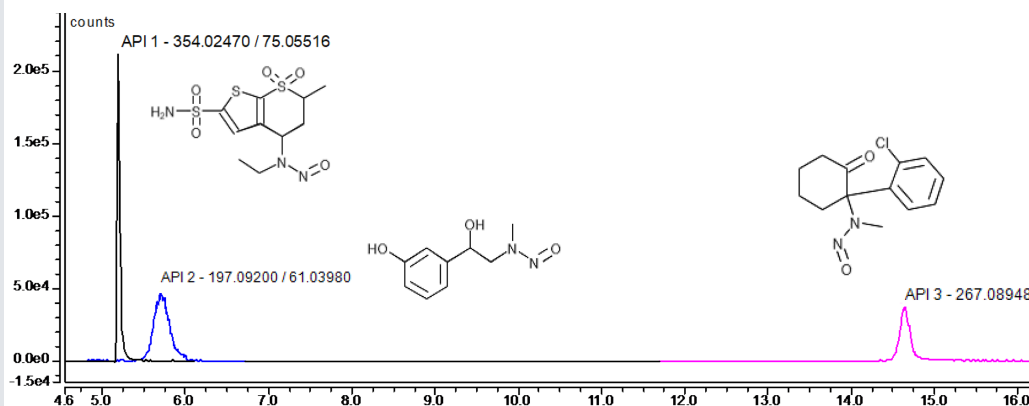




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GMP Testing at the Highest Level.

**PHARMACEUTICAL PRODUCT SAFETY AND RISK MANAGEMENT
REGARDING N-NITROSAMINE CONTAMINATION**

**N-NITROSAMINES – QUALIFICATION AND QUANTIFICATION OF
RESIDUES**

GENERAL INFO

N-nitrosamines are a class of organic compounds characterized by the chemical structure $R_2N-N=O$, with R typically representing an alkyl group.¹ They contain a nitroso group (NO^+) bonded to a deprotonated amine. Under standard conditions, N-nitrosamines are typically found in a liquid or solid state. Due to their hydrophilic $N-N=O$ grouping, they are soluble in water and other polar solvents.² N-nitrosamines originate from nitrosating agents such as nitrite and nitrosatable amines, which are prevalent in various human environments. They can be found as contaminants in mostly cured foods, tobacco, cosmetics, latex products, and pharmaceuticals. Most N-nitrosamines are considered genotoxic and carcinogenic in animal studies.³

REGULATION

EU regulators first became aware of nitrosamines in medicines in mid-2018 when nitrosamine impurities, including N-nitrosodimethylamine (NDMA), were detected in blood pressure medicines known as “sartans”. There is a very low risk that nitrosamine impurities at the levels found in medicines could cause cancer in humans.⁴ Nevertheless, the European Medicines Agency (EMA) finalised a review under Article 5(3) of Regulation (EC) No 726/2004 in June 2020 to provide guidance to marketing authorisation holders on how to avoid the presence of nitrosamine impurities in human medicines. Thus, Companies are required to have appropriate control strategies to prevent or limit the presence of these impurities and, where necessary, to improve their manufacturing processes.⁵

With Appendix 1 (EMA/72902/2024 /Rev. 3, from 15.02.2024) to Questions and answers for marketing authorisation holders/applicants on the Committee for Medicinal Products for Human Use (CHMP) Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products, Acceptable intakes (AIs) in [ng/day] for N-nitrosamines were established by the Non-clinical Working Party (NcWP) and, where applicable, determined using the Carcinogenic Potency Categorization Approach (CPCA). These limits are applicable only if a finished product (FP) contains a single N-nitrosamine. The source refers to potential presence of nitrosamine impurities with structures derived from active substances or their related impurities. This does not mean that the impurity will be found in all products or pharmaceutical forms containing the named Active Pharmaceutical Ingredient (API).⁶

ROOT-CAUSES

The “Valsartan scandal” and its repercussions underscore the necessity of scrutinizing N-nitrosamine contamination in pharmaceuticals. Predicting or tracing their formation is not always simple, necessitating comprehensive knowledge of chemistry and the processes involved. N-nitrosamines pose a problem even in trace quantities, requiring instrumental analytics capable of detecting them in parts per billion [ppb]. Retrospective examination of N-nitrosamine contamination in pharmaceuticals is often impractical. A notable structural feature of N-nitrosamines is the tetrazole ring. The ring itself isn't problematic, but its synthesis process can be. Traditional methods involving tributyltin compounds are highly toxic. Alternatives using NaN_3 and $ZnCl_2$ with Dimethylformamide (DMF) as a solvent have been developed, although DMF can degrade into dimethylamine, reacting with $NaNO_2$ to form NDMA, highlighting the challenge of unintentional contamination.

