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Review Article

Nitrosamine Impurities in Pharmaceuticals: Regulatory Landscape and Challenges

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ABSTRACT

Nitrosamines have drawn considerable attention due to their recognized health risks, notably their association with carcinogenic effects. Ongoing research is dedicated to advancing our understanding of nitrosamines, focusing on their formation mechanisms, detection methods, and potential strategies for mitigation. The current review centers on the factors and origins of nitrosamine generation, exploring regulatory dimensions governing their control, assessing the challenges inherent in nitrosamine regulation, and delineating the prospective avenues for enhancing nitrosamine control measures in the future. Key aspects include a focus on risk assessment and mitigation, with experts stressing the importance of thorough assessments to identify potential sources of nitrosamine contamination. Mitigation strategies involve making changes in manufacturing processes, carefully selecting raw materials, and implementing robust analytical testing protocols. Communication and transparency are deemed crucial, with experts emphasizing the need for clear guidelines, regular updates, and effective communication channels to enhance understanding and compliance.

Keywords:
Pharmaceuticals; Drug, Nitrosamines;, Origin;, Regulation; Challenges; Mitigation

1. INTRODUCTION

Water and food sources, encompassing cured and grilled meats, dairy products, and vegetables, commonly contain nitrosamines, exposing individuals to varying degrees of Nitrosamines[1]. However, the potential carcinogenicity of nitrosamine impurities poses a significant risk to patients, even at low levels, making them a notable concern within the "cohort of concern" for high-potency mutagenic carcinogens outlined in ICH M7[2]. This cohort includes alkyl-azoxy compounds, N-nitroso-nitrosamines, and substances with aflatoxin-like properties. Metabolic activation is essential for the cytotoxic and carcinogenic effects of these substances[3].

The initiation of a discourse in July 2018 regarding the recall of batches of pharmaceutical products containing valsartan was prompted by concerns about potential contamination with N-nitrosodimethylamine (NDMA) in scientific literature[4]. Apprehensions escalated as it became apparent that the problem might not be limited to sartans; rather, it could potentially manifest in any active pharmaceutical ingredient (API) comprising a susceptible amine and a nitrosation source[5]. Certain nitrosamines are recognized carcinogens, posing substantial health risks. Notably, medications such as metformin HCl, ranitidine, and nizatidine were withdrawn from the market due to potential high levels of nitrosamine contamination[6].

Over 24 distinct N-nitrosamine compounds collectively contribute to the overall burden of N-nitrosamines (TNA), which is regularly monitored to evaluate human exposure to this significant category of known and suspected human carcinogens in scientific investigations[7].In response to these revelations and subsequent investigations, public health alerts and guidance documents with interim limits have been issued by organizations such as the World Health Organization (WHO), the US Food and Drug Administration (FDA), and the European Directorate for the Quality of Medicines (EDQM). Additional instructions can be found in inter-

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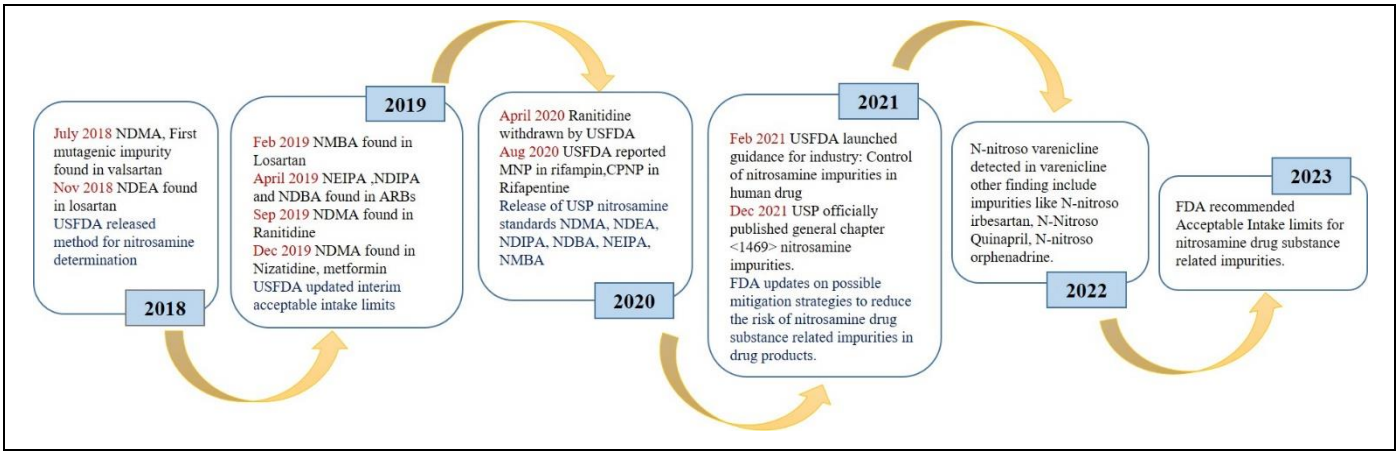


Figure 1. Timeline of emerging nitrosamine contamination

disciplinary guidelines, such as ICH M3(R2)15 and M7(R1)4, while the regulation of impurities in anti-cancer medications is governed by adherence to ICH S9[8].

2. TIMELINE OF EMERGING NITROSAMINE CONTAMINATION

In the late 1950s to 1960s, researchers initially identified nitrosamine compounds as potential carcinogens, especially after studies demonstrated their cancer-causing effects in laboratory animals. During the 1970s to 1980s, regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO) started acknowledging the potential health hazards linked with exposure to nitrosamines. From the 1980s to the 1990s, concerns about nitrosamine contamination heightened in the realm of food safety, particularly regarding processed meats and other food items preserved using nitrites and nitrates. In the 2000s, attention shifted towards pharmaceuticals as nitrosamines garnered recognition as impurities in certain drug substances, mainly attributed to specific reagents or manufacturing processes. Notable examples include ranitidine (Zantac) and valsartan[9].

In 2018, the FDA initiated voluntary recalls of various blood pressure medications, such as valsartan, due to the detection of nitrosamine impurities. Subsequently, in 2019, the FDA expanded its inquiry into nitrosamine impurities in angiotensin II receptor blockers (ARBs), prompting additional recalls and intensified scrutiny of pharmaceutical manufacturing practices. By 2020, apprehensions regarding nitrosamine contamination broadened beyond ARBs to encompass other drug categories, like metformin, a widely prescribed medication for type 2 diabetes. In 2021, global regulatory bodies such as the FDA and the European Medicines Agency (EMA) continued collaborating on guidelines and policies to mitigate nitrosamine contamination in pharmaceuticals. Concurrently, pharmaceutical enterprises adopted stricter manufacturing protocols to tackle the issue. In 2022 and beyond, sustained monitoring and regulatory endeavors persist to ensure that pharmaceuticals and various other products remain devoid of harmful levels of nitrosamine impurities. The pharmaceutical industry remains committed to refining manufacturing processes to minimize the risk of nitrosamine contamination[9].

