



PREVENTION AND CONTROL OF NITROSAMINE CONTAMINATION IN DRUG MANUFACTURING: INDUSTRY PRACTICES AND INNOVATIONS

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Abstract:

Nitrosamine contamination in pharmaceutical products has become a significant concern for public health and the pharmaceutical industry due to its potential carcinogenic risks. As regulatory agencies such as the FDA, EMA, and ICH have increasingly focused on controlling nitrosamine levels, understanding the sources and formation processes of these impurities has become critical. This paper explores industry practices and innovations aimed at preventing nitrosamine contamination in drug manufacturing. It examines the sources of nitrosamines, including raw materials, excipients, and manufacturing processes, and highlights environmental factors contributing to their formation. Case studies of drugs like ranitidine and valsartan demonstrate real-world contamination issues. The paper also reviews the regulatory landscape, focusing on guidelines for testing, monitoring, and controlling nitrosamine levels. Finally, it discusses best practices in raw material management and process controls to minimize nitrosamine risks during production.

Keywords: Nitrosamine contamination, pharmaceutical manufacturing, public health, FDA, EMA, ICH guidelines, drug substances, carcinogenic risk, raw materials, process controls, regulatory guidelines, contamination prevention.

1. Introduction

The presence of nitrosamines in pharmaceutical products has raised significant concerns within the healthcare sector due to their potential carcinogenic properties. Nitrosamines are a class of compounds that can form during the manufacturing, processing, and storage of certain pharmaceutical products, especially when drugs contain nitrite or amine groups. The presence of even trace amounts of nitrosamines can pose serious risks to consumers, making it essential for manufacturers to implement strict measures to prevent contamination. Given the widespread use of pharmaceutical products across the global population, ensuring the safety of these medications is of utmost importance. Nitrosamine contamination is not just a matter of regulatory compliance but a core public health issue, impacting the trust between consumers and the pharmaceutical industry.

Effective prevention of nitrosamine contamination requires rigorous oversight and continuous innovation in manufacturing practices. As such, the pharmaceutical industry must remain vigilant, employing advanced technologies and improved practices to detect, mitigate, and prevent the formation of these harmful substances during drug production. This becomes especially crucial for medications that are used on a long-term basis, as chronic exposure to nitrosamines can significantly increase the risk of developing cancers.

The Impact of Nitrosamine Contamination on Public Health and the Pharmaceutical Industry

The presence of nitrosamine contamination in drugs has far-reaching consequences for both public health and the pharmaceutical industry. From a health perspective, the ingestion of nitrosamines, even in low concentrations, can increase the likelihood of developing various cancers, including those of the stomach, esophagus, and liver. The International Agency for Research on Cancer (IARC) has classified certain nitrosamines as probable human carcinogens, a classification that underscores the potential dangers associated with these compounds. The long-term effects of exposure can go undetected for years, adding to the complexity of addressing this issue.

On a broader scale, nitrosamine contamination can severely damage the reputation of pharmaceutical manufacturers. It can lead to widespread product recalls, which, in turn, can result in financial losses, legal ramifications, and loss of consumer trust. Furthermore, when nitrosamines are found in widely used medications, such as antihypertensives or antacids, the impact on public health can be catastrophic, resulting in mass panic, heightened scrutiny, and the necessity for more stringent regulatory oversight. Such events not only affect consumer confidence but also have regulatory implications, requiring pharmaceutical companies to adopt more rigorous quality control systems and safety measures.

In many cases, the detection of nitrosamine contamination has led to market disruptions and the withdrawal of products from circulation, highlighting the importance of preventative measures in drug manufacturing. The overall trust in the pharmaceutical industry can be jeopardized by such contamination issues, making it crucial for manufacturers to take proactive steps in ensuring drug safety at every stage of production.



2. Understanding Nitrosamine Contamination Sources

Sources of Nitrosamine Impurities in Drug Substances

Nitrosamine contamination in pharmaceutical products can arise from various sources during the manufacturing process. These impurities are primarily formed when nitrites (or compounds that release nitrites) react with amines, which are often present in drug substances. This process can occur both intentionally and unintentionally, depending on the raw materials and manufacturing methods used.

