

Risk evaluation for potential nitrosamine impurities for national authorised medicines for human use in the competence of the Paul-Ehrlich-Institut (Updated October 2023)

Marketing authorisation holders of medicines containing chemically synthesised active pharmaceutical ingredients and biological active pharmaceutical ingredients are requested to submit a risk evaluation for their medicinal products to the Paul-Ehrlich-Institut regarding the possible presence of nitrosamines (**step 1: risk evaluation**). Medicinal products for which a risk has been identified are to be tested and the corresponding test results to be submitted (**step 2: risk assessment**). Any relevant variations must be submitted if changes to the marketing authorisation are necessary to eliminate or reduce the nitrosamines to below the limits identified for the protection of public health (**step 3: changes to the marketing authorisation**).

The request follows the procedure under Article 5 (3) of Regulation (EC) No 726/2004 on nitrosamines in medicinal products for human use.

Nationally authorised medicinal products subject to Directive 2001/83/EC

Different submission timelines apply for medicinal products with chemically synthesised active pharmaceutical ingredients and biological active pharmaceutical ingredients. The deadlines are as follows:

Latest submission date:	MPs with chemically synthesised active pharmaceutical ingredients	MPs with biological active pharmaceutical ingredients
Step 1 (obligatory)	31/03/2021	01/07/2021
Step 2	26/09/2022	01/07/2023
Step 3	01/10/2023 ¹	01/07/2023

The deadlines have passed.

Any marketing authorisation holder that has not yet notified the relevant national competent authority about any nitrosamine impurities they have identified should do so as a matter of priority, in line with the CHMP's Article 5(3) opinion. Marketing authorisation holders should also update any previous notifications if needed, using the response templates and reporting mechanisms established.

Marketing authorisation holders and manufacturers should work together and take precautionary measures to mitigate the risk of presence of nitrosamines during the manufacturing and storage of all authorised medicines.

For nationally authorised products, the submission should be conducted in accordance with these guidance documents:

- 'CMDh practical guidance for marketing authorisation holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5 (3) Referral on Nitrosamines'
- 'CMDh questions and answers'.

The website of the CMDh provides information with regard to procedural details as well as templates to be used.

Of note:

¹ New deadline acc. to Communication EMA/640344/2022 dated 29.07.22

- It is possible to combine information for several medicines in one submission (one template), as long as the outcome or the risk evaluation is identical for the products concerned (see No. 1.2 of the CMDh 'practical guidance').
- According to the CHMP Assessment Report² (EMA/369136/2020) dated 25/06/2020, there is a risk of presence of nitrosamines for biological medicinal products with certain risk factors. These are also listed under Q&A No. 2 in EMA/CMDh 'Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (EMA/409815/2020)'.

Medicinal products approved according to section 4b of the AMG

Holders of approvals according to section 4b of the AMG (German Medicinal Products Act) are also requested to submit a risk assessment with regard to a possible contamination with nitrosamines for their medicinal product approved according to section 4b of the AMG. The request applies mutatis mutandis to applicants who have not yet received a final decision on their application for initial or subsequent approval and for whom no corresponding subsequent requirements have been formulated in the procedure.

Deadlines for products approved according to section 4b of the AMG:

Latest submission date:	ATMP according to section 4b of the AMG
Step 1 (obligatory)	01/10/2021
Step 2 and 3	01/10/2023

The deadlines have passed.

Any marketing authorisation holder that has not yet notified the relevant national competent authority about any nitrosamine impurities they have identified should do so as a matter of priority, in line with the CHMP's Article 5(3) opinion. Marketing authorisation holders should also update any previous notifications if needed, using the response templates and reporting mechanisms established.

Medicinal products approved under section 21a of the AMG and certain medicinal products authorised under section 21 of the AMG

The submission of a risk evaluation (step 1) is not required for marketing authorisation holders of blood components for transfusion and marketing authorisation/approval holders of human tissue preparations and stem cell preparations for haematopoietic reconstitution if no risk has been identified.

However, if a risk has been identified, steps 2 and 3 must be carried out.

Information and Templates from the CMDh and EMA

- Information from the Coordination Group (CMDh):
 - [Information on nitrosamines for marketing authorisation holders](#)
 - [CMDh Press Release \(03/2022\)](#)
- Information from the EMA: [Nitrosamine impurities](#)

² See Section 5 Recommendations, bullet point no. 2.

Submission and contact

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Background

In June 2018, a contamination of valsartan with nitrosamine N-nitrosodimethylamine (NDMA) was detected.

Since that time, nitrosamine impurities were identified in batches of other medicines with chemically synthesised active pharmaceutical ingredients. It is now known that these impurities can form during production under certain conditions and when certain solvents, reagents and other raw material are used.

On the basis of animal experiments, nitrosamines have been classified as potentially carcinogenic in humans. They may be present in certain foodstuffs and potable water. Nitrosamines are not expected to cause harm when ingested in marginal amounts.

Despite the low risk of the presence of nitrosamine impurities, a [scientific evaluation on nitrosamine impurities](#) by the Committee for Medicinal Products for Human Use (CHMP) was initiated in September 2019 in accordance with Article 5(3) of Regulation (EC) No 726/2004.

As a result, a risk evaluation and any relevant testing was requested. Initially, this request was only made for medicinal products with chemically synthesised active pharmaceutical ingredients. According to the CHMP Assessment Report (EMA/341963/2020) dated 25/06/2020 a risk of nitrosamine contamination was also identified for biologics with certain risk factors and further measures were adopted. As of July 2020, marketing authorisation holders of medicinal products with biological active pharmaceutical ingredients are also requested to conduct a risk evaluation. This applies to centrally authorised ATMPs as well.

To ensure patient protection, a corresponding risk assessment procedure is now being carried out for nationally approved ATMPs according to section 4b of the AMG.