The illustration in Figure 1 portrays the chronological progression of the emergence of nitrosamine contamination.

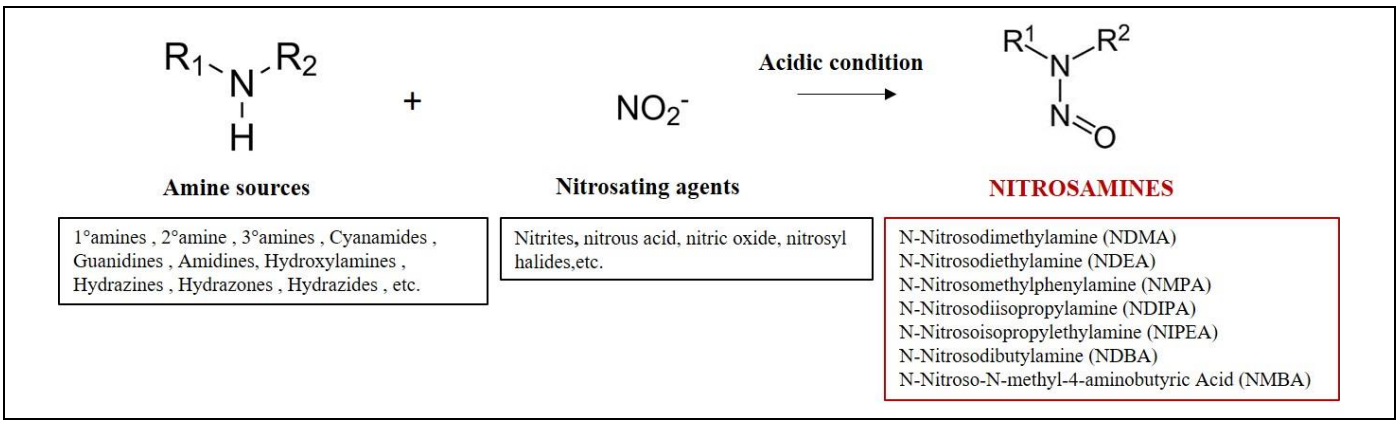


Figure 2. Generation of nitrosamines

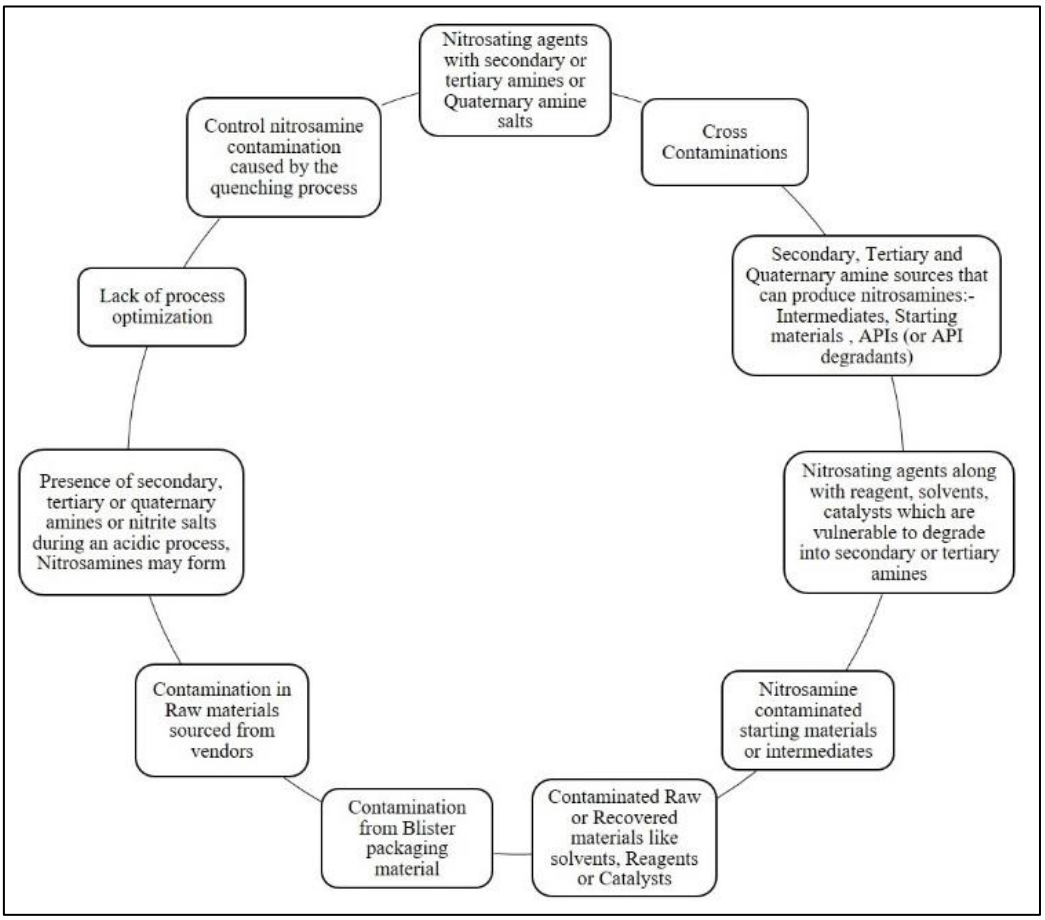


Figure 3. Factors accountable for the existence of nitrosamines

3. FORMATION OF NITROSAMINES

Nitrosamines, or more precisely N-nitrosoamines, denote molecules characterized by the presence of the nitroso functional group. Nitrosation is commonly conducted in an acidic aqueous environment using nitrous acid (HNO_2) or in organic solvents employing substances like NOCl, N_2O_3, N_2O_4, $NOBF_4$, or NO-3-nitrocarbazole[10,11]. Figure 2 illustrates the general scheme for nitrosamine formation.

In the prevalent route leading to the synthesis of N-nitrosamines, three essential elements are necessary:

1. Existence of amines.
2. Existence of a nitrosating agent.
3. Conditions favorable for the formation of N-nitrosamines[10].

Underlying factors accountable for the existence of nitrosamines in pharmaceutical products are depicted in Figure 3.

Standard nitrosation conditions entail the interaction between amines and the nitrite ion in an acidic environment.

