Evaluation of the risk of nitrosamine impurities

in chemical drugs

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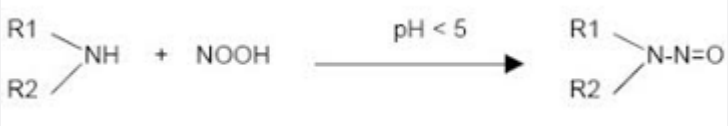
Introduction

Nitrosamines, or N-nitroso compounds, are substances produced essentially unintentionally during chemical synthesis. Their formation process (called nitrosation) requires both a nitrosatable substrate precursor (primary amine, secondary amine, quaternary ammonium salt) and a nitrosating agent.

The main reaction of nitrosamine formation is the following:



Several nitrosamines were classified as carcinogens 2A (probable carcinogens) and more recently in Group 1 (human carcinogens) for NNN (N-nitrosonomicotine). The REACH[1] regulations also list the following nitrosamines as category 1B carcinogens: NDMA, MNNG, NDELA, NDPA).

Nitrosamines in medicinal products for human use

During the summer 2018, authorities become aware of the presence of some nitrosamines in API – (Valsartan – presence of N- nitrosodimethylamine (NDMA) - other sartans – presence of N-nitrosodiethylamine NDEA). These nitrosamines were already known as probable carcinogenic compounds but their presence in the sartans was not then identified

Article 31 review findings 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. Subsequently, a nitrosamine impurity was detected in batches of ranitidine, batches of pioglitazone, and recently batches of metformin. An EU-wide review has been initiated.

The EMA requested MAHs to take precautionary measures to mitigate the risk of nitrosamine formation or presence during the manufacture of all medicines containing chemically synthetized APIs. In September 2019, EMA began a review under Article 5(3) of Reg (EC) 726/2004 to provide guidance to MAHs on how to avoid the presence of nitrosamine impurities in human medicines.

As part of this review, the CHMP has requested MAHs for human medicines (all products including generics and OTC) containing chemically synthetized APIs to review their medicines for the possible presence of nitrosamines and test all products at risk.

MA holders are responsible for ensuring that their medicinal products are manufactured in accordance with Directive 2001/83/EC and Good Manufacturing Practice.

They must ensure that they are familiar with the published guidelines, the sartans recommendations, their manufacturing processes for their products and all other scientific data relevant to the evaluation and interpretation of the results generated.

The MA holders have 6 months to carry out this risk assessment, in accordance with the Risk Management principles of ICHQ9.This request applies to all marketing authorisations regardless of the procedure (national, MRP, DCP, CP).

[1]Registration, Evaluation, Authorization and restriction of CHemicals (REACH)

The following steps should be taken:

STEP 1: RISK EVALUATION

The risk evaluation of all products should be concluded at the latest within 6 months of the publication of the notification. MAHs should inform the concerned competent authority when the risk evaluation is concluded. Risk evaluation document do not need to be submitted but should be made available upon request.

STEP 2: IF RISK OF PRESENCE OF NITROSAMINES IS IDENTIFIED AS RESULT OF EVALUATION

- Confirmatory testing using validated and sensitive methods

- Products identified as high priority should be tested as soon as possible

- MAHs should inform HC immediately if tests confirm the presence of a nitrosamine impurity irrespective of the amount detected

STEP 3: MAA changes= MAHs should apply for a variation within 3 years

Initially, MAHs should report the outcome by 26 March 2020 at the latest for Step 1 Risk evaluation. However, the EMA network has agreed to extend the deadline to complete step 1 to 1 October 2020. This follows reports of the challenges encountered in meeting the original deadline of 26 March 2020, and the impact of the severe restrictions in place to combat the COVID-19 pandemic.

Other regulatory agencies have also issued statements or precautions on this issue such as the FDA or Health Canada.

Practical guide and associated forms

For national, decentralised or mutual recognition procedures, the CMDH published a practical guide for MAHs in December 19 to facilitate their assessment and to communicate easily with the authorities. A question/answer document was also published to answer the most frequently asked questions.

It should be noted that the possibility of contamination by packaging interaction was part of the additions of this new information document completed.

All competent authorities have implemented an email address in nitrosamines@AGENCY.COUNTRY code to facilitate communication.

Some intermediate limits for nitrosamine levels in finished products have been proposed in the practical guide (see table below), but the applicable limits are still under discussion. These rates must be expressed as ng or ppm.

Nitrosamines	Intermediate Limits
NDMA, NMBA	96 ng/day
NDEA, NDBA, DIPNA, EIPNA	26,5ng/day

Forms have been put in place by the EMA and by each competent authority.
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

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