to ensure a control strategy for confirmed presence of nitrosamines is provided below:

- Change in the control strategy of the manufacturing process of the active substance or intermediates, a type IB variation application (B.I.a.4.f) to change in-process tests, a type IB variation B.I.b.1h to change specifications parameters of a starting material/intermediate/reagent should be filed by the MAH for drug substances based on an updated ASMF or full data presented in Module 3.2.S. If the change is included in the restricted part of the ASMF, a type IB variation (B.I.a.2.e) could be submitted. CEP holders should file variation applications at EDQM. For drug substances documented in a CEP, the updated CEP should be filed by the MAH via type IA or IB (B.III.1a) variation application.
- Change of the manufacturing process, a type II variation application (B.I.a.2.b) should be filed by the MAH for the drug substances based on an updated ASMF or full data presented in Module 3.2.S. CEP holders should file a variation application at EDQM. The updated CEP should be filed by the MAH via type IA or IB (B.III.1a) variation application.
- Change in the drug substance specification with adaptation of the sections 3.2.S.3.2 and 3.2.S.4.1.-5. For drug substances documented in a CEP, CEP holders should file a variation application at EDQM. The updated CEP should be filed by the MAH via type IA or IB (B.III.1a) variation application and, if needed, the amended specifications should be introduced into the dossier by a type IB variation (B.I.b.1.h).

Change in the drug substance specification with adaptation of sections 3.2.S.3.2 and 3.2.S.4.1.-5. A type IB variation application (B.I.b.1.h) should be filed by the MAH for drug substances documented in an ASMF or where full data is documented in Module 3.2.S.

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

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

10. What about regulatory requirements in other regions?

Regulatory authorities in the EU have been cooperating with international partners in the United States, Canada, Japan, Switzerland and other countries to limit or eliminate nitrosamines from medicinal products and to align requirements. For questions about regulatory requirements outside the EU, please contact the relevant authorities.

11. How will regulators ensure ongoing dialogue with industry? *(UPDATED)*

EMA has launched an exercise with experts from across the EU regulatory network including national authorities, the EDQM and the European Commission to determine what can be learned from the presence of nitrosamine impurities in sartans and to make recommendations to prevent and manage such situations in the future.

As part of this exercise, EMA hosted the Lessons Learnt face-to-face meeting on Sartans on the 4th and 5th of November 2019 with stakeholders, including representatives from the pharmaceutical industry. The scope of the workshop was to discuss the lessons learnt from the recent cases of sartan medicinal products (angiotensin receptor blockers) with nitrosamine impurities.

12. What are the currently identified root causes for presence of nitrosamines? *(UPDATED)*

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, tertiary amines or quaternary ammonium salts within the same or different process steps (if carry over can occur).
2. Use of sodium nitrite ($NaNO_2$), or other nitrosating agents, in combination with reagents, solvents and catalysts, which are susceptible to degradation to secondary or tertiary amines, within the same or different process steps (if carry over can occur).
3. Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts).
4. Use of recovered 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 routine recovery processes carried out in non-dedicated equipment.
5. Use of contaminated starting materials and intermediates supplied by vendors that use processes or raw materials which may allow nitrosamine formation.
6. Cross-contaminations due to different processes run on the same line and due to operator-related errors such as inadequate phase separations.
7. Degradation processes of starting materials, intermediates and drug substances, including those induced by inherent reactivity in combination with carry-over of sodium nitrite ($NaNO_2$), or other nitrosating agents. This could potentially occur also during finished product formulation or storage.
8. Use of certain packaging materials. Nitrosamine contamination has been observed by one MAH in a finished product stored in blister. The MAH has hypothesised that the lidding foil containing nitrocellulose printing primer may react with amines in printing ink to generate nitrosamines, which would be transferred to the product under certain packaging process conditions (e.g. during heat-sealing blistering processes via vaporization and condensation onto the drug product).