3.1 Sources of amines

The API, intermediates, or initial materials may contain secondary or tertiary amine functional groups. These various amine species are susceptible to reaction with nitrous acid or similar nitrosating agents, resulting in the formation of nitrosamines. Moreover, secondary amines can arise from the degradation of amide solvents under specific reaction conditions, providing another route for the generation of nitrosamine impurities. Impurities in the form of secondary amines may also be present in amide solvents. Furthermore, tertiary and quaternary amines utilized as reagents in API synthesis might contain additional amine impurities[12]. Possible sources of amines are depicted in Figure 4

3.2 Sources of nitrosating agents

A nitrosating agent is a chemical entity with the capability to induce nitrosation, i.e., the process of nitrosamine formation[13].Nitrosating agent precursors and sources are diverse and include intentional use of nitrite ions in manufacturing processes like diazotization chemistry, as well as their presence as impurities in reagents such as sodium azide. Common non-medicinal ingredients like microcrystalline cellulose and magnesium stearate, nitrogen oxides, nitric acid, nitrosyl halides, alkyl nitrites, nitro compounds, and potable or purified water embodying nitrite also contribute. Nitrite is commonly found as an

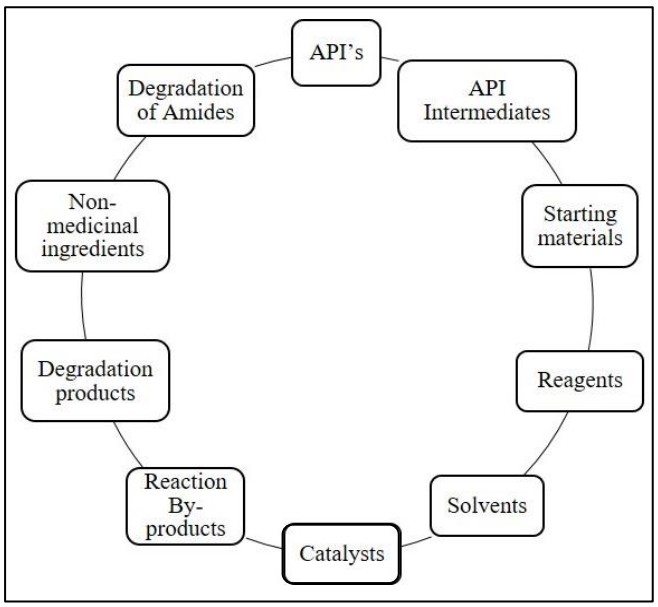


Figure 4. Sources of Amines

impurity in excipients at parts per million (ppm) concentrations, while susceptible amines, if they exist, primarily originate from the drug substance or its principal impurities[14].

Nitrosamines can result from inadequate conversion or downstream purging when initiating with or employing them as synthetic intermediaries. Other factors include reactions with amines in a high pH state, oxidation of functional groups in hydrazines, use of specific materials like nitrocellulose in container closures, recycled materials contaminated with nitrosamines, vulcanization accelerators in rubber manufacturing, contamination in multi-product facilities, ineffective nitrosamine elimination during liquid-liquid phase separations, and adoption of production processes facilitating contact between nitrosamine precursors, such as nitrogen oxides during fluid bed drying[15].

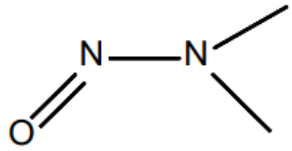
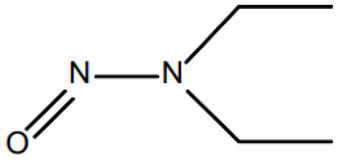
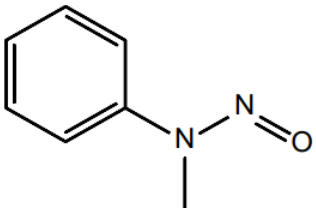
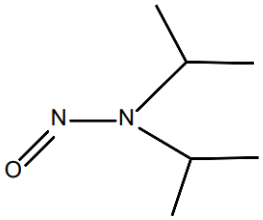
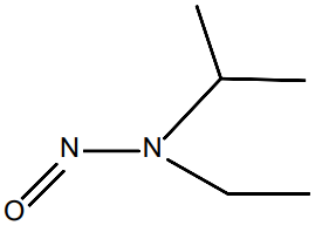
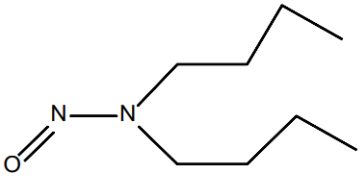
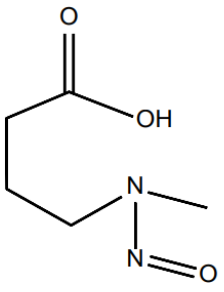
The various regulatory authorities have published the press release or notice in regards to control of potential impurities with interim control limit. Table 1 illustrates the chemical strucures of potential nitrosamine impurities.

4. SOURCES FOR GENERATION OF NITROSAMINE IMPURITIES

4.1. ARBs (angiotensin II receptor blockers)

Angiotensin II receptor blockers (ARBs) face a heightened risk of nitrosamine contamination due to specific manufacturing processes, particularly those involving tetrazole rings in the molecular structure of certain ARBs like valsartan, losartan, and irbesartan. Nitrosamines, a class of chemical compounds, can form during the synthesis of pharmaceuticals, particularly those with secondary amines[16]. In the manufacturing of

Table 1. Structures of potential nitrosamine impurities

Sr no.	Impurity name	Structure
1	N-Nitrosodimethyl-amine (NDMA)	
2	N-Nitrosodiethyl-amine (NDEA)	
3	N-Nitrosomethyl-phenylamine (NMPA)	
4	N-Nitrosodiiso-propylamine (NDIPA)	
5	N-Nitrosoisopro-pylethylamine (NIPEA)	
6	N-Nitrosodibutyl-amine (NDBA)	
7	N-Nitroso-N-methyl-4-amino-butyric Acid (NMBA)	

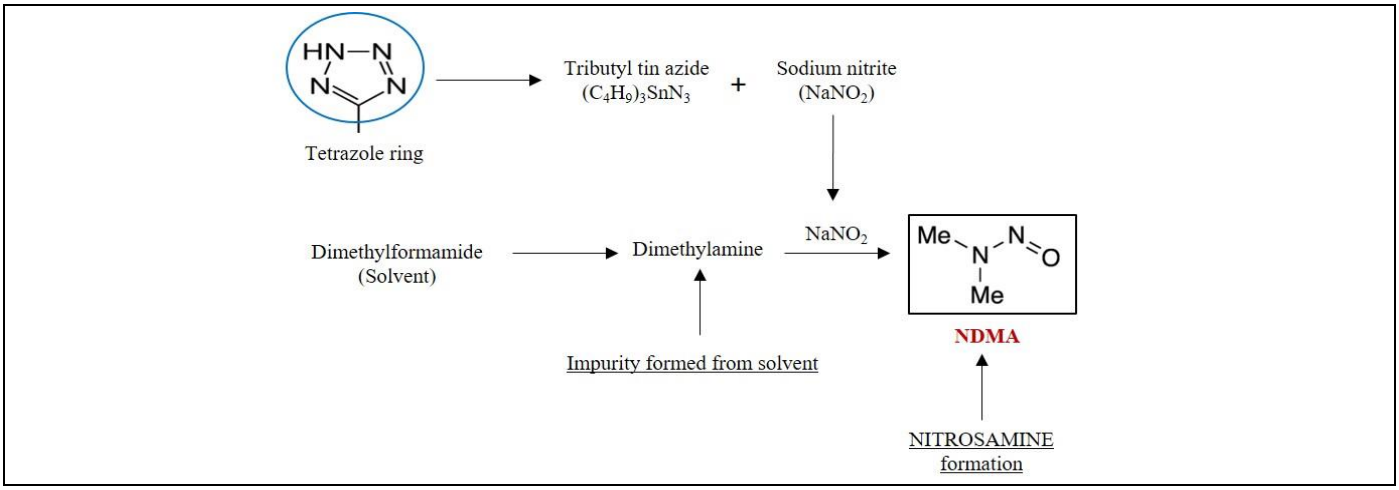


Figure 5. Mechanism for formation of nitrosamines in ARBs

ARBs, the presence of tetrazole rings poses a risk of reacting with other chemicals, leading to the generation of nitrosamines. Notably, nitrosamines, including N-nitrosodimethylamine (NDMA) and N-nitrosodi-ethylamine (NDEA), are recognized potential human carcinogens. This contamination concern has prompted regulatory authorities to implement stringent measures, recalls, and guidelines to detect and prevent nitrosamine impurities in ARBs, underscoring the importance of ensuring the safety of pharmaceutical products and safeguarding public health[17].

