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FDA Issues New Guidance on Nitrosamine Impurities in APIs and Drug Products

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On September 1, 2020, the U.S. Food and Drug Administration (FDA) issued Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs to provide the agency's current thinking on the issue of nitrosamine impurities in active pharmaceutical ingredients (APIs) and drug products. The Guidance describes what the FDA has learned from its investigation of nitrosamine impurities, the manufacturing conditions that have the potential to introduce these impurities, and the steps that manufacturers of APIs and drug products should take to prevent unacceptable levels of nitrosamine impurities. The Guidance also discusses risk assessment strategies to identify drugs[1] that may be at risk for the presence of these impurities.

Background

The FDA has been investigating the presence of nitrosamine impurities in certain drug products since 2018. The FDA is concerned about exposure to nitrosamine impurities above acceptable levels over long periods of time, which may increase the risk of cancer. The FDA became concerned about seven nitrosamine impurities that theoretically could be present in drug products: NDMA, NDEA, NMBA, NIPEA, NDIPA, NDBA, and NMPA. Five of these impurities (NDMA, NDEA, NMBA, NIPEA, and NMPA) have already been detected in drug substances or drug products.

The FDA's earlier investigations led to industry-wide recalls of valsartan and other "sartan" (losartan, irbesartan) angiotensin II receptor blockers (ARBs). More recently, the nitrosamine impurities findings have been extended to ranitidine, nizatidine, and metformin, leading to recalls of these drug products. In April 2020, the FDA requested that manufacturers remove all prescription and over-the-counter (OTC) ranitidine products (commonly known by its brand name, Zantac) from the market because preliminary findings from stability testing performed by the agency suggested that NDMA levels increase with storage time, especially if ranitidine is kept at room temperature.

In May 2020, the FDA requested another voluntary recall following further FDA testing, which revealed that certain lots of metformin extended-release formulation contained NDMA above the agency's recommended acceptable intake limit.

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[1] The Guidance applies to all chemically synthesized APIs, drug products containing chemically synthesized APIs, and drug products at risk due to other factors described in the Guidance, including compounded and OTC drugs.

Many manufacturers have communicated with the FDA on these issues, providing testing data, findings from investigations, and responses to additional requests for information, to address the agency's concerns regarding the risk of nitrosamine impurities. In this Guidance, the FDA for the first time provides comprehensive insight into its current thinking and recommendations for steps that manufacturers can take to prevent unacceptable levels of nitrosamine in drugs. This systemic, risk-based approach is consistent with the FDA's overall approach to risk management within the framework of the quality system.

Why Are Nitrosamine Impurities Present in APIs and Drug Products?

The Guidance describes the agency's current understanding of root causes for the presence of nitrosamine impurities in APIs, including the general conditions that lead to nitrosamine formation, the sources of contamination from secondary, tertiary, and quaternary amines that can form nitrosamine, vendor-sourced raw materials, recovered materials, quenching process, and lack of process optimization and control.

The Guidance also discusses excipients and degradation as sources of nitrosamine impurities in drug products other than API contamination.

Key Points from the FDA's Guidance

The Guidance provides the following recommendations for manufacturers of APIs and drug products to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products.

Acceptable intake limits

The FDA has established the acceptable intake limits for the following nitrosamine impurities: NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA. If more than one nitrosamine impurity is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the acceptable intake for the most potent nitrosamines) based on the maximum daily dose (MDD), the FDA requests that the manufacturer contact the agency for evaluation.

Risk assessment

The FDA recommends that API and drug product manufacturers consider the ways nitrosamines form and evaluate the risk for nitrosamine contamination or formation in their products, prioritizing evaluation of APIs and drug products based on factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated.[2]

Confirmatory testing

API and drug product manufacturers should perform confirmatory testing with suitable analytical methods when there is *any risk* for the presence of nitrosamine impurities.

Root cause investigation

If a nitrosamine impurity is detected in confirmatory testing, API and drug product manufacturers should investigate the root cause.

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[2] Another possible factor to consider, which is not mentioned in the Guidance, is whether the drug is used to treat vulnerable populations, such as infants or children, the elderly, or medically compromised individuals. Manufacturers should refer to the FDA's Guidance for Industry, Q9 Quality Risk Management (June 2006) for details related to quality risk identification, analysis, and management.

Process changes

API and drug product manufacturers should also implement changes in the manufacturing process to reduce or prevent nitrosamine impurities. The Guidance recommends a list of actions, including:

- For API manufacturers:
  - Optimizing the design of the manufacturing process for APIs during route of synthesis (ROS) development.
  - Auditing supply chains and monitoring them for any at-risk raw materials, starting materials, and intermediates.
  - Using recovered material only in the same step or in an earlier step (if there is sufficient purification) of the same process from which it was collected.
  - Developing an appropriate control strategy, which should include specification limits, if a nitrosamine impurity is detected above the limits of quantitation (LOQ).
- For drug product manufacturers:
  - Testing representative samples of all incoming components, before use.
  - Developing an appropriate control strategy, which should include specification limits, if a nitrosamine impurity is detected above the LOQ.
  - Contacting the FDA if drug product batches with unacceptable levels of nitrosamine impurities are already in distribution.

Report changes

API and drug product manufacturers should report changes implemented to prevent or reduce nitrosamine impurities in products to the FDA in accordance with applicable FDA regulations.[3]

Timelines

- For approved products – Manufacturers should conclude a risk assessment of approved or marketed products *before March 1, 2021*. Confirmatory testing should start when a nitrosamine risk is identified and begin immediately for high-risk products, and confirmatory testing of drug products and submission of required changes in drug applications should be concluded *before September 1, 2023*.
- For pending applications – Applicants with pending applications should conduct the risk assessment *expeditiously* and inform the FDA if confirmatory testing finds nitrosamine levels above the acceptable intake limit. If a nitrosamine impurity is detected above the LOQ but is within the acceptable intake limit, the applicant should amend the application as appropriate. For applications that have not yet been submitted, the FDA recommends that applicants conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed *before submission* of an original application.

While the Guidance is not legally binding, manufacturers that do not take the steps outlined in the Guidance bear the burden of demonstrating why an alternative approach is acceptable. If a manufacturer does not take the steps recommended in the Guidance, and does not establish controls that are adequate to prevent nitrosamine impurity

[3] This includes submission of any drug master file (DMF) amendments in accordance with 21 CFR 314.420(c) and changes to approved applications as required under 21 CFR 314.70 and 314.97 and pending applications under 21 CFR 314.60 and 314.96.

formation or contamination, there is a risk that drugs containing nitrosamine impurities could be released to the market. Drugs that are manufactured, processed, packed, or held in a manner that is inconsistent with current good manufacturing practices (CGMPs) are deemed to be "adulterated." The Federal Food, Drug, and Cosmetic Act prohibits introduction of adulterated product into interstate commerce.[4]

Recommendations

In response to the Guidance, both API and drug product manufacturers should take a systems-based approach to mitigate the risk of nitrosamine impurities.

Evaluation

API and drug product manufacturers should evaluate the steps that have already been taken to address the nitrosamine impurities concerns. A gap analysis should compare the recommendations in the Guidance to steps the manufacturer has already taken to determine what other actions need to be taken. This evaluation should be performed for *each individual API* in order to identify which APIs have the possibility of either forming or containing a nitrosamine impurity. The FDA's concerns extend beyond ARBs, ranitidine, nizatidine, or metformin (known risk), and the FDA notes that manufacturers should take a risk-based approach to prioritizing such evaluations based on factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated.

Plan

Based on this gap analysis, each manufacturer should develop and implement a plan that is anchored to the quality management system and that addresses each of the points in the Guidance. This plan will address the following fundamental questions:

- Does the API have the possibility of forming a nitrosamine impurity?
- Is it possible for a nitrosamine impurity to be introduced into the process?

Nitrosamine impurity risk mitigation plan

Below, we provide a high-level checklist for development of a nitrosamine impurity risk mitigation plan. This checklist is not all-inclusive, but it should give manufacturers a starting point for the development of their plans.

For each drug substance:

- Conduct an appropriate risk assessment using recognized quality risk management tools and taking into consideration appropriate risk factors.
- Review the **Supplier Qualification Program** to:
  - Ensure that vendors are also cognizant that impurities can be introduced during production or transport.
  - Monitor vendors for any at-risk raw materials, starting materials, and intermediates.
  - Request documented records of the name of the raw material manufacturer and its supplier and the roles of the actual manufacturers of such materials and any other supply chain entities that handle the materials before the API manufacturer.

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[4] Introducing adulterated product into the market can result in actions such as the issuance of an FDA warning letter or enforcement actions that can include seizure of product, civil injunctions, and criminal prosecutions.

  - Verify whether the purchased materials in their processes are recovered.
  - Determine whether to establish additional controls or revise specifications for at-risk materials.
- Evaluate **Incoming Materials**, including starting materials containing sodium nitrite, raw materials that may have previously been subject to contamination, fresh solvents, recovered solvents, including those comingled from different processes or across manufacturing lines, and potable water. Establish appropriate procedural controls for evaluation and rejection of materials that contain nitrosamine impurities.
- Identify **Lack of Process Optimization and Control**, including reaction conditions such as temperature, pH, and the sequence of adding reagents, intermediates, or solvents.
- Evaluate **Facilities and Equipment** to ensure adequate cleaning of equipment between customers, or between different materials, and that processes are validated as capable of removing impurities.
- Review of **Analytical Testing Methods** to ensure:
  - Established methods for which the LOQ and limit of detection (LOD) are as low as reasonably practical for products with a high maximum daily dosage.
  - Validated analytical methods for LOQs at or below 0.03 ppm.
  - A review of the FDA's validated laboratory methods used in assaying nitrosamine impurities in various drugs.
  - Confirmatory testing with suitable analytical methods when there is *any risk* for the presence of nitrosamine impurities.
- Evaluate **Laboratory Controls and Testing**, including:
  - If a nitrosamine impurity is detected in confirmatory testing, conduct a thorough investigation to determine the root cause.
  - Any reduced testing programs and consideration of release testing of every batch when there is any risk for the presence of nitrosamine impurities.
  - Upstream testing of intermediates.
  - Justification of process understanding and adequate statistical control to support testing.
- Analyze nitrite and nitrosamine levels in water and use water that has been purified to remove unacceptable impurities.
- Review of **Stability Testing** data to determine whether nitrosamine levels can increase over time to unacceptable levels.
- Develop an appropriate control strategy, which should include specification limits, if a nitrosamine impurity is detected above the LOQ.
- Review the **Manufacturing Process** to determine whether it is susceptible to nitrosamine formation, including factors such as:
  - The route of synthesis (ROS) of key starting materials.
  - The use of nitrites in the presence of secondary, tertiary, or quaternary amines.
  - Presence of amines added intentionally as reagents or catalysts (which can react with nitrosating agents to form nitrosamines).

- Quenching steps.
- The use of amide solvents that are susceptible to degradation under certain reaction conditions.
- Other reagents containing amine functional groups.

Note: If a nitrosamine impurity is detected in confirmatory testing and the root cause is not analytical error, design and implement corrective and preventive actions (CAPAs) in the manufacturing process to reduce or prevent nitrosamine impurities.

- Submit any DMF amendments or report any changes implemented to prevent or reduce nitrosamine impurities.

Finished dosage form (FDF) manufacturers should consider the applicable steps described above that impact their finished product and take the following additional steps to mitigate nitrosamine impurities:

- Assess the risk of nitrosamine impurities in APIs, marketed products, products subject to a pending application, and drugs in R&D.
- Submit any amendments to approved or pending applications or report any changes implemented to prevent or reduce nitrosamine impurities.

Preparation for questions from the FDA

Manufacturers should collect evidence for actions taken to mitigate the risk of nitrosamine impurities and be prepared to answer questions about these risk mitigation efforts in response to potential requests for information from the FDA.

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