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Review Article **Pharmaceutical Analysis**

Emerging Perspectives on Nitrosamine Impurities in Pharmaceuticals: Risks, Regulatory Frame Works, and Mitigation Strategies

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Abstract

N-nitrosamines are carcinogenic impurities most commonly found in groundwater, treated water, foods, beverages and consumer products. The recent discovery of N-nitrosamines in pharmaceutical products and subsequent recalls pose a significant health risk to patients. Initial investigation by the regulatory agency identified Active Pharmaceutical Ingredients (API) as a source of contamination. However, N-nitrosamine formation during API synthesis is a consequence of numerous factors like chemistry selection for synthesis, contaminated solvents and water. Furthermore, apart from API, N-nitrosamines have also been found to embed in the final product due to degradation during formulation processing or storage through contaminated excipients and printing inks. The landscape of N-nitrosamine contamination of pharmaceutical products is very complex and needs a comprehensive compilation of sources responsible for N-nitrosamine contamination of pharmaceutical products. Therefore, this review aims to extensively compile all the reported and plausible sources of nitrosamine impurities in pharmaceutical products. The topics like risk assessment and quantitative strategies to estimate nitrosamines in pharmaceutical products are out of the scope of this review.

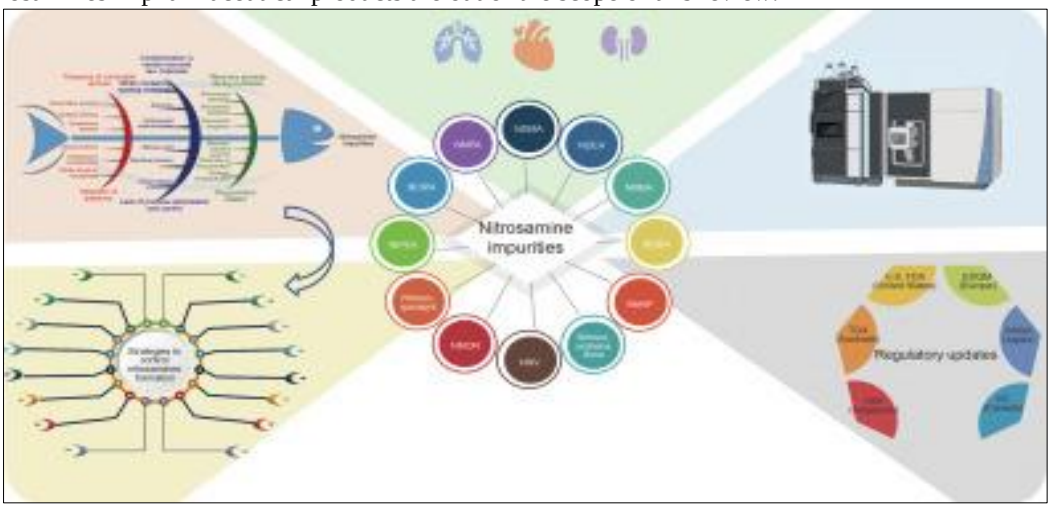

Figure 1: Graphical abstract of Nitrosamine impurities

Keywords: Nitrosamine Impurities, Carcinogenicity, Limits, Regulations, Global Risk.

INTRODUCTION

Nitrosamines are chemicals commonly found in water and foods like cured meats, grilled foods, dairy products and vegetables. While everyone is exposed to some level of nitrosamines, their presence in medications -even in trace amounts – poses significant safety risks for patients, as nitrosamine impurities are considered probable human carcinogens known as the "cohort of concern" in the ICH M7 guidelines. This group includes

aflatoxin -like compounds, N-nitroso compounds (such as nitrosamines), and alkyl-azoxy compounds.

Pharmaceutical impurities refer to unwanted substances present in active pharmaceutical ingredients (APIs) or drug formulations, often as byproducts of synthesis. Among these, nitrosamines impurities have gained attention due to their potential health risks. Many commonly used excipients contain nitrite impurities at trace levels (ppm), which can contribute to the formation of nitrosamines in drug substances during manufacturing and storage. Pharmaceutical companies are actively detecting and addressing nitrosamine contamination, as these compounds are known carcinogens [1].

