

Information Circular

N.º 113/CD/100.20.200

Date: 26/09/2022

Subject: Review on the risk of nitrosamine impurities in human medicines

To: Marketing Authorisation Holders (MAH)

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The review on the risk of nitrosamine impurities in human medicines started in 2019. Marketing Authorisation Holders should assess the presence of nitrosamines and test all medicinal products with potential risk. In both cases, the results should be reported to the National Competent Authorities.

This evaluation should be performed in 3 Steps:

Step 1: Risk evaluation

Conduct a risk evaluation to identify active substances and finished products at risk of N-nitrosamine formation or (cross-)contamination and report the outcome by 31 March 2021 for chemical medicines and 1 July 2021 for biological medicines.

Step 2: Confirmatory testing

Perform further confirmatory testing on the products identified to be at risk of N-nitrosamine formation or (cross) contamination and report confirmed presence of nitrosamines as soon as possible. The **deadline** for completing confirmatory testing for chemical medicines is 26 September 2022.

Step 3: Update marketing authorisations

Apply for any necessary changes to the manufacturing process resulting from this review, by requesting a variation to the marketing authorisation via standard regulatory procedures. The **deadline** for submission of variations is 1 October 2023 for chemical medicines and 1 July 2023 for biological medicines.



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Infarmed in cooperation with the European network has promoted the implementation with all Member States on the review of the presence of nitrosamines in medicinal products, and has contributed to the European guidance [Practical Guidance \(PG\)](#) and [Question and Answers \(Q&A\)](#) in order to provide [additional guidelines](#). These documents are frequently updated and should be consulted frequently.

Therefore, considering the Marketing Authorisation Holder's responsibilities, INFARMED reinforces the need to communicate the assessment done on step 1 and step 2 of the procedure. The nitrosamine's [Notice To Applicants](#) has been updated regarding the step 2 submission in the SMUH-Alter platform . Whenever a risk is identified, the corresponding CMDh templates should be submitted via this platform.

The Presidente of the Executive Board


(Rui Santos Ivo)