Dr. BM Rao
C.E.O
QDOT Associates
Hyderabad
drbmrao@qdotassociates.com

Nitrosamine Impurities and NDSRIs

- Current Regulatory Updates

*This is in continuation of the articles published in December 2021, July 2022 and in February 2023 in **CuttingEdge**. In the past five months there were few important updates on Nitrosamine impurities / NDSRIs from key regulatory agencies. Comprehensive summary of updates was covered in this article.*

This article covers the information related to:

A. *FDA: Federal register Volume 88, No. 86, May 4, 2023-Information related to Nitrosamines page 28557 to 28562.*
B. *Update from European Directorate for the Quality of Medicines & HealthCare (EDQM); Submission of Nitrosamine impurity risk assessment*
C. *Updates from EMA, 30 March 2023, EMA/409815/2020 Rev.15*
D. *Updated guidance from ANVISA, Brazil: Nitrosamine Control Guide at Active Pharmaceutical Ingredients and Medicines, Guide No. 50/2021 - Version 3*
E. *Updated guidance from Health Canada: April 2023, Health Canada, Guidance on nitrosamine impurities in medications.*

A. FDA Issues notice on "Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities (NDSRIs) and requests comments".

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 nitrite impurities (such as those found in commonly used excipients and in water), many drug products are now known to be at risk for nitrosamine formation.

On May 4th, 2023, 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.

Highlights of FDA Notice

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.

Risk assessment for NDSRIs

- 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.

Acceptable Intake (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.

FDA's Ongoing Work on Nitrosamine Risk Assessment and Mitigation

FDA explains that it has continued to work to understand the root causes of nitrosamines and develop mitigation strategies for the presence of nitrosamines. In line with this work, FDA has published two examples of mitigation strategies related to formulation design on its website. The first was derived from reports that 'commonly used antioxidants, such as ascorbic acid (vitamin C) or alpha tocopherol (vitamin E), inhibit the formation of nitrosamines *in vivo*, based on data from human gastric fluid *in vitro* studies.' The second was 'based on the fact that the formation of nitrosamines typically occurs under acidic conditions, whereas, in a neutral or basic environment, the kinetics of these reactions are significantly reduced.' Incorporating antioxidants and excipients that keep the pH neutral or basic are strategies that applicants should consider employing to mitigate the risk of nitrosamine formation.

Collaborative Efforts to Develop NDSRI Data

FDA describes its role collaborating with applicants, stakeholders, other regulators, multi-laboratory projects, and model developers and stakeholders to advance predictive toxicology over the course of the investigation into nitrosamine impurities. For example, FDA mentions its collaboration on multi-laboratory projects being organized by the Health and Environmental Sciences Institute's Genetic Toxicology Technical Committee (HESI GTTC). In the FRN, the Agency also identifies the development of laboratory test methods to identify NDSRIs as an area that could benefit from collaboration. Furthermore, the Agency encourages applicants to publish scientific research and test results to further scientific knowledge on NDSRIs and facilitate regulatory decision-making.

Summary and expectation

FDA 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, Marketing Authorization Holders (MAH's) should consider sharing their perspectives on the topics outlined above to assist the FDA in developing appropriate guidance for industry. The deadline for submission of comments is July 3, 2023.

B. Updates from European Directorate for the Quality of Medicines & HealthCare (EDQM)

Submission of Nitrosamine impurity risk assessment: Call for review

For existing Certification of suitability to the monographs of the European Pharmacopoeia (CEPs), an assessment of the risk for nitrosamines formation is required to be made, using quality risk management principles, as outlined in the ICH Q9 guideline. The principles described in the ICH M7 guideline and Questions and Answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products EMA/409815/2020, in relation to toxicology assessment, control strategy and changes to the manufacturing process for active substances used in human medicinal products, should be applied. Where no risk is identified, EDQM does not have to be informed however companies may decide to introduce the risk assessment in their CEP dossier *via* a minor revision.