The primary factors contributing to nitrosamine formation in pharmaceuticals include contamination from amines, which can lead to secondary, tertiary and quaternary nitrosamines; the use of raw materials from various suppliers; recycled materials; certain high temperatures manufacturing processes; and inadequate process control.

The detection of nitrosamine impurities in several medicinal products has raised safety concerns. While nitrosamines also exist in food and water, their presence in pharmaceuticals is considered unacceptable. This risk assessment aims to determine the potential sources of nitrosamine formation and outline strategies to minimize their presence in APIs and drug formulations.

Following the discovery of nitrosamines in several drug products, the FDA and other international regulatory agencies conducted extensive investigations into these contaminants. The FDA continues to study nitrosamine impurities in medications and in collaboration with global regulatory bodies, has set internationally recognized daily intake limits. Nitrosamine levels below these limits are considered acceptable. If a drug product exceeds the permissible daily intake, the FDA recommends a recall.

Some pharmaceutical companies have voluntarily withdrawn affected medications, while others have recalled products due to detected nitrosamine levels exceeding regulatory thresholds. several drugs, including metformin, valsartan, losartan, and ranitidine (Zantac), have been pulled from the market or recalled due to nitrosamine contamination surpassing the allowable limits [2].

Classification of Nitrosamine Impurities

Nitrosamine impurities can be classified based on their chemical structure and origin.

A. Small – Molecule Nitrosamines:

These are simple nitrosamine compounds that are commonly found as contaminants in pharmaceuticals, food, and the environment.

Examples:

- N-Nnitrosodimethylamine (NDMA) – Found in contaminated ranitidine and Sartans (e.g., valsartan).
- N-Nnitrosodimethylamine (NDEA) – Found in some contaminated sartan drugs.
- N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) - Detected in losartan.
- N-Nitrosopiperdine (NPIP) - Found in certain contaminated drugs.
- N-Nitrosopyrrolidine (NPYR) - Present in some food and tobacco products

B. Nitrosamine Drug Substance – Related impurities (NDSRIs)

These impurities are structurally related to the active pharmaceutical ingredient (API) and can form during drug synthesis, storage, or degradation.

Examples:

- N-Nitroso-atenolol - Related to atenolol (a beta – blocker).
- N-Nitroso-propranolol - Detected in quinapril (an antihypertensive).
- N-Nitroso-metformin – Found in metformin - based diabetes medications.

C. Nitrosamines from Excipients or Contaminants

These nitrosamines are not directly related to the API but originate from excipients, solvents, or packaging materials.

Risks

Residual impurities can arise from the synthesis of both active pharmaceutical ingredients (APIs) and excipients. Nitrosamine precursors may be present in the water used during drug product manufacturing. Potable water at the initial stages of purification could contain low levels of chloramine, nitrites, or nitrates additional precautions are necessary if the water system undergoes chlorination for sanitation. Nitrosamines or their precursors may also be introduced through the manufacturing process. Furthermore, they have the potential to leach into the drug product from primary packaging materials. For example, nitrocellulose in the printing ink of press – through packaging (PTP) aluminum foil is a known source of contamination [3]. The WHO and other regulatory authorities require pharmaceutical manufacturers to conduct a risk assessment to determine the potential presence of nitrosamines. This process involves three key steps:

1. **Risk Evaluation**: Identify whether Active Pharmaceutical Ingredients (APIs) or finished products are at risk of nitrosamine contamination. The WHO highlights additional source such as recycled solvents, reused catalysts and cross contamination from different manufacturing processes due to insufficient monitoring and control.

2. **Confirmatory Testing**: If a risk is detected, conduct analytical testing to confirm or rule out the presence of nitrosamines. Any findings must be promptly reported to the relevant regulatory authorities.
3. **Risk Mitigation**: If nitrosamines are confirmed manufacturers must implement appropriate control measures and submit necessary changes to the regulatory body.

The WHO guidance provides further considerations, including:

- The daily dosage of the medication,
- The duration of use, and.
- The concentration of nitrosamine impurities in the final product like temperature and storage duration affecting product stability [4].

Manufacturing conditions also play a role as some chemicals that remain stable under certain settings may degrade when exposed to different reactions, such as high temperatures during production, which can increase nitrosamine formation risk.

