EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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

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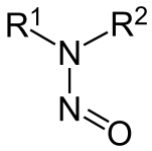
impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients.

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?

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.

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.

Further instructions will be provided in due course. After that further questions should be addressed directly to the licensing authorities.

6. What limits will apply for nitrosamines detected in any products?

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 Intakes (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?

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 plans to hold a workshop by the end of 2019 where stakeholders, including representatives from the pharmaceutical industry, will be able to share their knowledge and experience. EMA will extend invitations to industry associations and provide further information through EU trade associations closer to the date of the workshop.

12. New! What are the currently identified root causes for presence of nitrosamines?

Potential sources of nitrosamine impurities currently identified 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.