1. **Raw Materials:** One of the primary sources of nitrosamine impurities is the raw materials used in the synthesis of drug substances. Active pharmaceutical ingredients (APIs) and excipients can contain amines or other compounds that, when exposed to nitrites, can undergo chemical reactions that form nitrosamines. Nitrites, commonly found as preservatives or by-products of certain chemicals, are often introduced into the manufacturing process during the synthesis of these materials. For instance, certain amines in drugs such as ranitidine or valsartan, when exposed to nitrites, can lead to the formation of nitrosamine compounds.
2. **Excipients:** Excipients, the inactive ingredients used in drug formulations (such as binders, fillers, stabilizers, or preservatives), can also contribute to the formation of nitrosamines. These excipients may contain amines or other reactive substances that can undergo nitrosation under certain conditions. Some excipients, especially those derived from natural sources like proteins or plant extracts, may inherently contain higher levels of amines or nitrogenous compounds, making them more susceptible to nitrosamine formation.
3. **Manufacturing Processes:** The drug manufacturing process itself can introduce or exacerbate the formation of nitrosamines. Nitrosation reactions can take place during various stages, including synthesis, formulation, and packaging. For example, high temperatures, the presence of certain solvents, or improper storage conditions (such as exposure to humidity) can facilitate nitrosamine formation. Certain pharmaceutical processes, such as the use of acidic or basic catalysts, can also lead to the formation of nitrosamines by enabling the nitrosation of amines. Additionally, cross-contamination during manufacturing, where nitrosamine-forming chemicals are introduced into a drug batch, is another potential source of contamination.

Environmental Factors Contributing to Nitrosamine Formation During Drug Production

Environmental factors can significantly influence the formation of nitrosamines in drug manufacturing, as they affect the chemical reactions that take place during production. These factors include temperature, humidity, light exposure, and the pH of the manufacturing environment.

1. **Temperature:** The temperature at which drugs are processed can have a considerable impact on the rate of nitrosamine formation. High temperatures can accelerate the nitrosation reaction, promoting the creation of nitrosamines in the presence of amines and nitrites. This is especially true during processes that require heat, such as drying or sterilization. If these processes occur in an environment where trace amounts of nitrites are present, nitrosamines may form as unwanted by-products.
2. **Humidity:** The presence of moisture can also contribute to nitrosamine formation. In humid conditions, certain chemicals may become more reactive, creating a conducive environment for the nitrosation reaction. Moreover, humidity can affect the stability of certain excipients or active ingredients, potentially causing them to break down and release amines or other reactive species.
3. **Light Exposure:** Some nitrosation reactions can be influenced by light, especially ultraviolet (UV) light. In the presence of UV light, certain chemicals may undergo photochemical reactions that generate nitrosamine compounds. For example, if a drug product is exposed to light during storage, it could result in the degradation of ingredients that leads to nitrosamine formation.
4. **pH Levels:** The pH of the manufacturing environment can affect the stability and reactivity of both the drug substances and the impurities present. In acidic or alkaline conditions, certain amines may become more reactive, leading to an increased likelihood of nitrosamine formation. For example, if the pH of a reaction mixture is not carefully controlled, it could encourage the nitrosation reaction.

Case Studies of Specific Drug Substances and Their Contamination Issues

Ranitidine: Ranitidine, a popular histamine H₂-receptor antagonist used to treat acid reflux, became infamous in 2019 when it was found to contain unacceptable levels of NDMA (N-Nitrosodimethylamine), a type of nitrosamine. The contamination was traced back to the manufacturing process, where the active ingredient was synthesized under conditions that facilitated the formation of NDMA. It was discovered that the manufacturing process involved the



use of raw materials that contained dimethylamine, which, when combined with nitrites under certain conditions, formed NDMA. As a result, multiple batches of ranitidine were recalled globally, leading to major regulatory scrutiny and a re-evaluation of manufacturing standards for nitrosamine formation in pharmaceutical products.