To ensure comprehensive risk assessment, manufacturers should evaluate

- Facility conditions,
- Equipment design and usage
- Material details
- Synthesis routes,
- Production processes (e.g., granulation and drying, which may elevate contamination risks),
- Chemical interactions between excipients, solvents
- Synthesis routes,
- Production processes (e.g., granulation and drying, which may elevate contamination risks),
- Chemical interactions between excipients, solvents (especially amide solvents), APIs, packaging components
- The intended product use and route of administration.

Nitrosamines have long recognized as carcinogenic, yet their potential presence in pharmaceutical products was previously overlooked due to limited understanding of their formation during manufacturing. Many pharmaceutical ingredients contain nitrosamines precursors, raising concerns about contamination. Risk assessments indicate that nitrosamines or their precursors may be found in any component of a finished drug formulation. To mitigate this risk, ingredients with a high likelihood of forming nitrosamines should be avoided. If no suitable alternatives exist, measures must be implemented to ensure nitrosamine levels remain below acceptable intake limits. A thorough investigation of excipient manufacturing processes is necessary to identify components that may contribute to nitrosamine formation manufacturers should be beyond pharmacopeial standards for active pharmaceutical ingredients (APIs) and excipients by adopting additional control strategies. Incorporating nitro sating inhibitors, such as vitamin c, in formulations can help prevent nitrosamine formation. This review aims to highlight the key risk factors associated with nitrosamine contamination in pharmaceutical dosage forms and propose effective control strategies to maintain their levels within acceptable limits [5].

Regulatory Updates on Nitrosamine Impurities

In mid-2018, the initial detection of nitrosamines began with NDMA in sartan APIs, which prompted the recall of batches from the markets. International regulatory authorities, such as U.S. FDA, EMA, European Directorate for the Quality of Medicines & Healthcare (EDQM), Health Sciences Authority (HAS, Singapore), Pharmaceuticals and Medical Devices Agency (PMDA, Japan), Therapeutic Goods Administration (TGA, Australia), and Health Canada collaborated to alert API manufacturers. They put forth several regulations, recommendations, and guidance's to review their manufacturing process and to initiate risk assessments regarding nitrosamines formation. The primary focus was on evaluating raw materials, intermediates, solvents, and reagents used in API manufacturing for the presence of vulnerable amines. In 2018, valsartan products were recalled from the market. In 2019, ranitidine, nizatidine, and metformin extended - release products were found to contain nitrosamines levels in ranitidine products was linked to storage conditions. Subsequently attention shifted onto examining key factors that might cause the formation of nitrosamines in drug products [6].

Contamination in drug formulations, ultimately safeguarding public health. Regulatory bodies have intended the manufactures to perform root cause analysis to determine how nitrosamines are incorporated into drugs and drug products. The U.S.FDA put forth a three – step mitigation strategy to control and prevent nitrosamines formation in APIs and drug products. Step 1, manufactures should prioritize risk assessments for their API and drug product portfolios, and they must document and report their findings to regulatory bodies by march 31,2021 (U.S.FDA), EMA gave a timeline of march 31, 2021(chemical medicines), and till July 1,2021 (biological medicines). Step 2, confirmatory testing using sensitive analytical techniques to quantify nitrosamines in necessary until October 1, 2023 (U.S.FDA), September 26, 2022for chemical medicines, and July 1, 2023 for biological medicines by EMA. Step 3, manufacturers must report the identified root causes of nitrosamine formation and implement of changes to their processes or approaches to eliminate nitrosamine formation [6].

In 2020, Lhasa Limited (UK) initiated the creation of database on nitrite levels in excipients used in drug product manufacturing. This initiative involved representation from industry experts and researchers, as nitrite levels in excipients make drug products more prone to nitrosamine impurities. Additionally, in 2020, the Committee for Medicinal Products for Human Use (CHMP), constituted by EMA, conducted scientific review of the entire situation and submitted its report in this regard. In 2021, the European medicines regulatory network established an intellectual group known as "Nitrosamine Implementation Oversight Group "to discuss development and the current scenario regarding the emergence of nitrosamine impurities. EMA asked marketing authorization holders of sartan, rifampicin, ranitidine, metformin -containing, and varenicline medicines to release their products into the market only after stringent testing [7].

