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USP Proposes Analytical Methods For Drug Makers To Detect Nitrosamine Impurities

by Joanne S. Eglovitch

The USP has launched an initiative to address the nitrosamine crisis by proposing a new general chapter that outlines a set of analytical methods that manufacturers can use to demonstrate their products are free from unsafe levels of these potential carcinogens. The chapter is aligned with the FDA's guidance on nitrosamine impurities.

The USP has proposed guidance on how to test active pharmaceutical ingredients and drug products for nitrosamine impurities, which have been discovered in a growing array of blood pressure medications and other pharmaceuticals.

The USP general chapter was proposed the day the US Food and Drug Administration issued guidance on controlling nitrosamines in all drug products. (Also see "*US FDA Expectations For Removing Nitrosamines From All APIs, Drug Products*" - Pink Sheet, 1 Sep, 2020.) Both are aligned in that they target a similar list of nitrosamine impurities and espouse a risk-based approach to evaluating them. The USP chapter also defers to the daily acceptable intake limits the FDA set for nitrosamine impurities.

The USP guidance was issued in response to the 2018 discovery of carcinogenic nitrosamines in active pharmaceutical ingredients for certain blood pressure medicines known as angiotensin II receptor blockers or sartans. This led to discovery of nitrosamine impurities in other medicines such as ranitidine and metformin. These drugs have been the source of numerous recalls and multiple warning letters and import alerts.

USP senior science official Jaap Venema and senior director of chemical medicines Edwin Gump recently discussed some of the elements of the proposed new general chapter <1469> with the *Pink Sheet*.

Alarm Bells Went Off

Venema said the USP ramped up its efforts promptly to address the crisis when nitrosamines were detected in angiotensin II receptor blockers and later on in the additional types of medicines. “This set off a lot of alarm bells, so we quickly convened our efforts and staff and we met with FDA to take of care of this.”

In July 2020, USP launched a broad-based outreach program to provide more direction to pharmaceutical manufacturers on preventing supply chain vulnerabilities relating to nitrosamines. It released six new reference standards to support manufacturers and regulators in analyzing and monitoring potential harmful N-nitrosodimethylamine, or NDMA, and other nitrosamine in the supply chain. (Also see "*Quality Lowdown: FDA Defends Nitrosamine Testing Methods While US, EU Enforcement Continues*" - Pink Sheet, 22 Jul, 2020.)

Venema added that nitrosamines are “ubiquitous compounds,” and while they should not be in medicines, they can still form “everywhere,” such as from the active pharmaceutical ingredient synthesis routes, or from excipients or solvents.

USP Chapter Aligned With FDA’s Guidance

Gump said that one of the strengths of the chapter is that it is largely aligned with the FDA’s guidance.

Both target an almost identical list of nitrosamine impurities that should be studied. The USP chapter identifies six nitrosamines that should be tested in drug products, including NDMA, N-nitrosodiethylamine (NDEA), N-nitrosodiisopropylamine (NDIPA), nitrosoethylisopropylamine (NEIPA), nitrosodibutylamine (NDBA), and nitrosomethylaminobutyric (NMBA).

The USP list differs from the FDA’s list in that it includes NEIPA, while the FDA list has a compound that's not on the USP list, N-nitrosomethylphenylamine (NMPA).

Both the USP chapter and the FDA guidance call for a risk assessment strategy for potential nitrosamines.

The USP chapter, like the FDA’s, states that all potential sources for the introduction of nitrosamines should be considered in the risk assessment, including the drug substance, excipient, water, solvents, the manufacturing process and packaging components.

If not controlled, the chapter states that “nitrosamines can be introduced into or generated as impurities in pharmaceutical drug products, and examples and sources reported in the literature include API processing with certain reagents, solvents and raw materials, the API itself, which may degrade in some conditions resulting in the formation of nitrosamines, the degradation of solvents.”

Gump said that it is “impressive” how the USP chapter is aligned with the FDA guidance.

“I was pleasantly surprised that I did not see any significant misalignment that could create

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problems for industry."

Chapter Does Not Prescribe Limits

The USP chapter also defers to FDA's guidance on ensuring that drugs do not exceed acceptable daily intake limits for nitrosamine impurities. The FDA sets a limit of 96 nanograms a day for NDMA and NMBA and 26.5 nanograms a day for NDEA, NMPA, NIPEA and NDIPA. The USP chapter avoids the setting of acceptable daily intake limits.

Gump said that "one of the things we were careful about was not to put prescriptive limits in this guideline that could be out of alignment with FDA."

One of the major early stumbling blocks to implementing an earlier International Council on Harmonization Q3D guideline on elemental impurities was the different impurity thresholds set by USP's Chapter 232 and the ICH. (Also see "*ICH and USP Agree to Harmonize Metal Impurity Limits*" - Pink Sheet, 19 Dec, 2014.)

Gump said that instead of prescribing limits, information was included in the chapter to help manufacturers "understand the acceptable daily intake and to decode that to a concentration threshold for their medicine based on the maximum daily dose."

Four Methods Proposed

The USP chapter proposes four analytical methods that manufacturers can use to identify possible nitrosamines in their products.

- The first method recommends high performance liquid chromatography-high resolution mass spectrometry (HPLC-HRMS) for measuring NDMA, NDEA, NDIPA, NEIPA, NMBA and NDBA.
- The second recommends gas chromatography-mass spectrometry (GC-MS) for NDMA, NDEA, NDIPA, and NEIPA.
- The third recommends HPLC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NEIPA, NEIPA, NEIPA, and NMBA.
- The fourth recommends GC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NMBA and NDMA.

Gump said that the chapter also gives manufacturers the leeway to use their own analytical methods so they would be fit for their intended purpose.

The USP is accepting comments until 30 November on the proposal, which was published in the Pharmacopeial Forum Issue 46 Number 5 and can be accessed online here: https://online.usppf.com/usppf.

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Ranitidine Testing Debate

Gump also stressed the importance of using the correct analytical testing method, and to show that the method is fit for its intended purpose, measuring nitrosamine impurities.

A controversy erupted in September 2019 when Valisure, an online pharmacy, filed a citizen petition that called for recalls of ranitidine due to high NDMA impurity levels it found in the drugs. The FDA asserted that it had found NMDA but at lower levels than Valisure and attributed the discrepant findings to the relatively high temperatures of Valisure's GC-MS test method. (Also see "*US FDA Questions Valisure's Zantac Carcinogenicity Findings*" - Pink Sheet, 2 Oct, 2019.)

Gump said ranitidine is an "unstable product" and when it was heated, it generates a high level of nitrosamines. For this reason, he said, the method Valisure used "may not have been appropriate for that molecule." He added that using a chromatographic method that can be run at moderate ambient temperatures may have been a better choice.