Valsartan: Valsartan, an angiotensin II receptor blocker (ARB) commonly prescribed for hypertension and heart failure, also faced significant contamination issues due to the presence of nitrosamines. The contamination was linked to the use of contaminated raw materials, particularly the manufacturing of valsartan at certain facilities where the process conditions allowed for the formation of NDMA and NDEA (N-Nitrosodiethylamine), two potent carcinogens. It was found that the impurity was a result of the use of certain solvents and reagents during the synthesis of valsartan. The contamination led to recalls of valsartan products in multiple countries and a comprehensive review of manufacturing processes for the entire class of ARBs.

Both of these case studies highlight the importance of rigorous quality control, proper raw material sourcing, and close monitoring of manufacturing processes to prevent nitrosamine contamination. The lessons learned from these incidents underscore the necessity of revising industry practices to ensure safer production environments, better raw material vetting, and more comprehensive testing for nitrosamines.

These cases also exemplify the risks associated with seemingly minor variations in manufacturing conditions and how they can lead to significant contamination issues that affect public health and industry reputation. The actions taken in response, including reformulating drugs and altering production processes, have pushed the pharmaceutical industry to adopt more robust methods for controlling nitrosamine levels, including greater transparency and stricter regulatory compliance.

3. Regulatory Guidelines for Nitrosamine Control

Review of FDA, EMA, and ICH Guidelines Regarding Nitrosamine Control

The global regulatory landscape for nitrosamine control is shaped by key health authorities, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). These organizations have issued comprehensive guidelines to safeguard public health by controlling nitrosamine contamination in pharmaceutical products.

1. **FDA Guidelines:** The FDA's guidance on nitrosamine impurities was first issued in 2020, following the widespread contamination issues in drugs like ranitidine and valsartan. The FDA outlined that pharmaceutical manufacturers must assess and control the levels of nitrosamines in drug products to ensure safety for patients. The FDA requires manufacturers to perform risk assessments for their products and identify potential sources of nitrosamine contamination. Additionally, the agency has stipulated that manufacturers of certain drugs must test finished products for nitrosamine impurities if a risk of contamination exists, particularly for drugs that use raw materials or synthetic processes known to be prone to nitrosation reactions. The FDA's guidance includes specific recommendations for the limits of individual nitrosamines based on the type of drug and its intended use.
2. **EMA Guidelines:** The EMA, through its Committee for Medicinal Products for Human Use (CHMP), has been at the forefront of issuing nitrosamine-related guidelines in Europe. The EMA's approach has focused on ensuring that all drug products, especially those for chronic use, are free from unacceptable levels of nitrosamines. It published a set of guidelines in 2020, directing manufacturers to carry out a risk assessment to identify potential nitrosamine risks in both active pharmaceutical ingredients (APIs) and finished products. These guidelines also recommend testing methods for nitrosamines and require that the levels be kept well below established safety thresholds. The EMA has been particularly focused on ensuring that patient safety is protected, with a strong emphasis on withdrawing or recalling products that exceed acceptable nitrosamine limits. The agency also advises that new manufacturing processes should be carefully evaluated to prevent the introduction of nitrosamines, recommending that companies implement process controls to reduce nitrosamine risks at the outset of production.
3. **ICH Guidelines:** The ICH plays a critical role in harmonizing global regulatory standards, and its guidelines reflect a comprehensive approach to controlling nitrosamine impurities. ICH guidelines focus on ensuring that pharmaceutical products meet the highest safety standards globally, and this includes the control of nitrosamines in drugs. ICH Q3E, which deals with impurities in new drug substances and products, specifically addresses the risk of nitrosamine contamination. According to ICH guidance, manufacturers must conduct risk assessments to determine whether their products could be at risk for nitrosamine contamination, based on their chemical structure, manufacturing processes, and raw materials. The ICH also encourages collaboration between manufacturers and regulatory bodies to ensure that

appropriate testing and control measures are in place, particularly for drugs that could potentially be consumed over a long period.

