VIA ELECTRONIC SUBMISSION

November 10, 2020

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

Re: Docket No. FDA-2020-D-1530; Control of Nitrosamine Impurities in Human Drugs; Guidance for Industry

Dear Sir/Madam,

The United States Pharmacopeia (USP)[1] appreciates the opportunity to comment on the Food and Drug Administration's (FDA or the Agency) Guidance for Industry, *Control of Nitrosamine Impurities in Human Drugs.*

We commend FDA on the issuance of this guidance to help drug product and active pharmaceutical ingredient (API) manufacturers detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products. USP supports the Agency's efforts to minimize the public health risk caused by the presence of these potential carcinogenic impurities. USP is committed to working with industry, FDA, and other regulators to assist API and finished drug product manufacturers in proactively identifying materials that could potentially contain these impurities. USP is working to provide stakeholders with tools, such as analytical methods to detect nitrosamine impurities, and recommendations on control strategies which can be utilized to reduce or prevent the possible presence of nitrosamine impurities in APIs and finished drug products.

Since nitrosamine impurities were initially found in angiotensin II receptor blockers, USP has been working with its volunteer experts to develop solutions to mitigate this risk to public health. USP formed a Joint Subcommittee, which includes members from our Chemical Analysis, Chemical Medicine 2, and Chemical Medicines 3 Expert Committees, to develop standards for the control of nitrosamine impurities. On September 1, 2020, USP published the proposed General Chapter <1469> *Nitrosamine Impurities* based on the work of the Joint Subcommittee. The proposed chapter is currently open for public comment until November 30, 2020.[2] We encourage the Agency and other stakeholders to provide feedback on this proposed general chapter.

[1] USP is an independent, scientific, nonprofit organization dedicated to improving public health for medicines, foods, and dietary supplements. USP public standards are developed through an open, transparent, expert-based process, offering the ability to confront public health emergencies, adapt to new industry practices, and support evolving science and technology.

[2] Proposed USP General Chapter <1469> *Nitrosamine Impurities* is posted in the Pharmacopeial Forum (PF) 46(5) [Sept.-Oct. 2020]. To submit comments, *see* https://www.uspnf.com/pharmacopeial-forum/pf-table-contents.

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The objective of this proposed chapter is to provide a science and risk-based approach for the control of nitrosamine impurities to eliminate or reduce their presence in finished drug products and APIs, thereby helping to ensure the quality of the drug product or API. The proposed USP chapter recommends utilization of a risk assessment and control strategy to identify potential sources and mitigate the risks of nitrosamine impurity formation or presence in finished drug products and APIs. Additionally, the proposed chapter provides specific analytical methods and test method performance characteristics. The proposed chapter also includes links to testing methods from FDA and the European Directorate for the Quality of Medicines & Healthcare. At this time, USP has no plans to update individual drug product or drug substance monographs with regard to information on nitrosamines.

In addition to the development of a proposed general chapter, USP released six new reference standards[3] for nitrosamine impurities in June 2020. These reference standards include: N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosodiisopropylamine (NDIPA), N-Nitrosodibutylamine (NDBA), N-Nitrosoethylisopropylamine (NEIPA),[4] and N-Nitrosomethylaminobutyric Acid (NMBA).[5] USP notes that FDA's guidance identifies a seventh nitrosamine impurity, N-nitrosomethylphenylamine (NMPA). USP has not yet developed a reference standard for NMPA and did not include it in the proposed General Chapter <1469> *Nitrosamine Impurities*. However, based on the inclusion of NMPA in FDA's guidance, USP will consider future revisions to the chapter and expansion of its portfolio of nitrosamines impurity reference standards.

USP continues to support FDA in addressing the detection and prevention of unacceptable levels of nitrosamine impurities in pharmaceutical products. We welcome the opportunity to work with FDA to help protect the public from potential exposure to unsafe levels of nitrosamines.

Thank you again for the opportunity to comment. For more information, please contact Marissa Chaet Brykman, Esq., Director, U.S. Regulatory Policy, at marissa.brykman@usp.org; (301) 692-3660.

Sincerely yours,

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[3] Physical reference standards are used in conjunction with documentary standards, including general chapters, to verify that a medicine and its ingredients can pass tests to ensure adherence to quality requirements.

[4] We note that the FDA guidance lists this impurity name as N-Nitrosoisopropylethylamine.

[5] We note that the FDA guidance lists this impurity name as N-Nitroso-N-methyl-4-aminobutyric Acid.