Among angiotensin II receptor blockers (ARBs), those containing a specific structural feature called a tetrazole ring are susceptible to nitrosamine formation[18]. The tetrazole ring is commonly synthesized by adding hydrazoic acid to alkyl carbonitrile [19] A safer alternative to using hazardous hydrazoic acid involves creating the tetrazole ring through the [1 + 3] cycloaddition involving nitriles and azides [20]. This method, which employs azide reagents, is predominantly utilized in the concluding phases of sartan synthesis. Despite their potential human hazards, sodium azide (NaN_3) and organometallic azide derivatives like tributyltin azide [$(C_4H_9)_3SnN_3$] and trimethyltin azide [$(CH_3)_3SnN_3$] are favored azide reagents due to their manageable handling and facile disposal[21]. Figure 5 illustrates the mechanism for formation of nitrosamines in ARBs.

Conventionally, any residual azides produced during the tetrazole synthesis process are eliminated through the addition of sodium nitrite under acidic conditions. This method induces the production of nitrous acid, which facilitates the liberation of nitrogen gas and nitrous oxide by-products. However, the removal of unreacted azides carries the risk of generating associated nitrosamines, potentially arising from alkyl amine remnants present in solvents, reagents, or inadvertent upstream impurities. This contamination risk is unintentional and unpredictable[22].

4.2. Histamine-2 (H2) receptor antagonists

Histamine-2 (H_2) receptor antagonists, including medications like ranitidine, famotidine, and nizatidine, are at risk of nitrosamine formation due to specific chemical structures that contains a nitrosatable moiety and reaction pathways during their synthesis and storage processes[23]. The concern primarily revolves around ranitidine, a widely used H_2 receptor antagonist, which contains a nitrosatable moiety in its chemical structure[24]. This moiety has the potential to react with nitrite, a common impurity, resulting in the formation of N-nitrosodimethylamine (NDMA) and other nitrosamine impurities. NDMA is a recognized human carcinogen[25,26]. This issue has prompted regulatory scrutiny, recalls, and heightened quality control measures to address and mitigate the risk of nitrosamine contamination in H_2 receptor antagonist medications, emphasizing the importance of ensuring their safety for patients with conditions such as gastroesophageal reflux disease (GERD) and peptic ulcers[27,28].

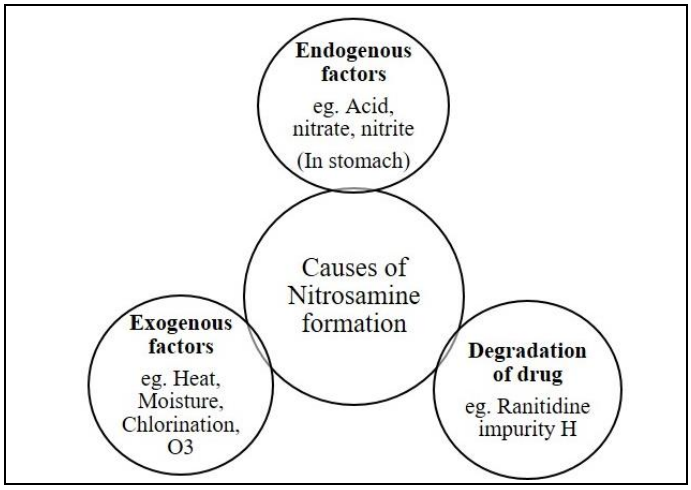


Figure 6. Potential causes of nitrosamine formation in histamine-2 (H2) receptor antagonists

The emergence of NDMA in ranitidine and nizatidine can be attributed to the nitro functional group and dimethylamine side chain. The probability of NDMA origination is associated with the chemical structures of compounds that possess functional moieties favorable for N-nitrosation.

In comparison, there is no NDMA contamination observed in cimetidine and famotidine. The inherent stability of H2-receptor antagonists has been extensively studied, especially concerning ranitidine and nizatidine[29,30,31]. Figure 6 summarizes the potential causes contributing to NDMA contamination in these compounds.

4.3. Antidiabetic agents

There hasn't been a widespread issue of nitrosamine contamination specifically associated with a particular class of antidiabetic agents.

The specific reasons for nitrosamine contamination in metformin were not universally attributed to the drug's intrinsic structure but rather to variations in manufacturing processes and conditions. Manufacturing processes, including the use of certain solvents and reaction conditions, can potentially lead to the formation of nitrosamines[32].

NDMA is produced during the production of metformin drug formulations[33]. Nitrites and nitrates present in pharmaceutical excipients, including CMC sodium, HPMC E5, HPMC K15M, and PolyoxTM, play crucial roles in nitrosamine contamination. The initiation of nitrosation reactions in the production of metformin tablets occurs due to elevated temperatures during the drying phase and an excess of moisture in wet granulation. The potential mechanisms for formation of nitrosamines in metformin is depicted in Figure 7.

4.4. Antimicrobial agents

The FDA identified two nitrosamine impurities present in the antitubercular medicines Rifampin and Rifapentine in August 2020.

The structurally related contaminated nitrosamines, MNP and CPNP, are believed to originate during the drug synthesis process, indicating their connection to the APIs. CPNP is presumed to emerge from an intermediate stage in rifapentine production. Despite manufacturers not identifying the root cause of MNP formation, it is likely to have a similar origin to the contamination observed in rifapentine[35].

The contamination of rifampin and rifapentine with MNP and CPNP can occur through the reaction of nitrosating agents introduced during the manufacturing step with 1-methyl piperazine and 1-cyclopentyl piperazine, respectively. MNP and CPNP are presumed to have lower carcinogenicity compared to NDMA[36]. Figure 8 illustrates the Scheme for formation of MNP and CPNP in Rifampin and Rifapentine.

4.5. Other medicines

The concurrent generation of nitrosamines is facilitated by the chloramine disinfection procedure. In a study by Shen and Andrews (2010) evaluating the potential for nitrosamine formation, numerous active pharmaceutical ingredients (APIs) were identified with the capability for NDMA conversion following exposure to chloramine disinfectants. Conversely, lidocaine is susceptible to NDEA contamination. Employing oxidizing agents for pretreating wastewater proves effective in minimizing NDMA generation via introducing lone pair electrons to nitrogen through an ozonation pathway, yielding N-oxide[37,38].