Overview of Accepted Limits for Nitrosamine Impurities

The guidelines issued by the FDA, EMA, and ICH all establish specific limits for nitrosamine impurities in pharmaceuticals, based on their carcinogenic potential and the level of patient exposure. The limits are set in a way that ensures the safety of patients, especially in drugs used for long-term conditions.

1. **FDA Limits:** The FDA has set a threshold for acceptable levels of nitrosamine impurities based on the acceptable daily intake (ADI) for carcinogenic substances. In general, the FDA has recommended that the limit for individual nitrosamine impurities should not exceed 96 nanograms (ng) per day in drugs that are taken daily. For drugs that are not intended for long-term use, the FDA typically recommends a lower threshold. For example, the acceptable levels of nitrosamines in over-the-counter drugs may be lower than for prescription drugs taken for chronic conditions.
2. **EMA Limits:** The EMA follows a similar approach to the FDA in setting nitrosamine limits. The European agency recommends that nitrosamine levels be limited to 100 ng per day for drugs with chronic exposure, with stricter limits depending on the drug's duration of use and the nature of the nitrosamine involved. EMA guidelines suggest that products for short-term use, such as those used for acute conditions, may have higher acceptable limits compared to long-term therapies. For nitrosamines like NDMA and NDEA, which have been identified as highly carcinogenic, the limits are set even lower.
3. **ICH Limits:** ICH guidelines generally align with those of the FDA and EMA, setting strict limits for nitrosamine levels based on the ADI. The ICH recommends that the acceptable levels for nitrosamines should be below 100 ng per day for drugs that are used chronically. For drugs taken less frequently or for short periods, the ICH allows higher levels, though it stresses that manufacturers must make every effort to limit nitrosamine exposure as much as possible. These guidelines also emphasize the need for robust analytical methods to detect nitrosamine impurities, especially in drugs that are consumed over a long period.

Specific Regulatory Requirements for Testing, Monitoring, and Controlling Nitrosamine Levels

All three regulatory bodies—FDA, EMA, and ICH—have laid down detailed requirements for testing, monitoring, and controlling nitrosamine levels in drug manufacturing. These requirements are designed to ensure that manufacturers can proactively identify and mitigate the risk of contamination.

1. **Risk Assessment:** The first step in nitrosamine control is conducting a thorough risk assessment to evaluate the potential for nitrosamine formation in a given product. The FDA, EMA, and ICH all emphasize the importance of a detailed risk assessment that includes an evaluation of the drug's raw materials, manufacturing processes, and storage conditions. This assessment should take into account any historical data on nitrosamine contamination and the chemical structure of the drug in question.
2. **Testing Requirements:** Once the risk assessment is complete, manufacturers are required to implement testing procedures to quantify the levels of nitrosamines in both active pharmaceutical ingredients (APIs) and finished drug products. The FDA and EMA provide detailed guidelines on how to perform these tests using validated analytical methods, such as gas chromatography-mass spectrometry (GC-MS) or high-performance liquid chromatography (HPLC). The results of these tests must be documented and reported to the regulatory authorities to demonstrate compliance with safety limits.
3. **Process Controls:** Regulatory bodies require that manufacturers establish robust process controls to minimize the risk of nitrosamine formation. This includes ensuring that raw materials are carefully selected to avoid any potential sources of nitrites or amines, optimizing the manufacturing process to reduce the likelihood of nitrosation reactions, and using specific solvents and reagents that do not contribute to nitrosamine formation. Process optimization may involve changes in temperature, humidity, and pH conditions to limit the chemical reactions that lead to nitrosamine generation.
4. **Monitoring and Continuous Improvement:** Regular monitoring of the production process is a critical requirement for manufacturers to maintain control over nitrosamine contamination. This includes periodic testing of finished products and APIs throughout the product lifecycle. Manufacturers are also encouraged to continually evaluate their processes and improve their control strategies, adopting new technologies and best practices to minimize nitrosamine risks as they arise.

By adhering to these regulatory guidelines, pharmaceutical manufacturers can ensure that their products remain safe



for consumers and compliant with industry standards, thereby minimizing the public health risks associated with nitrosamine contamination.

