EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/189634/2019
OBSOLETE PLESE REFER TO CHMP ASSESSMENT REPORT OF ARTICLE 5 (3) REFERRAL ON NITROSAMINES IMPURITIES IN HUMAN MEDICINAL PRODUCTS AND RELATED GUIDANCE

Information on nitrosamines for marketing authorisation holders

Request to evaluate the risk of the presence of nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients

Background

In June 2018, authorities in the EU became aware of the presence of a nitrosamine, N-nitrosodimethylamine (NDMA), in valsartan from one manufacturer of active pharmaceutical ingredients (APIs). Subsequently another nitrosamine, N-nitrosodiethylamine (NDEA), was detected and other sartans from more API manufacturers were later implicated. NDMA and NDEA are classified as probable human carcinogens and their presence in sartans was, at the time, unexpected.

An Article 31 review of sartans at risk of containing nitrosamine impurities (i.e. sartans with a tetrazole ring) concluded that manufacturers must review and make necessary changes to their manufacturing processes to minimise nitrosamine impurities as much as possible. In addition, strict limits were set for nitrosamines in these products.

The findings of the review indicate that there is a potential for nitrosamines to be present in APIs for other medicines (i.e. non-sartans APIs), depending on the API and the finished product manufacturing processes.

It should be also noted that traces of NDMA have been found in pioglitazone hydrochloride from one API manufacturer. As the nitrosamine levels in this case were within the interim limits established in the sartans review, no market action was deemed necessary. As a precaution, companies using certain reagents to manufacture pioglitazone have been requested to test their products and check their processes to rule out the presence of nitrosamine impurities. More recently nitrosamine impurities have been identified in batches of ranitidine and consequently an EU-wide review has been initiated.

Nitrosamines are not expected to be formed during the manufacture of the vast majority of APIs outside the class of sartans with a tetrazole ring. However, it is now known that these impurities can form during production under certain conditions and when certain solvents, reagents and other raw materials are used. In addition, impurities can be carried over during the manufacturing process when using already-contaminated equipment or reagents. Furthermore, in cases where nitrosamines can

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

form or are carried over during production, the impurities should normally be controlled and removed during the manufacturing process. Therefore, despite the low risk of nitrosamines being present, Marketing Authorisation Holders (MAHs) are asked to take precautionary measures to mitigate the risk of nitrosamine formation or presence during the manufacture of all medicinal products containing chemically synthesised APIs.

EMA and EU national competent authorities will continue to monitor and review the presence of nitrosamine impurities in medicines, and will consider which other active substances, manufacturing processes, or materials used during manufacturing (if any) could lead to an increased risk of nitrosamines impurities.

Regulatory authorities in the EU will continue to cooperate with international partners and will work with MAHs to find rapid solutions to address any adverse findings.

In September 2019 it was considered that it was of public health interest to have a scientific opinion from the Committee for Human Medicinal Products (CHMP) in accordance with Article 5(3) of Regulation (EC) No 726/2004.

Responsibilities of MAHs

MAHs are responsible for ensuring that their medicinal products are manufactured in accordance with the requirements laid down in Directive 2001/83/EC. MAHs are responsible for the quality, safety and efficacy of their products, including the quality of the APIs, excipients and raw materials used in the manufacture of finished products. MAHs should therefore ensure (via quality agreements) that they and the holder of the manufacturing authorisation have access to relevant information from the API manufacturers concerning potential formation of nitrosamine impurities and the potential for cross-contamination. The holder of the manufacturing authorisation is also reminded of their responsibility to ensure the use of APIs that have been manufactured in accordance with good manufacturing practice (GMP) for active substances.

The information necessary for risk evaluation should be made available to the MAHs by the manufacturers. Even for products with active substance master files (ASMFs) and certification of suitability to the monographs of the European Pharmacopoeia (CEPs) containing information that is not available to MAHs, MAHs remain responsible for ensuring that robust risk evaluations have been appropriately carried out by the ASMF or CEP holder to enable the MAH to take responsibility for the quality of the active substance and the medicinal product.

Potential sources of nitrosamine impurities

The Article 31 review of sartans identified a number of root causes of nitrosamine formation and contamination.

1. Nitrosamine impurities can form during API processing under certain processing conditions and in the presence of some types of raw materials, starting materials, and intermediates. They may not be fully purged in subsequent steps of the API manufacturing process.
2. The use of sodium nitrite ($NaNO_2$), or other nitrites, in the presence of secondary or tertiary amines is a potential cause of nitrosamine formation.

   Secondary amines can be present in reagents and solvents as impurities or degradants. They may also be part of reagents, solvents, APIs, their degradants, and precursor structures. For example, amide solvents can degrade to secondary amines which are known sources of nitrosamines (such as *N*,*N*-dimethylformamide [DMF], *N*-methylpyrrolidone [NMP], or *N*,*N*-dimethylacetamide [DMA]).