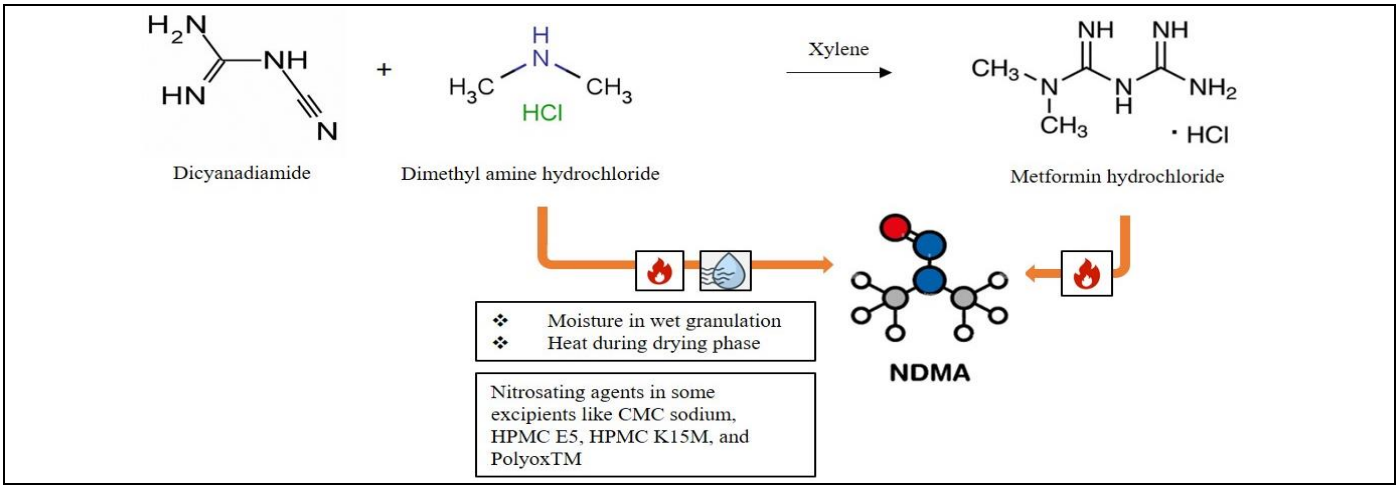


Figure 7. Mechanisms for formation of nitrosamines in metformin

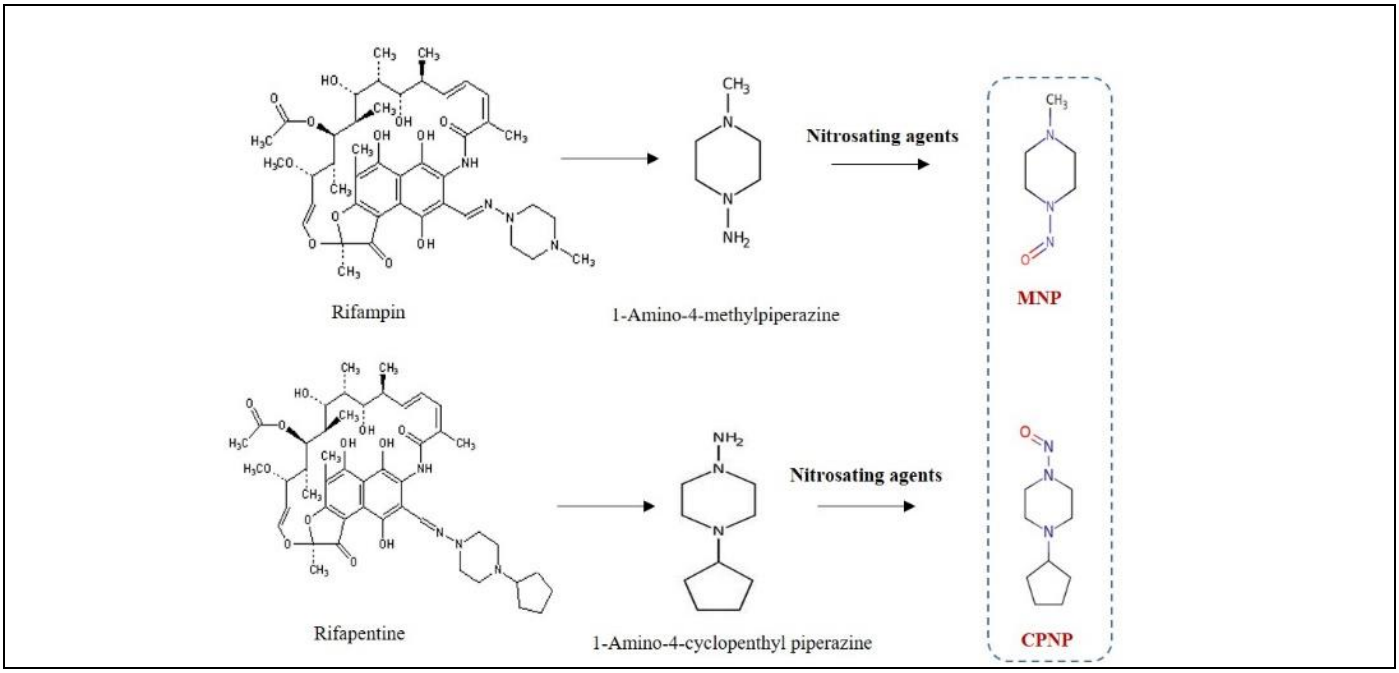


Figure 8. MNP and CPNP formation in Rifampin and Rifapentine

5. HEALTH CONSEQUENCES OF NITROSAMINES

Activation of nitrosamines by cytochrome P450 (CYP450) enzymes initiates electrophilic alkylation, leading to the generation of mutation-inducing DNA adducts. Hepatic enzymes play a pivotal role in nitrosamine metabolism, exhibiting heightened activity in the liver compared to other tissues[39].

Nitrosamine impurities possess the capacity to induce lung cancer by stimulating proliferation, migration, and cancer cell survival through modulation of G-protein coupled receptor (GPCR), nicotinic acetylcholine receptor (nAChR), and epidermal growth factor receptor (EGFR) signaling pathways. Furthermore, alterations in nAChR signaling, voltage-gated calcium channels (VGCC), calcium signaling, and protein kinase C (PKC) modulation contribute to cancer progression via migration and survival mechanisms. Interaction with beta-adrenergic signaling pathways modulates HIF1-alpha signaling, promoting angiogenesis for nutrient supply to proliferating cancer cells[39].