4. Process Controls and Raw Material Management

Role of Raw Material Quality in Preventing Nitrosamine Formation

Raw materials play a pivotal role in the formation of nitrosamine impurities during the manufacturing of pharmaceutical products. Nitrosamines are often formed when nitrogen-containing compounds, particularly amines, react with nitrites in the presence of favorable conditions such as high temperatures, acidic environments, or certain solvents. Therefore, the quality and selection of raw materials are essential to controlling nitrosamine contamination.

1. **Amines in Active Pharmaceutical Ingredients (APIs):** Many active pharmaceutical ingredients (APIs) contain amines or amine-like structures that can act as precursors for nitrosamine formation. For instance, secondary and tertiary amines in APIs can be readily susceptible to nitrosation when exposed to nitrites. These amines are commonly found in drugs used for chronic conditions, such as antihypertensives (e.g., valsartan) or gastrointestinal treatments (e.g., ranitidine). The presence of even trace amounts of these amines in raw materials used for API production creates a risk for nitrosamine formation.
2. **Nitrites in Raw Materials and Excipients:** Nitrites, either as contaminants or as added components (e.g., preservatives), can also contribute to nitrosamine formation. Some excipients, such as those used as stabilizers or antioxidants, may contain residual nitrites that could react with amines during the manufacturing process, leading to the formation of nitrosamines. Raw materials that contain elevated levels of nitrites must be carefully monitored to avoid unintentional nitrosation reactions.
3. **Contaminants and Impurities:** Raw materials may also carry other impurities that can facilitate the nitrosation process. These include trace amounts of residual chemicals from previous synthesis steps, solvents, or reagents used during the production of raw materials. Even very low levels of these impurities can contribute to the formation of nitrosamines, especially under certain environmental conditions during manufacturing. The presence of such impurities underscores the importance of sourcing high-quality raw materials and rigorously testing them before use in drug manufacturing.

Best Practices for Selecting and Testing Raw Materials to Minimize Risk

To minimize the risk of nitrosamine contamination, pharmaceutical companies must adopt best practices for raw material selection and testing. Implementing a thorough quality assurance program for raw materials is crucial in preventing nitrosamine formation at every stage of production.

1. **Supplier Qualification and Raw Material Sourcing:** One of the first steps in preventing nitrosamine contamination is to ensure that raw materials are sourced from qualified suppliers who adhere to stringent quality standards. Manufacturers should collaborate with suppliers to guarantee that raw materials are free from unwanted nitrite and amine contaminants. This may involve selecting suppliers who provide materials with documented testing results and certificates of analysis that confirm the absence of nitrosamine precursors. Additionally, ensuring that raw materials are manufactured under controlled conditions (such as low-temperature synthesis or minimal exposure to nitrites) is essential in reducing nitrosamine formation risks.
2. **Routine Testing for Nitrosamine Precursors:** Comprehensive testing should be conducted on incoming raw materials to check for both primary and secondary amines, as well as nitrites or other potential nitrosation agents. Using validated analytical methods, such as high-performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC-MS), manufacturers can measure the levels of amines and nitrites in the raw materials before they enter the production process. This testing ensures that only raw materials that meet the necessary quality standards are used, reducing the likelihood of nitrosamine formation.
3. **Batch-by-Batch Testing:** For particularly high-risk raw materials (such as amine-based ingredients or those with known nitrosation potential), batch-by-batch testing should be performed. This ensures that even small batches of raw materials with potentially elevated levels of contaminants are identified and addressed before they are incorporated into drug formulations. Testing should also be repeated periodically for raw materials that are used in large quantities or for long-term production runs.
4. **Ensuring Purity and Stability:** Raw materials should be tested for purity and stability over their shelf life to ensure they do not degrade into nitrosamine precursors during storage or transport. Manufacturers should ensure that raw materials are kept under optimal storage conditions (e.g., controlled temperature, humidity, and light) to maintain their integrity and avoid the formation of contaminants that could promote nitrosamine formation.