Where a risk is identified, the companies should inform EDQM of the risk and of the plan and timescales to introduce any required changes to reduce the risk, such as amendment of the manufacturing process or changes to specifications and introduction of controls. Confirmatory testing should be carried out using appropriately validated and sensitive methods and EDQM should be informed immediately, i.e., before submitting a revision application, if the tests confirm the presence of a nitrosamine impurity, irrespective of the amount detected, and the test results should be provided.

CEP holders should apply for a revision to their application(s) in a timely manner to introduce the required changes. Revision applications for existing CEPs should be submitted at the latest by 1 October 2023 or at an earlier time if otherwise justified.

Requests for revision and risk for nitrosamines

Any request for revision should address the risk of nitrosamine contamination if the revised process modifies or introduces such a risk (e.g., new route of synthesis or new risk identified).

A risk assessment for nitrosamine impurities should be submitted at renewal of the CEP if it has not already been submitted. A risk assessment for nitrosamine impurities should be submitted for a sister file. EDQM reminds CEP holders that they should provide the appropriate information relating to the risk evaluation they have performed for their CEP to their customers in all cases (even if no risk has been identified) such that the Marketing Authorisation Holders can use this information to fulfil their responsibilities for the respective medicinal products.

C. EMA Update, 30 March 2023, EMA/409815/2020 Rev.15:

In the last article published in **CuttingEdge** in February 2023, EMA updates EMA/409815/2020 Rev.14 were covered with examples. With recent updates to its Q&A on nitrosamines (EMA/409815/2020 Rev 15 – 30 March 2023), an amendment of Q&A 22 (What is the approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation?) has been made to indicate that no variation is required to be submitted to implement interim limits above the acceptable intake (AI) during CAPA implementation. The use of interim limits based on a less than lifetime (LTL) approach is a supportive measure to minimise supply disruptions, recognising that implementation of changes to mitigate the presence of identified N-nitrosamine(s) below the established acceptable intake (AI) may take some time. Marketing authorisation holders (MAHs) should still act without delay.

D. Updated guidance from ANVISA, Brazil, June 2023:

ANVISA has recently released version 3 of the Guide on the Control of Nitrosamines in Active Pharmaceutical Ingredients and Medicines Guide No. 50/2021 - version 3 (IN FORCE AS OF 13, June 2023). ANVISA's publication demonstrates the regulatory body's commitment to monitoring scientific and regulatory developments, ensuring the safety and quality of medicines available on the Brazilian market. This update is extremely important for the pharmaceutical industry, and everyone involved in drug production, as nitrosamines have been the subject of increasing concern.

1. The guide brings several relevant updates, one of which is the expanded table with limits for twenty-eight nitrosamine impurities/NDSRIs. This table is a valuable resource for ensuring drug safety and assisting companies in identifying and controlling these potentially harmful substances. With established limits, it is possible to implement preventive measures and ensure the quality of pharmaceutical products.
2. Another important highlight is subject code 12194 (Safety Assessment for Nitrosamines). This channel will allow companies to report the identification of new nitrosamines and request the definition of specific limits through a protocol in the Solicita system.

In addition to the above, the information contained in ANVISA's Guideline is indeed aligned with what is stated in EMA/409815/2020 Rev.15. Both documents highlight two acceptable approaches for determining limits in cases where multiple nitrosamines are present, to ensure that the acceptable risk level of 1:100,000, as outlined in the ICH M7(R1) guideline, is not exceeded.

The two approaches are as follows:

1. The total daily intake of all identified N-nitrosamines should not exceed the Acceptable Intake (AI) of the most potent N-nitrosamine identified.
2. The total risk level calculated for

Nitrosamine impurity	AI (ng/day*)
N-nitroso-mefenamic acid	78000
N-nitroso-diphenylamine	78000
N-nitroso-diethanolamine (NDELA)	1900
N-nitroso-paroxetine	1300
N-nitroso-fluoxetine	100.0

Table 1: *Acceptable Intakes for five additional nitrosamine impurities*

all identified N-nitrosamines should not exceed 1 in 100,000.