The U.S. FDA primarily recommended following steps 2 and 3 of the three-step mitigation strategies in response to the emergence of NDSRI issues. They also called upon all concerned stakeholders to review, discuss, provide information, and update their suggestions and approaches for regulatory bodies to effectively address this problem. The recent findings on nitrosamines in several products and the subsequent recalls just the tip of the iceberg. There is a looming possibility of a higher incidence and risk associated with numerous products already in the market in the coming days. To address this potential crisis, a united task force should be formed in collaboration with all regulatory bodies with an aim of devising a strategy a tackle the upcoming crisis.

The presence of nitrosamine impurities in pharmaceutical products, such as sartans and ranitidine, has led to significant regulatory responses due to the potential health risks posed by compounds like NDMA (N-Nitroso dimethylamine) and NDEA (N-Nnitrosodimethylamine), which are considered probable carcinogens .Regulatory bodies like the European Medicines Agency (EMA),U.S.Food and Drug Administration (FDA),and others worldwide have taken steps to address this issue [7].

European Union (EU) Regulations:

- **Article 31 Evaluation:** The EU carried out an article 31 evaluation for sartans, especially those with a tetrazole ring**,** which are more likely to contain nitrosamine impurities. Manufactures were instructed to review and adjust their production processes to minimize nitrosamine levels, with a two-year period given to implement these changes**.**
- **Interim Limits:** During the transition period, the EU set temporary limits on nitrosamine contamination in sartan medications, prohibiting batches that contain both NDMA and NDEA or exceed the specified limits for any single impurity.
- **Pharmacopeia Updates:** The European Pharmacopeia is being updated to include nitrosamine testing for sartan drugs, and the general monographs for active pharmaceutical ingredients (APIs) are also being revised to include the required testing procedure [8].

U.S.FDA Response:

- **Voluntary Recalls**: The FDA has implemented voluntary recalls of medications found to contain excessive nitrosamine levels. For example, when NDMA and NDEA were detected in Valsartan, the FDA set interim acceptable limits for these impurities and requires manufactures to test their products for nitrosamine impurities in pharmaceutical ingredients.
- **Public Health Protection:** The FDA stressed that the risk of continuing treatment with low nitrosamine levels is generally lower than the potential dangers of abruptly discontinuing medications, such as the risk of a stroke.
- **Ongoing Monitoring:** The FDA continues to collaborate with manufacturers to ensure medication safety, with over 226 recalls reported in two years. The actual number of recalls may be higher [8].

Other Regulatory Agencies:

- **Australia (TGA):** The Therapeutic Goods Administration (TGA) in Australia has required manufactures to assess the risk of nitrosamine formation in sartan drug and to conduct batch testing. Products exceeding the acceptable nitrosamine levels are subject to recalls or restrictions**.**
- **Canada Health Canada:** Health Canada has also required manufacturers to review their processes and test for nitrosamine contamination, recalling or restricting products that exceed permissible limits.
- **Japan (PMDA):** Japan's Pharmaceuticals and Medical Devices Agency PMDA has taken similar steps to address nitrosamine contamination in sartan drugs and has worked with international regulatory bodies to ensure the safety of these products [8].

CONCLUSION

Nitrosamine impurities in pharmaceuticals pose a significant health risk due to their carcinogenic potential. While these compounds are commonly found in food and water, their presence in medications in unacceptable, necessitating stringent regulatory oversight. The primary sources of nitrosamine contamination include raw materials, excipients, manufacturing processes, and packaging components. To address these risks, pharmaceutical companies must conduct thorough risk assessments, implement robust quality control measures and adopt mitigation strategies such as alternative synthesis routes, improved process monitoring and the use of nitro sating inhibitors.

Regulatory agencies like the FDA, EMEA, WHO have established strict guidelines for permissible nitrosamine levels, requiring manufacturers to ensure compliance through routine testing and reporting. The voluntary recall of several affected medications highlights the industry's commitment to patient safety. Moving forward, continuous research, improved analytical methods, and proactive risk management will be essential to minimizing nitrosamine contamination.

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