Process Modifications and Controls to Prevent Nitrosamine Contamination During Manufacturing

In addition to careful raw material selection, process modifications and controls are critical in minimizing the risk of nitrosamine contamination during drug manufacturing. Process optimization can prevent the conditions that lead to nitrosation reactions, ultimately ensuring the production of nitrosamine-free pharmaceutical products.

1. **Controlling Environmental Conditions:** One of the most effective ways to prevent nitrosamine formation is by controlling the environmental factors that contribute to nitrosation. These include temperature, humidity, and pH levels during various stages of production. High temperatures can accelerate chemical reactions, including the formation of nitrosamines, especially in drug substances containing amines. By optimizing the temperature conditions during synthesis and formulation, manufacturers can reduce the likelihood of nitrosamine formation. Additionally, humidity levels should be closely monitored during the storage and mixing of raw materials, as moisture can enhance the reactivity of certain chemicals.
2. **Minimizing Nitrite Exposure:** Nitrites are one of the primary reagents responsible for nitrosamine formation. To minimize the risk of nitrosamine contamination, it is essential to reduce the exposure of raw materials and drug substances to nitrites during the manufacturing process. This can be achieved by eliminating unnecessary use of nitrite-containing chemicals in formulation and manufacturing steps. Additionally, manufacturers should implement quality control measures to ensure that nitrite contamination in excipients and solvents is minimized. This may involve selecting nitrite-free raw materials or purifying solvents to remove nitrite traces.
3. **Process Design and Optimization:** The design of the manufacturing process itself is crucial in preventing nitrosamine contamination. This includes selecting appropriate solvents, catalysts, and reagents that do not contain nitrosamine precursors or facilitate nitrosation reactions. Process modifications may involve changing the sequence of operations to reduce the exposure time of amine-containing ingredients to potential nitrosating agents, such as nitrites. For example, using inert gases or vacuum environments during the synthesis or blending of raw materials can help reduce the possibility of nitrosation reactions. In addition, the introduction of certain chemicals, such as antioxidants, may help neutralize any free radicals or reactive nitrogen species that could facilitate the nitrosation process.
4. **Incorporating In-Process Controls:** In-process controls are essential for detecting any nitrosamine formation during the manufacturing process. Continuous monitoring of critical process parameters, such as pH, temperature, and humidity, should be implemented to ensure that the conditions remain within safe limits that minimize the risk of nitrosamine formation. This can be supported by in-line testing or sampling of intermediate products to detect the presence of nitrosamine impurities early in the process. If any nitrosamine is detected above predefined limits, immediate corrective actions, such as halting production or modifying process conditions, should be taken.
5. **Post-Manufacturing Testing:** After production, post-manufacturing testing of finished drug products for nitrosamine contamination is a critical control step. This testing ensures that the drug product is free from nitrosamine impurities before it is distributed to patients. Manufacturers should use validated analytical methods to confirm that nitrosamine levels in the final product are within the acceptable safety limits as outlined by regulatory authorities. These tests should be conducted on a routine basis and whenever there are changes to raw materials or the manufacturing process.

By implementing these process controls and modifications, manufacturers can significantly reduce the risk of nitrosamine contamination. Rigorous monitoring, thorough testing, and continuous improvements in process design will help ensure the consistent production of safe, nitrosamine-free pharmaceutical products that meet regulatory standards and protect public health

Conclusion

Preventing and controlling nitrosamine contamination in pharmaceutical manufacturing is of paramount importance to safeguard public health and ensure the safety of consumers. The primary sources of nitrosamine formation—raw materials, excipients, and manufacturing processes—demand careful oversight and stringent quality control measures. By understanding the role of amines and nitrites, implementing best practices for raw material selection, and optimizing manufacturing processes, pharmaceutical companies can minimize the risk of nitrosamine contamination. Regulatory bodies like the FDA, EMA, and ICH have established clear guidelines for testing, monitoring, and controlling nitrosamine levels, offering a framework for the industry to follow. Through diligent risk assessments, process modifications, and continuous improvements in raw material management, the pharmaceutical industry can reduce contamination risks and produce safer, higher-quality drugs for patients



worldwide.

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