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

The potential presence of nitrosamines will be evaluated as part of the marketing authorisation application as follows:

- **At the submission stage:**
  - Applicants are required to submit a risk evaluation as per principles outlined in step 1 of the *Information on nitrosamines for marketing authorisation holders* as part of their MAA.
  - If at this stage, a risk of presence of nitrosamines in the medicinal product is already identified, the 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 the step 2 of the "*Information on nitrosamines for marketing authorisation holders*".
  - 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 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 on the 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 would have to be addressed before the final opinion on the granting of the MA;
  - If concerns on the possible presence of nitrosamines in the product are still not addressed at the time of opinion, then this will be factored into the benefit/risk assessment and may impact the granting of a marketing authorisation.

Note: for the purpose of this Q&A please see below definition:

Risk evaluation: all activities in step 1.

Risk assessment: all activities in step 2 and 3.

14. Are biological products containing excipients potentially at risk of contamination with Nitrosamines in the scope of the review? *(NEW)*

The present request for review applies only to human medicines containing chemically synthesised APIs. As part of the Article 5(3) procedure, the EMA's human medicines committee (CHMP) will evaluate all available scientific knowledge on nitrosamine impurities and will also consider whether to broaden the scope of the review to include medicines other than those containing chemically

synthesised active substances and/or excipients. However, if any MAH or manufacturer identifies that any non-chemically synthesised products, including biological products, contains nitrosamine impurities, they should inform the competent authorities immediately.

15. What to do if after completing step 1 and /or step 2 new information on new potential root causes is identified? *(NEW)*

Once steps 1 and 2 are completed, MAHs together with API and finished product manufacturers are expected to maintain the quality of the product throughout its lifecycle and therefore to review the outcome of the risk evaluation and testing as and when new information 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. EMA and CMDh will continue to publish any newly identified sources of nitrosamine impurities on their websites.

16. What limits will apply for nitrosamines in medicinal products based on lifetime and less than lifetime use? *(NEW)*

Long-term limits of nitrosamines for non-sartan products are still under consideration.

For any new cases of nitrosamine detection in a medicinal product, the MAH should apply, whilst waiting for the outcome of the CHMP Art 5(3) procedure, interim limits calculated for a lifetime treatment and based on a maximum daily dose of the medicine. These interim limits (ILs) have been defined for NDMA and NDEA impurities in the Article 31 referral assessment report. Furthermore, for NMBA, NDBA, DIPNA and EIPNA, additional interim limits calculated by the Safety Working Party (SWP) and agreed by the CHMP and CMDh are summarised in the table below and are available for reference at the following ink:

https://www.ema.europa.eu/en/documents/other/temporary-interim-limits-nmba-dipna-eipna-impurities-sartan-blood-pressure-medicines_en.pdf (calculation for NDBA not yet published).

Nitrosamine	Interim Limit*
NDMA, NMBA	96 ng/day
NDEA, NDBA, DIPNA, EIPNA	26.5 ng/day

**These limits are not applicable for batches where more than one of the above N-nitrosamines has been identified simultaneously; such batches should be rejected.*

If this interim limit is not exceeded, competent authorities shall be informed on the levels of the impurities detected (see Q6). MAHs should also follow the Notice to MAHs through step 1 and step 2 as described in that notice.

Where the interim limit is exceeded for medicinal products with a limited treatment period or intermittent treatment (e.g. once a week), higher daily exposures may be used as an adjusted interim limit. The approach described in the ICH M7 guideline as the Less Than Lifetime (LTL) approach can be used to calculate adjusted interim limits for impurities present in medicinal products given for LTL and these are described in the following table:

Duration	1 day - 1 month	1 month – 1 year	1 year - 10 years	10 years - lifetime
Daily intake	80 x IL	13.3 x IL	6.7 x IL	IL

The risk approach is applicable to all routes of administration and no corrections to interim limits are generally warranted unless data justify route-specific differences that should be evaluated case by case.

If nitrosamine impurities are detected, levels should be reported in ng and ppm, along with the relevant calculations used to describe the potential exposure to the detected nitrosamine based on the maximum daily dosage and duration of treatment described in the SmPC. If the SmPC varies between Member States, then the calculations for each different maximum exposure should be provided. These exposures should then be compared to the interim lifetime or less than lifetime approaches set out in the table above. Sufficient detail should be provided to enable the calculations to be reviewed and verified.

MAHs should in all cases also follow the Notice to MAHs through step 1 and step 2 as described in that notice.
MAHs should always take precautionary measures to mitigate the risk of nitrosamine formation or presence during the manufacture of their product.