Hepatocellular carcinoma emerges as a fatal consequence of nitrosamine metabolism involving P450 enzymes. Lifestyle factors, particularly dietary exposure to elevated nitrosamine levels, have been associated with cancer development. Nitroso compounds specifically form DNA adducts within the nuclei of cells in digestive organs and the liver, bolstering their carcinogenicity. Additionally, exposure to N-nitrosamines perturbs hepatic lipid metabolism by affecting mitochondrial DNA, oxidative phosphorylation signaling, and other mitochondrial metabolic pathways[39].

Tobacco harbors an array of nitrosamines, with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) emerging as a significant carcinogen known to fuel malignant cancer cell proliferation. These tobacco-derived carcinogens notably contribute to various cancers, including breast cancer. NNK plays a pivotal role in breast cancer development and progression by interacting with nicotine acetylcholine receptors (nAChRs) present in cancer cells. Particularly, the α9nAChR receptor is implicated in breast cancer cell development and progression. Additionally, nicotine and NNK can modulate cancer cell proliferation by influencing critical cell signaling pathways like mitogen-activated protein kinase (MAPK) and the PI3K-Akt pathway[39].

According to the ICH Harmonised Guideline M7(R1), a lifetime intake of N-nitrosamines at the interim-limit levels would cause less than one additional case of cancer for every 100,000 population[40].

6. REGULATORY ASPECTS FOR CONTROL OF NITROSAMINES

6.1. EMA (European Medicines Agency)

In 2018, the European Union (EU) authorities became aware of nitrosamine impurities, notably N-nitrosodimethylamine (NDMA), in blood pressure medications of the 'sartan' class. This prompted the Executive Director of the European Medicines Agency (EMA) to issue guidelines on September 10, 2019, directing the Committee for Medicinal Products for Human Use (CHMP) to conduct a comprehensive examination and provide a scientific opinion on concerns related to pharmaceuticals using chemically processed drug substances. The focus included the

presence of N-nitrosamines in active pharmaceutical ingredients (APIs), such as pioglitazone, ranitidine, and sartans with a tetrazole ring. The scope of the guidance extends to all medicinal products for human use approved in the EU and the UK, encompassing both chemically synthesized active pharmaceutical ingredients and biological medicinal products, with an emphasis on evaluating the impact of N-nitrosamine impurities on the safe use of these medicines[41].

6.2. USFDA (United States food and drug administration)

The FDA has issued crucial recommendations to manufacturers concerning timely risk assessments, testing, and measures for eliminating and mitigating nitrosamine impurities in active pharmaceutical ingredients (APIs) and drug products. These guidelines, prompted by the unexpected discovery of nitrosamine impurities, potential human carcinogens in medications like angiotensin II receptor blockers (ARBs) such as ranitidine, nizatidine, and metformin, underscore the need for a risk assessment strategy for pharmaceutical products containing nitrosamines. It's emphasized that the FDA's guidance does not establish legally enforceable obligations but reflects the Agency's current perspectives. The guidance outlines actions for API and drug product manufacturers to identify and prevent pharmaceutical products with undesirable levels of nitrosamine impurities. The scope covers both drugs with pending applications and those currently on the U.S. market, with recommendations for collaboration between owners of marketed products and their contract manufacturers to implement these guidelines[12].

6.3. Health Canada

Health Canada's guidance reflects their current perspective on N-nitrosamine contaminants, with a primary focus on addressing concerns related to the health and safety of Canadians. In response to worries about nitrosamine impurities, Health Canada prioritizes transparency and will continually update a list of pharmaceuticals known to contain these impurities. They are actively investigating the formation and presence of nitrosamine impurities in drugs, holding companies accountable, and working to mitigate their presence. Collaboration with companies and global regulatory partners is ongoing to identify underlying causes and ensure necessary steps are taken. Upon obtaining authorization for marketing in Canada, Marketing Authorization Holders (MAHs) are tasked with the responsibility of continuously confirming the safety, efficacy, and quality of pharmaceuticals. This involves the establishment of an enduring monitoring program designed to identify trends in quality. The program must be based on effective controls for raw materials, every processing stage, critical process parameters, and critical quality attributes[42].

The guidance mandates risk analyses for nitrosamine contaminants in all biological and radiopharmaceutical products for human use, including vaccines and biologics. Products with a Drug Identification Number (DIN), such as non-prescription items and topical antiseptics, are subject to evaluation, while cosmetics and certain exclusions, such as veterinary products and natural health products, fall outside the scope of coverage. The guidance also emphasizes routine communication of information on health hazards, test findings, recalls, and other actions taken[42].

6.4. TGA (Therapeutic goods administration)

The primary objective is to mitigate or eliminate nitrosamine levels in pharmaceutical drugs due to their deemed unsatisfactory presence in terms of quality and safety. The Therapeutic Goods Administration (TGA) has set acceptable intake (AI) limits for various nitrosamine contaminants, serving as benchmarks for determining the need for regulatory action on affected products. Regulatory measures, including recalls, product registration conditions, and manufacturing-related actions, are employed to address the issue, with careful consideration of the impact on medicine availability. The TGA collaborates with international regulatory partners to investigate nitrosamine contamination, involving information exchange, risk assessment, and coordinated initiatives. International alignment is acknowledged for addressing this issue comprehensively. The scope includes investigations into potential nitrosamine impurities, prioritizing APIs flagged by international reports, and applying the strategy to both existing and new finished products to ensure medication safety and quality in Australia[43].

6.5. Other regulatory authorities

In France, the regulatory authority AFSSAPS emphasizes the importance of cooperation between the United States Food and Drug Administration (USFDA) and Afssaps to enhance medical safety and public health protection. This involves sharing non-public information as part of cooperative law enforcement or regulatory activities. New Zealand's MedSafe aligns with the EMA's risk evaluation process and nitrosamine limits, requiring sponsors to provide risk assessments and testing results for new medicines. Switzerland's Swissmedic aims to harmonize its requirements with European authorities when scientifically justified. In

India, the CDSCO introduces a new chapter on nitrosamine impurities in IP 2022, applicable to sartan API monographs, with the expectation that stakeholders adopt it for other drugs as deemed necessary. The UK's MHRA, following EMA guidance, advises Marketing Authorization Holders (MAHs) to review manufacturing processes for nitrosamine risk, and in May 2023, additional guidance emphasizes lifecycle management, requiring ongoing risk evaluation throughout a product's lifecycle and updates to CTD documentation for variations related to changes in substance source, manufacturing, composition, or