Tertiary amines include common bases which have already been observed to allow nitrosamine formation (i.e. triethylamine, diisopropylethylamine [Hunig's base=DIPEA]). However, other less common bases are sometimes used in manufacturing processes, for example *N*-methylmorpholine (NMM), tributylamine (TBA) and many others which would lead to formation of different nitrosamines. Tertiary amines are also common functional groups in many APIs and their precursors.

Secondary and tertiary amines could also be present as impurities in or degradants of quarternary ammonium salts such as tetrabutylammonium bromide (TBAB) or even in primary amines such as monoethylamine.

This list of sources is not exhaustive as many other amine reagents, catalysts or solvents can be used to mediate a range of synthetic transformations. Other reagents containing amine functionality should be considered for the potential risk of nitrosamine formation.

In most confirmed cases of nitrosamine contamination of APIs to date, the nitrite source and amine have been used in the same step. However, other cases have been identified where sodium nitrite used as a reagent in one step has been carried over into subsequent steps, despite extensive purification operations, and then reacted with an amine to generate a nitrosamine impurity. Since carry-over from one step to the next cannot be completely ruled out, all processes that use sodium nitrite (or other sources of nitrite) should be considered at risk of generating nitrosamine impurities if amines (see examples above) are present in any step of the synthesis.

3. Nitrosamines may also be present in APIs following the use of contaminated raw materials in the manufacturing process. Recycled solvents, reagents and catalysts, may pose a risk for nitrosamine formation due to the presence of amines in the waste streams sent for recovery and the subsequent quenching of these materials with nitrous acid to destroy residual azide, without adequate control of nitrosamine formation or adequate purification.

   Examples of recycled materials observed to be contaminated with nitrosamines include orthoxylene and tributyltin chloride (used as a source of tributyltin azide). It has also been suggested that *N*,*N*-dimethylformamide (DMF) could be contaminated in this way. Nitrosamines may be entrained if they have similar boiling points or solubility properties to recovered materials depending on how recovery and subsequent purification takes place (e.g. aqueous washes or distillation).

4. It is also known that the recovery of materials (e.g. solvents, reagents and catalysts) is often outsourced to third parties. In some cases, the third party recovery facilities do not receive enough specific information on the content of the materials they are processing and rely on routine recovery processes carried out in non-dedicated equipment. This can potentially lead to cross-contamination of solvents, reagents and catalysts from various sources or processes if equipment is not adequately cleaned between customers, or if precautions to avoid nitrosamine formation are not in place.

5. Another source of nitrosamines may be contaminated starting materials, including intermediates supplied by vendors that use processing methods or raw materials causing formation of nitrosamines. For example, nitrites are known impurities in raw materials, including reagents, solvents, and excipients used in finished products.

   Contamination from vendor-sourced raw and starting materials poses particular challenges because a producer of an API whose manufacturing process is not capable of forming a nitrosamine compound may not be aware of the risk of such impurities being present.

   Please refer to the public assessment report for the Article 31 review of sartans.

Call for review

In accordance with the CHMP opinion under Article 5 (3) of Regulation (EC) No. 726/2004 on the presence of nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients, and as a precaution, MAHs should review their manufacturing processes to identify and, if found, to mitigate risk of presence of nitrosamine impurities.

MAHs should work with manufacturers of API and finished products in order to review the API and finished product manufacturing processes with respect to the arrangements for preventing nitrosamine formation as well as contamination or cross-contamination, taking into account their knowledge of the manufacturing processes as well as the potential sources of nitrosamine impurities described above.

As a reminder, MAHs for products containing sartans with a tetrazole ring included in the recent Article 31 review must implement the recommendations from the review within the timelines set out in the respective Commission Decisions.

For medicinal products containing APIs other than sartans with a tetrazole ring, the following steps should be taken:

Step 1 Risk evaluation: MAHs should perform risk evaluation of their medicinal products containing chemically synthesised API. 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.

MAHs should prioritise products in order to establish the sequence in which their products are to be evaluated. The factors that can be taken into account are outlined in the dedicated Questions and Answers.[1] For products identified as high priority, the risk evaluation should be done immediately.

The risk evaluation of all products should be concluded at the latest within 6 months of the publication of this notification. 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 below).

Step 2 confirmatory testing: in the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods in accordance with the prioritisation deriving from the risk evaluation conducted in step 1. Products identified as high priority should be tested as soon as possible. Confirmatory testing of all medicinal products identified to be at risk of presence of nitrosamines 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.

MAHs should inform the competent authorities immediately if tests confirm the presence of an nitrosamine impurity irrespective of the amount detected.

- **Step 3 changes to the marketing authorisation:** MAHs should apply for a variation in a timely manner to introduce any required changes, such as amendment of the manufacturing process or changes to product specifications.

[1] For additional details please refer to the Questions and Answers on "Information on nitrosamines for marketing authorisation holders".

At all steps, timelines should be shortened and authorities immediately informed if findings indicate an immediate risk to public health.

Further clarification on the call for review is available in the related Questions and Answers document "Information on nitrosamines for marketing authorisation holders".