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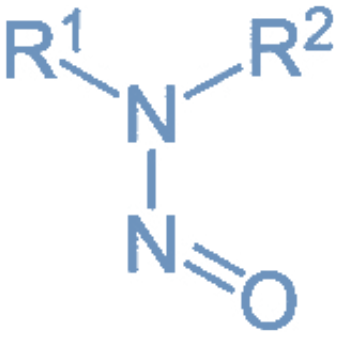
Nitrosamine Impurities



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. Losartan, Irbesartan, Valsartan, Metformin, Ranitinide, Rifampin/Rifapentine and Varenicline. Recalls and further reviews are being carried out by several national authorities in Canada, Switzerland and Singapore.

Recently, authorities have received additional reports of certain types of nitrosamine impurities that formed in several drug products. These nitrosamine drug substance related impurities (NDSRIs) are a class of nitrosamines sharing structural similarity to the API.

NDSRIs can be generated during manufacturing or during the shelf-life storage period of the drug product. In some cases, the root cause of NDSRI formation has been attributed to nitrite impurities present in excipients at parts-per-million amounts. Nitrite impurities have been observed in a range of commonly used excipients (as well as water) and may lead to the formation of NDSRIs in certain drug products.

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 part of cohort of concern of ICH M7(R1) Guideline, grouping mutagens that can display extremely high carcinogenic potency, based on both rodent carcinogenicity and mutagenicity data.[2] They are categorised by the International Agency for Cancer Research (IARC) as class 2A [3] or class 2B - Possibly carcinogenic to humans based on data available for each nitrosamine 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.

Root Causes for Presence of Nitrosamines

- Use of nitrite salts and esters (e.g.: NaNO2) or other nitrosating agents, in the presence of secondary or tertiary amines
- 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
- Oxidation of hydrazines, hydrazides, and hydrazones
- Cross-contaminations due to different processes run on the same line
- Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors, in the presence of secondary or tertiary amines
- 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, e.g. containing nitrocellulose
- Use of disinfected water in the presence of secondary or tertiary amines

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.

Since September 2019, all EU Marketing Authorisation Holders (MAH) of medicines for human use are facing a new requirement to review their drug products for the possible presence of nitrosamines.

Today, MAHs/Applicants of all human medicinal products should ensure that the presence of nitrosamines is controlled and kept as low as possible, irrespective of marketing status or the type of product (e.g. generics and over the counter (OTC) products)

This has now been extended to cover also all biological medicinal products for human use.

The call for review consists of 3 steps:

Step 1: Risk Evaluation

Conduct a risk evaluation to identify API and finished products (FP) at risk of N-nitrosamine formation or (cross-) contamination.

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.

Step 3: Changes to the Marketing Authorisation

MAHs should introduce changes to their API and/or FP (e.g. manufacturing process, controls and specification, product formulation, raw materials and packaging), through the timely submission of appropriate variation(s).

In principle, MAHs are expected to improve the manufacturing processes of their FPs, even when only very low levels (< 10% of AI) of nitrosamines are detected.
Deadline : 1 October 2023

Additional Testing provided by Eurofins (with GMP validated method and with QP release)

- QC release: When nitrosamine(s) is (are) identified, analysis should be introduced in the specifications of the FP
- In-process control (IPC) analysis for new manufacturing process validation
- Stabilities studies to support variation

Focus on Precursors

We at Eurofins, are now focusing on finding precursors of Nitrosamines: we developped methods to detect these precursors at very low levels (ppb levels)

Implemented Methods to Determine:

- Nitrites by derivatisation and detection by HPLC-UV – in different excipients and Purified water
- Nitrates and Nitrites by Ionic Chromatograpy - in different excipients and Purified water
- Dimethylamine (DMA) and Trimethylamine (TMA) by SPME-GC-MSMS – in Drug Product and Drug Substance

Why Choose Eurofins BioPharma Product Testing?

Our laboratories specialise 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).

The analysis of nitrosamines can be challenging. Ultra-low levels of these impurities must be quantified in diverse and complex matrices.

- Eurofins is equipped with all the required equipment to meet these limits, including, LC MSMS, GC MSMS, UPLC-HRMS and SPME-HS-GC-MSMS systems.
- Eurofins has experience with nitrosamine testing, including validating methods for Sartans, Ranitidine, Metformin & Ketamin, 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 perform this testing under GMP requirements.

Our Experience

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

All Drug Substance & Drug Products

- 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. Hundreds of screenings done on DS and DP

Sartans

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

Ranitidine/Metformin

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

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. CHMP ASSESSMENT REPORT OF ARTICLE 5 (3) REFERRAL ON NITROSAMINES IMPURITIES IN HUMAN MEDICINAL PRODUCTS AND RELATED GUIDANCE 25 June 2020 (EMA/369136/2020) https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

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