Table 2 Comparative analysis of regulatory aspects of nitrosamines

Parameters	USFDA	EMA	Health Canada	TGA
Practical Implications	• Offers guidance for reducing nitrosamine impurities in active pharmaceutical ingredients (APIs). • Sets acceptable intake limits for DNA-reactive impurities in pharmaceuticals.	• Establishes substance-specific limits for lifetime exposure to medicinal impurities. • Identifies the root causes of impurities in medicinal products for risk assessment.	• Engages stakeholders regarding nitrosamine risks in drug products. • Conducts ongoing safety and quality monitoring programs for drug products.	• Requires sponsors to monitor nitrosamine impurities to meet safety standards. • TGA collaborates internationally to oversee manufacturing and testing processes.
Scope	• Includes nitrosamine impurities, risk assessments, and mitigation strategies. • Applies to drug product manufacturers, APIs, and sources of nitrosamine contamination. • Involves testing API lots, control strategies, and regulatory actions.	• Covers all human medicinal products for nitrosamine impurities. • Includes biological products with specific risk factors for impurities.	• Involves human pharmaceutical products with Drug Identification Number (DIN). • Evaluates nitrosamine impurities in chemically synthesized APIs.	• Investigates nitrosamine impurities in medicines by sponsors. • Collaborates internationally to address nitrosamine impurities in medicines.
Contributions	• Recommends mitigation strategies for API and drug product manufacturers. • Determines acceptable intake limits for nitrosamine impurities.	• Implements a harmonized approach for CHMP scientific review. • Sets limits for N-nitrosamines in human medicinal products.	• Conducts nitrosamine risk assessments for non-authorized drug products. • Recommends guidelines for purchasing APIs and producing compounded products. • Consults Appendix 1 for APIs and drug products.	• Investigates nitrosamine impurities in medicines through international collaboration. • Provides guidance on testing methods and risk mitigation strategies. • Collaborates with global regulators and sponsors.
Regulation	• Regulates nitrosamine impurities in APIs and drug products. • Requires manufacturers to test APIs for nitrosamine impurities before use. • Mandates reporting changes to prevent nitrosamine impurities.	• Utilizes regulatory pathways including variations or referral procedures based on specific needs. • Considers factors like product criticality, contamination extent, and patient exposure.	• Shares testing methodologies with OMCLs and FDA. • Determines regulatory measures for nitrosamine impurities individually.	• Collaborates internationally to regulate nitrosamine impurities in medicines. • Aligns guidance with EMA and FDA for controlling nitrosamine impurities in drugs.
Acceptable intake limits	• Recommends acceptable intake limits for nitrosamine impurities in APIs.	• Acceptable intake limits based on ICH M7(R1) guideline. • Limits should be at or below the acceptable intake (AI).	• Sets AI limits for nitrosamine impurities applicable to all drug administration routes.	• Establishes AI limits for nitrosamine impurities to ensure safety. • Aligns AI limits with international standards for safety and quality.
Risk assessment	• Requires manufacturers to conduct risk assessments for nitrosamine impurities in products. • Uses risk assessments to identify and prevent nitrosamine impurities in pharmaceuticals.	• Involves evaluating N-nitrosamines in medicinal products. • Requires pharmaceutical companies to assess manufacturing processes for N-nitrosamines.	• Identifies root causes and potential nitrosamine impurities. • Guides the development of test methods for confirmatory testing.	• Assesses nitrosamine impurities in medicines for safety and quality. • Identifies sources of risk in manufacturing processes for medicinal products. • Ensures medicines meet TGA safety standards through testing.

packaging. European and US regulatory authorities are actively collaborating with international partners, including Canada, Japan, Singapore, Switzerland, Australia, China, and Brazil, to address the presence of nitrosamines in medicinal products and harmonize. regulatory requirements. This collaborative effort involves sharing information and aligning guidelines globally to ensure a consistent approach. Recognizing the discovery of nitrosamine impurities in drug products across different markets, these regulatory authorities are working together to publish guidelines for market authorization holders (MAHs). These guidelines encompass analytical methods aimed at detecting and identifying nitrosamine impurities in drug products, emphasizing a concerted international response to this critical pharmaceutical safety issue[41,12].

7. CHALLENGES IN REGULATION OF NITROSAMINES

In the realm of pharmaceuticals, addressing the obstacles associated with nitrosamine analysis revolves around the imperative considerations of sensitivity, selectivity, and adherence, all within the context of securing accurate and promptly available results. Meeting regulatory standards necessitates attaining heightened sensitivity, while ensuring selectivity remains paramount to prevent the occurrence of erroneous positive findings leading to non-compliance[44]

7.1. Optimizing nitrite control strategies in water and excipients

Optimizing nitrite control strategies in water and excipients is crucial, particularly considering the significant challenge posed by nitrosamine formation. In chloraminated drinking waters, NDMA has been the compound most frequently identified[45,46]. Nitrosamines, potential carcinogenic compounds, can arise under specific conditions, especially in the presence of nitrites and secondary amines. To effectively address this challenge, several key strategies can be employed. Firstly, conducting a comprehensive risk assessment is essential to identify potential sources of nitrosamine formation, prioritizing high-risk areas based on factors such as pH, temperature, and precursor presence[47]. Nitrite minimization measures involve optimizing manufacturing processes, utilizing nitrite-free alternatives, and selecting excipients with lower nitrite content. Careful pH control and amine management, along with material selection that minimizes nitrosamine contribution, are critical steps[48]. Exploring advanced water treatment technologies and implementing regular testing and monitoring for nitrosamine formation are additional layers of defense. Process optimization, a Quality by Design (QbD) approach, and adherence to regulatory compliance standards are integral aspects. Collaboration and information sharing with industry peers and regulatory agencies contribute to a comprehensive and proactive approach. By integrating these strategies into the quality management system, the risk of nitrosamine contamination can be minimized, ensuring product safety and compliance. NDMA is additionally generated as a byproduct in the rubber, dye, tanning, and pesticide sectors, and has been detected in groundwater in proximity to locations involved in the manufacture of rocket fuel containing unsymmetrical dimethylhydrazine (UDMH)[49,50].

7.2. Assessment of nitrosamine impurities in cleaning samples

Assessing nitrosamine impurities in cleaning samples presents distinctive challenges, given the potential presence of minute amounts of these carcinogenic compounds and the demand for highly sensitive analytical methods. To tackle this challenge effectively, several strategies can be employed. Rigorous and standardized sampling protocols should be developed, using techniques like swabbing, or rinsing that suit the cleaning process and surface characteristics. Employing sensitive analytical methods such as liquid chromatography coupled with mass spectrometry (LC-MS) or gas chromatography with mass spectrometry (GC-MS) is crucial, with validation and optimization for accurate quantification of trace nitrosamine impurities. The use of certified reference standards for calibration ensures precision and reliability, with regular updates and verification checks. Detection limits should align with expected nitrosamine levels, and methods should address matrix interference through optimized sample preparation and selective detection. Routine monitoring programs, risk assessments, and prioritization efforts contribute to early detection and effective management of nitrosamine contamination risks. Integration of nitrosamine assessment into cleaning validation studies, ongoing employee training, and a commitment to regulatory compliance further enhance the reliability and effectiveness of nitrosamine assessment in cleaning samples. By adopting these strategies, organizations can uphold safety standards and regulatory compliance in their processes[51].

