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POSITION STATEMENT

MEDICAL GASES AND THE POTENTIAL TO CONTAIN NITROSAMINE

Background

The discovery of nitrosamine impurity in one type of drug product in 2018, led the United States Food and Drug Administration (FDA), Health Canada, and other international regulators to begin to investigate the presence of this contaminant in other drugs. With additional drug products being identified leading to recalls in 2019, the FDA and Health Canada required firms to establish plans to conduct risk analysis of their manufactured drug products and the active pharmaceutical ingredients they used for the presence of nitrosamines. If nitrosamines were found to be present, firms were required to ensure that levels did not exceed recommended acceptable intake limits. Medical gases are classified as drugs in both the United States and Canada, therefore CGA evaluated the production inputs and outputs of common medical gases. CGA members have also received inquiries regarding nitrosamine contamination of gases used by pharmaceutical firms in the manufacture of their products. This position statement and the associated technical report reflect the results of the evaluation CGA performed and is consistent with CGA's March 26, 2020 letter to Health Canada in response to DEL Bulletin No 57 regarding nitrosamines.

Question

Do medical gases (oxygen, nitrogen, medical air, nitrous oxide, carbon dioxide, helium) and mixtures thereof contain nitrosamine contamination?

Answer

No, based on risk analysis and evaluation of production inputs.

Medical gases are human pharmaceutical products and are elements, simple molecules or compounds, or in some cases mixtures of medical gases. Bulk manufacturers of medical gases, through processes such as air separation, and carbon dioxide and nitrous oxide manufacturing and purification are subject in the United States to new drug application (NDA), and in Canada to Market Authorization (MA).

Of the medical gases listed the only chemically synthesized gas is nitrous oxide. CGA performed a risk analysis of the liquid ammonium nitrate process for the manufacture of nitrous oxide, which is currently the only bulk manufacturing process for nitrous oxide. Our analysis indicates that nitrosamine impurities cannot be produced under the conditions of manufacture because there is no possibility during the manufacturing process for nitrous acid to combine with amines to create nitrosamines, see CGA TR-5, *Technical Report on Nitrosamine Impurities in Nitrous Oxide and other Medical Gases* [1]. Based on the fact that nitrosamine impurities cannot be produced by this process, no further testing needs to be performed.

CGA has concluded, based on the manufacturing processes utilized for all other medical gases that nitrosamine contamination is not possible. Additionally, filling cylinders with medical gases does not add nitrosamine contamination.

Reference

Unless otherwise specified, the latest edition shall apply.

[1] CGA TR-5, *Technical Report on Nitrosamine Impurities in Nitrous Oxide and other Medical Gases*, Compressed Gas Association. www.cganet.com

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