These approaches aim to maintain a level of risk within the acceptable range and ensure the safety of the products in question. This initiative strengthens cooperation between the industry and ANVISA, streamlining the evaluation process and ensuring an adequate response to new discoveries.

E.Health Canada Update: April 2023, Health Canada, Guidance on nitrosamine impurities in medications.

An updated version of the Guidance on nitrosamine impurities in medications has been posted online on April 17, 2023. The updated guidance document includes established Acceptable Intakes for five additional nitrosamine impurities (see Table 1) and further guidance on general and quality related information.

* Limit to be applied to maximum daily dose (MDD) of the drug product

The key other update related to Q20 is as follows,

- ~ Risk assessments for the potential presence of nitrosamine impurities as part of the expected content for new submissions are also applicable for DINAs, DIBNs, Supplements, Notifiable changes, and Post-DIN (Drug Identification Number) Changes submissions, apart from New Drug Submission (NDSs), Abbreviated New Drug Submissions (ANDSs).
- ~ The summary and discussion of the risk assessment for the drug product is expected to include sufficient detail to allow Health Canada to assess the adequacy and robustness of the risk assessment. It should include a discussion of the risk factors and potential root causes considered in relation to specific knowledge of the drug product and its components (including the API). Checklists lacking sufficient discussion and detail should be avoided.

Conclusion

The presence of N-nitrosamines in drug products can be a potential health concern. Some N-nitrosamines and complex nitrosamines may increase the risk of cancer if people are exposed to them above acceptable intake limits and over long periods of time. Nitrosamine impurities can disrupt drug supply chains and even lead to shortages resulting from product recalls and withdrawals. Industry and regulators grapple with challenges in both nitrosamine detection and control. More recently discovered Nitrosamine Drug-Substance Related Impurities (NDSRIs) have further complicated the issue. Since the recent findings of N-nitrosamines in some types of drug products and considering their potential harmful effects to human health, regulatory agencies and drug manufacturers have been working continuously to understand the root causes of N-nitrosamine formation, assess the risks of N-nitrosamines, for human health, and take appropriate actions to reduce or prevent the presence of N-nitrosamines in active pharmaceutical ingredients (APIs) and drug products. Key regulatory agencies like FDA, EMA, Health Canada, ANVISA etc. are constantly updating the guidelines and providing directions to the drug manufacturers to ensure that right quality of medicines that are safe and effective will reach out to the patient.

References

- *Spinco Biotech, Cutting Edge, December 2021, Dr BM Rao 'Nitrosamine impurities – Current regulatory status'*
- *Spinco Biotech, Cutting Edge, July 2022, Dr BM Rao "N-Nitrosamine impurities – Recent updates and expectations from regulatory agencies"*
- *Spinco Biotech, Cutting Edge, Feb 2023, Dr. Ranjana Pathak and Dr BM Rao Nitrosamine Impurities & Nitrosamine Drug Substance-Related Impurities (NDSRIs) – Recent regulatory updates*
- *https://www.federalregister.gov/documents/2023/05/04/2023-09526/identification-assessment-and-control-of-nitrosamine-drug-substance-related-impurities-in-human-drug*
- *FDA Issues Notice on Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities and Requests Comments by Cathy Burgess, Ashley Yull, and Anthony Fanucci*
- *https://www.edqm.eu/en/submission-of-nitrosamine-impurity-risk-assessment*
- *EMA, 30 March 2023, EMA/409815/2020 Rev.15, Questions, and answers for marketing authorisation holders/ applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.*
- *Guidance on nitrosamine impurities in medications, Evaluating and managing the risks of N-nitrosamine impurities in human pharmaceutical, biological and radiopharmaceutical products, Date Adopted: April 17, 2023, Effective Date: April 17, 2023*
- *Nitrosamine Control Guide at Active Pharmaceutical Ingredients and Medicines, Guide No. 50/2021 - version 3 (https://nitrosamines.usp.org/t/guideline-anvisa-brazil-version-3-updates/6411/3).*
- *USP: Nitrosamines Exchange: A knowledge-based community for all-things Nitrosamine*