7.3. Challenges in synthesizing and characterizing unstable nitrosamine impurities

The synthesis and characterization of unstable nitrosamine impurities present unique challenges due to their reactive nature, potential hazards, and the requirement for precise analytical techniques. One challenge lies in their chemical reactivity and instability,

making synthesis and handling difficult. To address this, robust synthesis protocols should be developed to minimize exposure to reactive intermediates, utilizing inert atmospheres and specialized reaction vessels. Unstable nitrosamine impurities are often present in low concentrations, posing analytical detection limit challenges; employing highly sensitive methods like HPLC-MS or NMR spectroscopy and optimizing for lower detection limits is crucial[52]. Safety concerns arise due to potential carcinogenicity and reactivity, necessitating strict safety protocols, including PPE use and well-ventilated or closed-system syntheses. Characterization requires precise analytical techniques, prompting the combination of multiple methods like NMR and mass spectrometry. Stability studies and isolation/purification methods must address the rapid degradation and reactivity of these impurities. Quality control methods and regulatory compliance present additional challenges, demanding real-time or accelerated stability testing, continuous regulatory engagement, and comprehensive training of personnel. By implementing these strategies, the reliability, safety, and compliance of unstable nitrosamine impurity synthesis and characterization can be enhanced across industries such as pharmaceuticals and chemicals[53].

7.4. Establishing regulatory guidance and standards for nitrosamines in excipients.

Establishing regulatory guidance and standards for nitrosamines in excipients presents a multifaceted challenge owing to the intricacies of the issue, the demand for thorough risk assessment, and the dynamic nature of regulatory landscapes. Conducting a comprehensive risk assessment involves collaboration with experts across disciplines to consider factors such as precursor presence and manufacturing processes. The crucial identification of the origin (along with precise speciation) of the nitrosating agent in excipients is essential, as it would facilitate the reasoned application of corrective actions[54]. Analytical method validation poses a challenge, necessitating investment in advanced techniques and collaboration to establish standardized protocols[55]. An additional alternative could involve introducing a purification procedure for the specific excipient to diminish the nitrite content[56]. Determining acceptable limits requires a balance between safety and feasibility, requiring scientific research and collaboration with regulatory agencies. Achieving global harmonization faces hurdles due to regional variations; active participation in international forums and collaboration with regulatory bodies globally is crucial. Communication and transparency are essential, involving clear channels between agencies and stakeholders, guidance documents, and educational resources. Adapting to emerging science requires regular updates based on the latest findings, fostering collaboration with research institutions. Capacity building for effective enforcement and oversight may be limited in some regions, necessitating collaboration with international organizations. Compliance challenges for manufacturers can be addressed by providing transition periods and support, along with guidance on best practices. Public and stakeholder engagement may be challenging, requiring mechanisms for consultation and transparency to address diverse perspectives. Addressing these challenges demands a collaborative effort to develop robust, science-based, and internationally harmonized regulatory guidance for nitrosamines in excipients, emphasizing communication, flexibility, and inclusivity[57].

8. FUTURE SCOPE FOR CONTROL OF NITROSAMINES IMPURITIES

The regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have been actively addressing the issue and implementing measures to control and minimize nitrosamine contamination[58]. The future scope of the control of nitrosamines may involve several aspects:

1) Regulatory agencies are likely to continue refining and expanding guidelines related to nitrosamine impurities. Pharmaceutical companies will need to comply with these standards to ensure the safety of their products. Numerous international (ICH) and regional guidelines have been established to ensure the thorough validation of the nonclinical and clinical safety and effectiveness of medicinal products throughout their development and market utilization[44].

2) Advances in analytical techniques for detecting and quantifying nitrosamines will play a crucial role. Improved and more sensitive methods will be developed to detect even trace amounts of nitrosamines in pharmaceuticals and other relevant products[59]. As nitrosamines are typically found in minute quantities, meticulous procedures are essential when conducting analyses related to their presence[60].

Current methods Employed for Nitrosamine Detection[51]:

i) LC-MS & LC-MS/MS method

Reverse-phase liquid chromatography (LC) combined with mass spectrometry (MS) stands as the favored approach for quantitatively assessing minute impurities across diverse sectors, encompassing food science, environmental studies, and pharmaceuticals. MS facilitates the discernment and identification of charged analytes within intricate sample matrices. Triple quadrupole mass analyzers are frequently employed for the determination of nitrosamines.

ii) GC-MS & GC-MS-MS method

Gas chromatography (GC) proves highly advantageous for both qualitative and quantitative assessment of volatile and semi-volatile impurities within pharmaceuticals, encompassing residual solvents delineated in pharmacopoeial monographs.

iii) LC Coupled with Spectrophotometric detection

High-performance liquid chromatography (HPLC) combined with spectrophotometric detection represents a widely utilized instrument in laboratory environments for impurity characterization and is frequently advised for standard quality assurance procedures. A range of spectrometric detectors, such as ultraviolet-visible (UV-Vis) spectrophotometers, photodiode array (PDA) detectors, spectrofluorometric detectors, and chemiluminescence detectors, are employed for determining nitrosamines. Given the modest sensitivity and constrained specificity of UV detection, derivatization methods are frequently utilized to amplify nitrosamine detection signals.

3) There may be increased emphasis on risk assessments to identify potential sources of nitrosamine formation in manufacturing processes. Companies will likely implement more robust mitigation strategies to prevent or reduce nitrosamine contamination[61].

4) Given the global nature of the pharmaceutical industry, international collaboration among regulatory agencies is essential. Harmonization of standards and exchange of information will help ensure a consistent approach to controlling nitrosamines worldwide[61].

5) Pharmaceutical manufacturers may invest in new technologies and processes that minimize the risk of nitrosamine formation during drug production[61].

6) Companies may focus on improving supply chain transparency and collaboration with suppliers to ensure the quality and safety of raw materials used in the manufacturing of pharmaceuticals [40].

7) As awareness of nitrosamine contamination grows, there may be increased public and stakeholder pressure for stringent controls. This could lead to more proactive measures by companies and regulatory agencies[62]..

8) While the initial concern has been primarily focused on pharmaceuticals, the scope of nitrosamine control may expand to other industries, such as food and cosmetics, where similar chemical processes or ingredients are involved[63].

9. CONCLUSIONS

In conclusion, the review of nitrosamines highlights the significant concerns associated with their presence in pharmaceuticals and other products due to their potential carcinogenicity. Regulatory agencies, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have taken proactive measures to address this issue and have implemented guidelines to control nitrosamine impurities.

The future scope of nitrosamine control involves a multi-faceted approach. It includes the continuous refinement of regulatory standards and guidelines, advancements in analytical methods for detection, rigorous risk assessment and mitigation strategies in manufacturing processes, international collaboration for harmonization of standards, technological innovations to minimize nitrosamine formation, improved supply chain management, heightened public awareness, and potential expansion of control measures to other industries beyond pharmaceuticals.

The ongoing efforts in research, regulation, and industry practices underscore the commitment to ensuring the safety and quality of products by minimizing the risk of nitrosamine contamination. Stakeholders across the pharmaceutical and related industries, including manufacturers, regulatory bodies, and the public, play pivotal roles in maintaining vigilance and implementing measures to mitigate the potential health risks associated with nitrosamines. As developments unfold, staying informed about the latest guidelines and industry best practices remains crucial to addressing and preventing nitrosamine-related challenges effectively.

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