Research: Nitrosamines in Active Substance and finished medicinal products

Nitrosamines can have carcinogenic and mutagenic properties and were detected first in 2018 with higher concentrations in “sartan”-containing medicinal products. In subsequent developments, nitrosamine impurities were identified in further active substances and medicinal products. Consequently, the EMA and national competent authorities obliged marketing authorization holders of all human medicines to review their products for possible nitrosamine contaminations. All market authorization holders **for all active pharmaceutical substances and finished medicinal products** have to report the outcome of the risk assessment **for chemical medicines by 31 March 2021** and **for biological medicines by 1 July 2021.**

1. Risk analysis

In July 2020, the EMA published a 90-page assessment report on nitrosamine impurities in human medicinal products including risk analysis requirements. The risk of nitrosamine contamination has to be assessed based on the process, including the synthesis of the active ingredient, the manufacturing and packaging of the finished drug and its subsequent and interim storage, and the materials and conditions used in the process. For a comprehensive assessment, however, this requires both observations of the process itself and further information provided by the suppliers of reagents, excipients, active ingredients and packaging materials. The risk analysis needs to address both questions, whether nitrosamines may already be contained in the raw materials as well as information on impurities and precursors that can subsequently lead to the formation of nitrosamines. A possible source are nitrite impurities in excipients that could lead to the formation of nitrosamines.

Based on this data and chemical expertise on possible degradation and formation processes, it has to be assessed whether there is a risk of contamination with nitrosamines or not and which nitrosamines may be present. Especially the latter information is required to establish a suitable analytical method.

2. Current limits

At present, the limits of individual nitrosamine contaminations are still defined on a risk basis. For example for NDMA and NDEA a limit of less than 0.03 ppm (**no longer quantifiable**) will apply after the two-year transitional period from 01 April 2021. Further current limits for nitrosamines are defined by the EMA. As carcinogenic impurities are to be minimized if possible, increasingly stringent requirements concerning nitrosamine or precursor contaminations can be expected in the coming years.

3. State of the art of analytical technology

Nitrosamines are usually not determined as a sum parameter. Only individual nitrosamines can be quantified or checked against a limit value. Therefore, a risk analysis prior to analytics is required to predefine which nitrosamines could be present in the product. The analyses often consist of HPLC-MS or GC-MS and are, due to limited availability of reference substances, only suitable for the analysis of individual nitrosamines. Screening is very expensive, since for each nitrosamine a single standard is needed. A monograph (Ph. Eur. 2.4.36 "*N*-Nitrosamines in active substances") is currently in preparation. A draft has already been published in Pharmeuropa 32.2. This describes two GC-MS and one HPLC-MS method for the determination of seven nitrosamines in total. First contract analysis laboratories already offer the quantification of single nitrosamines.

4. Further reading and sources:

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities.
https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf