WINSTON & STRAWN LLP

CLIENT ALERT

FDA Provides Guidance to Manufacturers for Controlling Nitrosamine Impurities in Human Drugs

SEPTEMBER 18, 2020

Earlier this month, the U.S. Food and Drug Administration (FDA or the Agency) issued extensive new guidance on the control of nitrosamine impurities in human drugs. Nitrosamine impurities are classified as probable human carcinogens and have unexpectedly been found in drugs such as angiotensin II receptor blockers, ranitidine, nizatidine, and metformin. Based on these findings, the Agency has concluded that a risk-assessment strategy for potential nitrosamines is necessary for any pharmaceutical product at risk for their presence. The guidance describes potential root causes of nitrosamine formation and recommends steps that manufacturers of active pharmaceutical ingredients (APIs) and drug products should take to detect and prevent unacceptable levels in pharmaceutical products.

See Control of Nitrosamine Impurities in Human Drug Guidance*, available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs.

Presence of Nitrosamine Impurities in APIs and Drug Products

FDA has gathered recent information that suggests several root causes of the presence of nitrosamine impurities in APIs:

- **General conditions**: (a) formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines and nitrite salts under acidic reaction conditions; (b) nitrites used as reagents in one step can carry over into subsequent steps, despite purification operations, and react with amines to generate nitrosamine impurities.
- Contamination in vendor-sourced raw materials.
- Recovered materials such as solvents, reagents, and catalysts may pose a risk of nitrosamine impurities due to the presence of residual amines.
- There is a risk of nitrosamine formation when a quenching[1] step is performed directly in the main reaction mixture. Lack of optimization of the manufacturing process for APIs when reaction conditions such as temperature, pH, or the sequence of adding reagents, intermediates, or solvents that are inappropriate or poorly controlled can lead to the formation of nitrosamine impurities.

FDA notes that multiple strategies may be necessary to identify all potential sources of contamination as typical routine tests for API purity, identity, and known impurities are unlikely to detect the presence of nitrosamine impurities.

As for nitrosamine impurities in drug products from sources other than API, nitrite impurities can be found in a range of commonly used excipients, which could lead to nitrosamine impurities forming in drug products during the manufacturing process and shelf-life storage period. FDA also highlights that nitrite and nitrosamine impurities may also be present in potable water.

FDA Recommendations

Because nitrosamines are probable or possible human carcinogens, FDA recommends that manufacturers consider the potential causes of nitrosamine formation as described below, as well as any other pathways observed, and evaluate the risk for nitrosamine contamination or formation in their APIs and drug products. Manufacturers should prioritize evaluation of APIs and drug products based on factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated.

1. FDA recommends the following acceptable intake (AI)[2] limits for the following nitrosamine impurities:

    a. NDMA – 96 ng/day

    b. NDEA – 26.5 ng/day

    c. NMBA – 96 ng/day

    d. NMPA – 26.5 ng/day

    e. NIPEA – 26.5 ng/day

    f. NDIPA – 26.5 ng/day

These limits are applicable only if a drug product contains a single nitrosamine. If more than one of the nitrosamine impurities is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day based on the maximum daily dose, the manufacturer is encouraged to contact the Agency for evaluation.

2. FDA recommends that API manufacturers review their API manufacturing processes and perform risk assessments to identify the potential for nitrosamine impurities. If a risk of nitrosamine impurities is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods. If a nitrosamine impurity is detected, API manufacturers should investigate the root cause. They should implement changes in the manufacturing process to reduce or prevent nitrosamine impurities.
3. Drug product manufacturers should conduct risk assessments to determine the potential for nitrosamine impurities in drug products. A risk assessment should involve collaboration with the API manufacturer to aid in the identification of the API during route of synthesis (ROS) or other process conditions of the API's manufacture that put the drug product at risk for nitrosamine impurities. The risk assessment should also include evaluation of any pathway (including degradation) that may introduce nitrosamines during drug product manufacture or storage. If a risk of nitrosamines in a drug product is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods and manufacturers should investigate the root cause and implement changes in the manufacturing process to mitigate or reduce nitrosamine impurities.

Maintaining Drug Supply and Reporting Changes to FDA

Manufacturers are encouraged to immediately notify the Agency if manufacturing changes or recalls are likely to lead to a disruption of drug supply. FDA reinforces its commitment to working with manufacturers to mitigate the risk of nitrosamine impurities in APIs and drug products while avoiding drug supply interruptions.

Drug manufacturers must report changes implemented to prevent or reduce nitrosamine impurities in accordance with FDA regulations. If an API drug master file (DMF) holder makes process changes in the ROS as a result of the

risk assessment and confirmatory testing, the DMF holder must submit amendments and inform each drug product manufacturer that references the DMF (including pending and approved applications), in accordance with 21 C.F.R. 314.420(c). If the API is manufactured by the applicant and not covered by a DMF, the manufacturer must report such ROS changes in the application in accordance with 21 C.F.R. 314.70 and 21 C.F.R. 314.97. If changes to the drug product are needed to prevent nitrosamine formation, application holders must submit a supplement to notify FDA of any changes to conditions established in the approved applications beyond the variations already provided for in their applications, as required by 21 C.F.R. 314.70 and 314.97. Holders of pending applications must update their applications through submission of an amendment according to 21 C.F.R. 314.60 and 314.96.

FDA recommends implementation timelines for risk assessment, confirmatory testing, and submission of required changes dependent on the regulatory status of the drug product:

1. **Approved or marketed drug products**: Manufacturers should conclude a risk assessment of approved or marketed products *within 6 months* of publication of the guidance. Confirmatory testing should start as soon as the risk of nitrosamine is identified and confirmatory testing of drug products and submission of required changes in drug applications should be concluded *within three years* of the date of publication of the guidance.
2. **Pending applications**: If in the pre-submission stage, applicants should conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed prior to submission of an original application. For applications pending with the Agency, FDA recommends that applicants conduct the risk assessment expeditiously and inform FDA if confirmatory testing finds nitrosamine levels above the AI limit. FDA notes that it will work with the applicant to resolve issues during the review cycle or immediately after approval, and before distribution, if determined to be necessary by the Agency.

FDA's guidance documents do not establish legally enforceable responsibilities; instead, the guidance describes the Agency's current thinking on a topic.

We note that government orders on the local, state, and federal levels are changing every day, and the information contained herein is accurate only as of the date set forth above.

****

For further information or questions on FDA's guidance and the Agency's expectations for manufacturers regarding the control of nitrosamine impurities in human drugs, please contact Amandeep S. Sidhu, T. Reed Stephens, Christopher Parker, or your Winston relationship attorney.

[1] *Quenching* involves a nitrous acid being used to decompose residual azide.

[2] The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure.

5 Min Read

Related Locations

Charlotte | Chicago | Dallas | Houston | Los Angeles | New York | San Francisco | Silicon Valley | Washington, DC

Related Topics

Health Care | Health Care Regulation | FDA

Related Capabilities

Health Care

Related Regions

North America

Related Professionals

Amandeep S. Sidhu

T. Reed Stephens

Christopher M. Parker