The occurrence of other tetrazole-containing drugs like Irbesartan, Candesartan, Olmesartan, and Losartan, as well as other human medicinal products such as Pioglitazone, Ranitidine, and Metformin, raises concerns about potential N-nitrosamine contamination beyond Valsartan.

ANALYSIS

Testing for N-nitrosamines has been a hot topic in the pharmaceutical industry since 2018 when these potential carcinogens were found first in sartans and later on in ranitidine and some slow-release metformins. Manufacturing requirements have now become more stringent and demands on chromatography and mass spectrometry methods that meet regulatory requirements are increasing. Detection and quantification of these trace N-nitrosamines in APIs and drug products can be challenging and necessitate the use of advanced and sensitive tools to meet regulatory requirements.

GBA Pharma Labs is specialized in the analysis of API-related nitrosamines in complex matrices. Matrix-specific method development at [ppb] level often requires specific mass spectrometry (MS) techniques like selected reaction monitoring (SRM) mode to reduce matrix effects. To obtain the best possible signal intensity, GBA Pharma Labs has electrospray ionization (ESI) as well as chemical ionization at atmospheric pressure (APCI) probes at its disposal. Furthermore, GBA Pharma Labs offers targeted screening on common small N-nitrosamines as well as full scan measurements of samples including MS/MS experiments followed by data processing using CDS and database queries allowing untargeted screening for other N-nitrosamines present in the samples.

TREND

The Nitrosamine Implementation Oversight Group (NIOG) oversees the harmonised implementation of the CHMP's Article 5(3) opinion on nitrosamines. It was set up by the European medicines regulatory network under the February 2021 implementation plan, and reports on progress to EMA's Management Board and the Heads of Medicines Agencies (HMA). The group contains representatives from the CHMP, Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), EMA working parties, EDQM, and EMA staff. It also acts as the main interface for the pharmaceutical industry stakeholders to discuss regulatory and scientific developments on nitrosamines with EMA and the European medicines regulatory network.

Marketing authorisation holders should review their manufacturing processes for all products containing chemically synthesised or biological active substances to identify and, if necessary, mitigate the risk of presence of nitrosamine impurities. The call for review was extended to biological active substances in July 2020, as an outcome of CHMP's Article 5(3) opinion. This complements the review of chemically synthesised active substances, which has been ongoing since September 2019.

OUTLOOK

To allow marketing authorisation holders enough time to implement the Article 5(3) opinion, the European medicines regulatory network agreed new deadlines. 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.

BENEFITS

The GBA Group has a dedicated team, which performs N-nitrosamine studies, with a high level of expertise in untargeted screening in a GMP laboratory. Two Orbitrap Exploris instruments, connected to Chromeleon 7.3, are available to ensure short turnaround times.

We carry out these analyses together with additional services upon request as a complete package for you. That way, we can help you ensure the safety of your products. At the same time, by using our services, you can minimize risk throughout the entire supply chain and increase consumer trust in your products.

Take control of your product safety today-partner with us for reliable results.

ABOUT US

GBA Group is an international life science service company with broad range of analytical, logistical and specialist services in the fields of pharmaceuticals, medical products, cosmetics, chemicals, food, drinking water and the environmental sustainability.

The range of services offered by the GBA Group includes laboratory analytics, data management, special logistical services for clinical trials, as well as consulting services for private companies and public institutions in connection with their activities in the fields of research, product development, market development, and consumer protection.

Through its work, the GBA Group makes a sustainable contribution to public health, the environment and society as a whole.

The GBA Group operates sites in Austria, Belgium, Finland, France, Germany, India, Poland, Spain, Sweden, and the United States.

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