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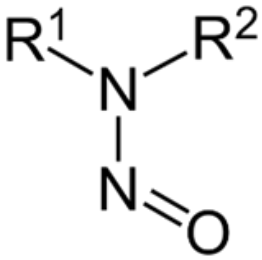
Nitrosamine Impurities

Nitrosamine impurities became a focus for authorities in July 2018, when they announced a recall of angiotensin II receptor blocker (ARB) medicines, known as "sartans", due to the presence of an impurity, N-nitrosodimethylamine (NDMA). Valsartan and Losartan are the worst affected and several lots of these products have been recalled.[1]

Since then, more cases of drug substance and drug product batches contaminated with Nitrosamines came to be known.
In the US, there was a recall of drug products containing the drug substance ranitidine, a histamine H2 receptor blocker. These products are also currently being reviewed by the EMA, which has urged manufacturers to test drug products containing pioglitazone, an insulin sensitizer, as well as Metformine, found in diabetes medicines.
Recalls and further reviews are being carried out by several national authorities in Canada, Switzerland and Singapore

What are nitrosamines?



Nitrosamines are a family of carcinogens impurities which are formed by the reaction of secondary amines, amides, carbamates, derivatives of urea with nitrite or other nitrogenous agents with the nitrogen in the +3 state.
Nitrosamines are classified by the ICH M7(R1) Guideline as Class 1 impurities, "**known mutagenic carcinogens**," based on both rodent carcinogenicity and mutagenicity data.[2] They are categorized by the International Agency for Cancer Research (IARC) as 2A – Probable Carcinogens [3] based on data on a number of species studied.

It is known that nitrosamines found in Sartans can form during the production of Sartans that contain a specific ring structure known as tetrazole ring under certain conditions and when certain solvents, reagents

and other raw materials are used. In addition, it is possible for impurities to become present in some products due to contaminated equipment or reagents used in the manufacturing process.

What are the currently identified root causes for presence of nitrosamines for all products?

- Use of sodium nitrite ($NaNO_2$), or other nitrosating agents.
- Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts).
- Use of recovered materials (e.g. solvents, reagents and catalysts).
- Use of contaminated starting materials and intermediates by nitrosamine.
- Cross-contaminations due to different processes run on the same line.
- Degradation processes of starting materials, intermediates and drug substances. This could potentially occur also during finished product formulation or storage.
- Use of certain packaging materials.

New Testing Requirements

It is imperative that manufacturers understand the possible source of nitrosamine formation in their manufacturing process and add proper controls to reduce the possibility of formation of these carcinogenic impurities.
The pharmaceutical industry needs to look beyond the obvious and understand that the quality of the reagents and solvents, even those used relatively upstream in the manufacturing process, are critical for assuring the quality of the final drug substance.

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Since September 2019, all EU Marketing Authorization Holders (MAH) of medicines for human use are facing a new requirement to review their drug products for the possible presence of nitrosamines.
The European Medicines Agency (EMA) has sent a notice[4], to marketing authorization holders to review their human medicinal drug products containing chemically synthesized APIs on the potential risk of containing nitrosamines impurities **before April 2020**, including:

- **Step 1: Risk Evaluation**
  MAHs should perform risk evaluation of their medicinal products containing chemically synthesized APIs.
- **Step 2: Confirmatory Testing**
  Confirmatory testing should be carried out using appropriately validated and sensitive methods in MAHs should inform the Competent Authorities immediately if tests confirm the presence of a nitrosamine impurity irrespective of the amount detected.
- **Step 3: Changes to the Marketing Authorization**
  MAHs should apply for a variation in a timely manner to introduce any required changes, such as an amendment of the manufacturing process or changes to product specifications.

Other authorities started an equivalent approach, e.g. Health Canada, TGA (Australia), Swissmedic.

New Limits

Regulatory agencies are setting interim limits based upon Maximum Daily Intake.
Limits will be lowered in the future with the expectation that manufactures will ensure quasi complete absence of nitrosamines impurities. For example, with the sartan there is a transition period of two years (ends 04/2021) after that the limits should then be 0,03 ppm.

Why Choose Eurofins BioPharma Product Testing?

The analysis of nitrosamines can be challenging. Ultra-low levels of these impurities must be quantified in diverse and complex matrices. The developed methods then need to be validated to conform to GMP requirements.

- Eurofins is equipped with all the required equipment to meet these limits, including, LC MSMS and GC MSMS systems.
- Eurofins has experience with nitrosamine testing, including validating methods for sartans and ranitidine, as well as screening testing methods.
- Eurofins can provide both toxicological and analytical support for risk evaluation.
- Eurofins is a network of laboratories with vast capacity at multiple sites globally.
- All Eurofins BPT laboratories performs this testing under GMP requirements.

Our laboratories specialize in method development and validation for highly sensitive and specific method to assess carcinogenic or genotoxic impurities in drug products. We regularly face the challenges of low detection levels, difficult matrices and identification of unknown impurities during the pharmaceutical method development process

In addition to experienced pharmaceutical impurity analysis, we can support MAH with toxicological risk assessments. Our experienced toxicologists conduct risk assessments to address extractables & leachables, elemental impurities (ICH Q3D).

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Our experience:

Eurofins BioPharma Product Testing has already assisted many clients to meet this timely new requirement with GMP-compliant services, including:

Sartans

- Validating methods for sartan DS, with lowest possible LOD/LOQ.

Ranitidine/Metformin

- Validating methods for DS and DP, with LOD/LOQ < Interim limit
- Limit test for product screening

Non Sartans Drug: (human medicinal products containing chemically synthesized active pharmaceutical ingredients)

- Risk evaluation and expert support services (chemistry and toxicology)
- Screening methods to support risk evaluation (on each matrix DS and/or DP)
- Confirmatory testing methods carried out using appropriately validated and sensitive methods.

References:

[1].U.S. Food and Drug Administration; "FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan";; https://www.fda.gov/drugs/drugsafety/ucm613916.htm; updated as of November 13, 2019.

[2] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; "ICH Harmonised Guideline - Assessment And Control Of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7(R1)"; March 31, 2017, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_2017_0331.pdf

[3] International Agency for Research on Cancer; "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines"; Volume 89, 2007, https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-32/

[4] Information on nitrosamines for marketing authorization holders (EMA/189634/2019) Questions and answers on "Information on nitrosamines for marketing authorization holders" (EMA/CHMP/428592/2019 Rev. 1)