VIA ELECTRONIC SUBMISSION

June 30, 2023

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-FDA-2023-N-1585 for "Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products; Establishment of a Public Docket; Request for Comments."

Dear Sir/Madam,

On behalf of the United States Pharmacopeia (USP), I appreciate the opportunity to provide comments to the Food and Drug Administration's (FDA) Request for Comments on the Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products. USP is an independent, scientific, global non-profit organization founded in 1820 and dedicated to building trust where it matters the most: in the world's medicines, dietary supplements, and foods through rigorous science and public quality standards.[1] USP is governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry communities, as well as dozens of government agencies, who together comprise the USP Convention.[2]

Since nitrosamine impurities were originally detected in anti-hypertensive drugs in 2018, they have been found in other commonly used medicines, and more recent drug recalls have been due to the sub-category of nitrosamine impurities known as nitrosamine drug substance-related impurities (NDSRIs). This has led to a major effort by industry, regulators, and stakeholders to reduce or eliminate their presence in the drug supply and help ensure the quality and safety of medicines for patients.

USP supports the efforts by the FDA to minimize the public health risk caused by the presence of these potential carcinogenic impurities and welcomes the opportunity to collaborate with and convene stakeholders from FDA and industry to address the scientific and regulatory challenges associated with NDSRIs. USP believes that the development and adoption of quality standards as well as tools and resources that enable information sharing and help to build a foundational knowledge base about the formation, identification, and mitigation of nitrosamines and NDSRIs can help regulators and stakeholders address these pressing challenges. Please see below our response to specific portions of the request.

A. General Questions

- **Other Considerations under General Questions**

Quality standards support identification, assessment, and control of NDSRIs.

[1] USP standards are developed by Expert Bodies comprised of more than 750 scientific experts and in close collaboration with stakeholders and government agencies, including more than 100 staff from the U.S. Food and Drug Administration (FDA) who participate as Government Liaisons to USP's Expert Committees and Expert Panels. These experts collaborate to develop USP standards through an open, transparent process, offering the ability to adjust standards to confront public health emergencies, adapt to new industry practices, and keep up with evolving science and technology.

[2] USP's governing bodies in addition to the Council of the Convention include its Board of Trustees and Council of Experts.

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Impurities are a typical byproduct in drug development and manufacturing, and NDSRIs can be generated during manufacturing or during the shelf-life storage period of a drug product. Having a strategy for identifying, evaluating, and minimizing the presence of impurities is vital to helping ensure product safety, efficacy, and quality throughout the product lifecycle. As part of this strategy, there is a need for quality standards to support the testing, monitoring, and control of nitrosamine impurities.

In response to the initial detection of nitrosamine impurities in drug products, USP formed a Joint Subcommittee which included members from several Expert Committees and government liaisons from FDA and European Pharmacopeia to develop standards for the control of nitrosamine impurities. USP relies on the collaboration of expert volunteers from academia, industry, regulatory, and healthcare fields who serve on USP's Council of Experts and expert committees and panels and contribute their individual expertise and knowledge in the standards setting process. The result of these efforts, General Chapter <1469> *Nitrosamine Impurities,* was published in the *USP-NF* and provides a science and risk-based approach to help manufacturers identify possible sources of nitrosamines in drug products, their components, and their manufacturing processes. It also provides recommendations on risk assessments and test methods for quantifying nitrosamines in products.

USP is considering how standards may be updated or developed to support manufacturers and regulators in addressing challenges with simple nitrosamine impurities and NDSRIs. This future work plan may include revisions to General Chapter <1469>, or potentially the development of new chapters, to provide further guidance as needed by stakeholders. Other standards, such as monographs, may be developed or modified to incorporate simple nitrosamines or NDSRIs based on new and relevant data or specific needs, along with General Chapters. USP welcomes input on the development of these chapters from stakeholders, including FDA, as well as FDA engagement with USP to identify potential priority areas for standards development.

Reference standards and other physical reference products can be beneficial to support testing and control of nitrosamine impurities.

Industry stakeholders have expressed a need for high-quality, reliable materials for analytical testing and studies, including product-specific methods and limits for NDSRIs. USP has developed eight[3] highly characterized nitrosamine Reference Standards for use with the methods described in General Chapter <1469>. Additionally, USP's line of pharmaceutical analytical impurities (PAIs) can be used in analytical testing along with USP's official documentary standards to benchmark pharmaceutical products. PAIs are released through a USP quality process developed by USP's subject matter experts and designed to help ensure identity and quality appropriate for analytical applications; currently there are more than 200 impurities and more in development.

PAI products are not required for compendial compliance and are different from official USP Reference Standards, but together, PAIs and official Reference Standards can be used for research and analytical needs across the drug lifecycle such as analytical testing during early formation feasibility studies; testing for and profile impurities not listed in drug substance and drug product monographs; develop, validate, and transfer analytical methods; and determine degradation impurities produced during stress studies. Nitrosamine Reference Standards and/or USP's PAI products may potentially be used in conducting in-vitro toxicity studies to establish safe dose and help industry and regulators derive safe limits.

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[3] Reference standards include *N*-Nitrosodimethylamine; *N*-Nitrosodiethylamine; *N*-Nitrosodiisopropylamine; *N*-Nitrosodibutylamine; *N*-Nitrosoethylisoproplamine; *N*-Nitrosomethylaminobutyric; *N*-Nitrosomethylphenylamine; and Deutero *N*-Nitrosomethylamine

B. NDSRI Risk Assessment

- **Other considerations under NDSRI Risk Assessment**

A quality-centered, uniform approach to risk assessments.

In 2020, FDA released a Guidance for Industry, *Control of Nitrosamine Impurities in Human Drugs*. In the guidance, FDA recommended API (active pharmaceutical ingredient) and drug product manufacturers should take certain steps to mitigate nitrosamine impurities in their products, including conducting risk assessments in a timely manner based on the prioritization of drugs but did not recommend requiring manufacturers to submit risk assessment documents to FDA.[4] The guidance was updated in 2021 to specify timeframes for completion of nitrosamine mitigation activates by manufacturers.

The FDA is seeking comments on scientific and technical factors to consider in developing best practices for conducting testing for NDSRIs in support of establishing acceptable intake limits (AIs). Approaches toward risk assessments are likely to differ from manufacturer to manufacturer resulting in variability in content. **USP recommends establishing a best practices approach to risk assessment that ensures a quality-centered and uniform approach and would welcome the opportunity to facilitate a discussion between regulators and stakeholders to identify common challenges and potential solutions.**

C. Collaborative Efforts to Develop NDSRI Data and Establish and Implement Recommended AI Limits

1. How can FDA facilitate collaborative efforts to generate reliable compound-specific data on NDSRIs and reduce the need for additional and potentially duplicative testing?

Continual engagement, learning opportunities, and technical assistance can help to address uncertainties and bolster coordinated efforts among stakeholders and regulators.

The discovery of NDSRIs in drug products has added another layer of complexity and underscores the ambiguous and evolving environment of nitrosamine impurities. Stakeholders experience numerous challenges including the lack of availability of toxicity data and acceptable intake limits for NDSRIs. Where research has been generated, it is not always contained in a centralized, accessible location.

Recognizing that there is a need for stakeholders to share up-to-date information, identify emerging trends, and learn from each other's experiences, USP launched the Nitrosamines Exchange. USP's Nitrosamines Exchange is an open-access platform and online community where over 3,200 members from more than 80 countries around the world share updates, learning, challenges, and solutions. The platform also allows participants to translate and post in multiple languages. The Exchange was launched less than two years ago but has already yielded collaborative research, problem-solving, and relationship-building.

Also housed within the Nitrosamines Exchange is the Nitrosamines Analytical Hub, a public online repository containing non-compendial analytical procedures for the testing of nitrosamine impurities and related substances curated by USP's science staff through internal development and validation or through scientific review of donated materials. The procedures published in the Analytical Hub can help fill gaps in users' knowledge about how nitrosamine impurities form and which analytical methods are most suitable for specific

[4] Food and Drug Administration. Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry. February 2021.

products. Access to this type of information in real-time is critical for addressing problems efficiently and quickly, and to eventually look toward more proactive approaches.

Web-based forums like the Nitrosamines Exchange and Nitrosamines Analytical Hub are effective settings to reach a broad group of diverse stakeholders who can share and collaborate in a neutral venue from a trusted source. Additionally, opportunities to disseminate educational resources, such as on-demand webcasts, video tutorials, toolkits, focused discussion groups and trainings for stakeholders that may be impacted by nitrosamines would be helpful in providing context and facilitate understanding of scientific issues and regulatory expectations from FDA and international regulators.

Collaboration among international regulators, industry, and other stakeholders is important to a coordinated approach to reducing the risk of simple nitrosamine impurities and NDSRIs in medicines.

Given the global nature of the pharmaceutical supply chain, collaboration among international regulators and global stakeholders, including pharmacopeias, it is needed to encourage information sharing and alignment of tests and procedures. USP is exploring how to best work with international health bodies to help ensure the quality of vital medicines and address challenges related to product-specific nitrosamines, including nitrosamine drug substance related impurities. USP is also planning to initiate discussions with the European Pharmacopeia and the Japanese Pharmacopeia on harmonization of existing standards related to nitrosamines and prospective development of new standards (such as nitrites in excipients) under the scope of the Pharmacopeial Discussion Group workplan.

USP is developing analytical procedures for determination of nitrates and nitrites in certain excipients to help manufacturers select excipients having low levels of nitrites as part of their risk mitigation strategies. USP is also planning to analyze certain excipients of different manufacturers and different batches to collect data on actual levels of nitrates and nitrites. USP can share the range of nitrate and nitrite results in the Analytical Hub as an Application Note and with FDA, if needed. USP is considering collaboration with software vendor/s to explore application of these in-silico tools to help us predict toxicity, identify potential surrogates for NDSRIs and inform tentative AIs. USP can also collaborate with research/ academic institutions to conduct relevant in-vitro toxicity studies using PAIs synthesized at USP India lab to correlate results with the predicted AIs and confirm genotoxicity.

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USP appreciates the efforts of FDA to address the identification, assessment, and control of NDSRIs in pharmaceutical products. We stand ready to assist FDA in identifying and developing suitable tools, resources, and supports needed by industry and regulators to help protect the quality and safety of medicines for patients. For more information, please contact Carrie A. Harney, Vice President, U.S. Government and Regulatory Affairs CXH@usp.org or (202) 239-4136.

Sincerely,

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