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FDA Compliance & Enforcement ADVISORY ■

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FDA Issues Notice on Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities and Requests Comments

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The Food and Drug Administration (FDA) announced today that it is requesting public comment on the identification, assessment, and control of N-nitrosamine drug substance-related impurities (NDSRIs). In the notice, the agency identified scientific and regulatory considerations and requested comments from stakeholders on these matters.

Background

While the FDA's investigation of the presence of nitrosamine impurities in drug products dates back to June 2018, it was not until more recently that the FDA began to focus on NDSRIs (a category of nitrosamines that are structurally similar to the active pharmaceutical ingredient (API) in drug products). The FDA first communicated the presence of NDSRIs to industry in November 2021 with its release of an update on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products.

NDSRIs can be formed during the synthesis, manufacture, and shelf-storage of drug products. These substances differ from the small molecule nitrosamine impurities that are identified in the FDA's Nitrosamine Guidance. Given that NDSRI formation can be triggered by part-per-million levels of nitrate impurities (such as those found in commonly used excipients and in water), a large number of drug products are now known to be at risk for nitrosamine formation.

In its first notice to industry concerning the presence of NDSRIs, the FDA directed manufacturers to use the same processes identified in the FDA's existing Nitrosamine Guidance for identifying the presence of NDSRIs. The FDA also discussed potential mitigation strategies and encouraged the development of control strategies or design of approaches to reduce NDSRIs to acceptable levels, or to eliminate these impurities.

The FDA has acknowledged that "NDSRIs present unique scientific and regulatory challenges for FDA because each NDSRI is unique to the API, and there is limited compound-specific data that is available to inform safety assessments." The FDA has been working to advance the use of predictive toxicology (e.g., (Q)SAR methodologies) to assess potential mutagenicity and carcinogenicity of NDSRIs. Nevertheless, to date, the FDA has only published acceptable limits based on available safety data for a small percentage of NDSRIs.

The identification of NDSRIs has implications for new and pending drug applications. For example, due to confidentiality issues, there are constraints on the impurity data that the FDA can disclose, leading to potentially duplicative non-clinical testing and supply chain disruptions. To avoid these issues, the FDA has published information and research that it has generated to support the development of acceptable limits for NDSRIs. The FDA has also encouraged collaboration among stakeholders and international regulatory agencies in the development of such information, including publication of scientific research and test results. This request for collaboration among stakeholders is reiterated in the recent notice.

Notice Highlights

The FDA is now requesting comments from the public on scientific and regulatory considerations related to the identification, assessment, and control of NDSRIs in drug products, including areas that the FDA believes may benefit from collaborative efforts. More specifically, as stated in the notice, the FDA is seeking comments from the stakeholders in response to three general topics:

- Factors to consider when prioritizing the evaluation of NDSRIs on a compound-specific basis.
- Mitigation strategies that the FDA should consider for reducing NDSRI formation or eliminating these impurities (where feasible).
- Additional topics related to the evaluation of nitrosamines that the FDA should prioritize addressing through guidance documents.

In addition to these general topics, the FDA included in the notice that it is particularly interested in comments on NDSRI risk assessment and acceptable intake (AI) limits.

NDSRI risk assessment

- Scientific and technical factors that the FDA should consider in developing best practices for conducting testing for NDSRIs (e.g., Ames test, enhanced Ames test, follow-up in vitro mutagenicity, in vivo transgenic gene mutation test) in support of establishing AI limits.
  - Other tests (and methods) recommended for assessing mutagenic potential of NDSRIs.
  - Usefulness of "short-term" carcinogenicity testing (e.g., six-month transgenic mouse model) for evaluating risk associated with NDSRIs, as well as the pros and cons associated with such testing.
  - Studies that may further inform the FDA about the risk associated with NDSRIs (e.g., in vitro/in vivo metabolism, DNA biomarkers, identification of reactive intermediates).
- Whether an extension of the recommended timeline for confirmatory testing of drug products and submission of required changes in drug applications (from October 1, 2023 to June 1, 2024) would allow for the additional assessment of NDSRIs and enable collaborative efforts among applicants.
- How the FDA can support manufacturers' efforts toward completion of such confirmatory testing.

AI limits

- How the FDA can facilitate collaborative efforts to generate reliable compound-specific data on NDSRIs, reducing the need for additional (and potentially duplicative) testing.

- Obstacles that industry has encountered when engaging in collaborative efforts that could allow companies to share data to assess the safety of NDSRIs, particularly with the intent of reducing redundant testing and integrating the 3R principles, as well as ways that the agency can help stakeholders overcome these obstacles.
- Difficulties manufacturers or suppliers have experienced in meeting recommended AI limits that have led to discontinuation of manufacturing or distribution of drug products.

Our Recommendations

This notice reflects the fact that the identification, assessment, and control of nitrosamine impurities in drug products remains a priority for the FDA. As the regulatory framework in this space is still under development, clients should consider sharing their perspectives on the topics outlined above to assist the FDA in developing appropriate guidance for industry. Alston & Bird's FDA Compliance & Enforcement Team is available to assist in drafting comments in response to the FDA's request for information. The deadline for submission of comments is **July 3, 2023**.

Clients with issues that require confidential communications with the FDA should correspond with the FDA separately on those issues. Our team is also available to assist with those communications.

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If you have any questions, or would like additional information, please contact one of the attorneys on our **FDA Compliance & Enforcement Team**.

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