

Pharmaceutical Drugs Directorate
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MECS 25-104773-88

Information to Market Authorization Holders (MAHs) of Human Pharmaceutical Products Regarding Nitrosamine Impurities

Expectations relating to the timeline for completing changes to the market authorization as outlined in Health Canada's letters of October 2, 2019 and December 15, 2020 (Step 3 of Health Canada's *Call for Review*)

As part of its efforts to mitigate the risk of nitrosamine contamination in drug products for human use, Health Canada requested in its letter of October 2, 2019 that MAHs follow a three-step process for conducting risk assessments, performing confirmatory testing and implementing risk mitigation measures for nitrosamine impurities for their drug products containing chemically synthesized Active Pharmaceutical Ingredients (APIs). In its letter of December 15, 2020, Health Canada expanded the scope of this Call for Review to include biological and radiopharmaceutical products.

Health Canada has received feedback from industry and its associations and acknowledges that timeframes for full implementation of nitrosamine control or mitigation strategies may vary depending upon the specific control strategy.

The following sets out Health Canada's expectations for MAHs regarding submitting and implementing necessary changes to their market authorizations effective August 1 2025:

- For those nitrosamine impurities with an established Acceptable Intake (AI) limit published in Appendix 1 of Health Canada's *Guidance on Nitrosamine Impurities in Medications* prior to August 1, 2025, MAHs are permitted to have a Corrective and Preventative Action (CAPA) implementation timeline of up to 3 years from August 1, 2025 (i.e., up to August 1, 2028).
- For those nitrosamine impurities with an established AI limit published in Appendix 1 of Health Canada's *Guidance on Nitrosamine Impurities in Medications* on August 1, 2025 or later, MAHs are permitted to have a CAPA implementation timeline of up to 3 years from the publication date of the AI limit.
- The applicable publication dates of AI limits can be obtained from Appendix 1 of the aforementioned Nitrosamine impurities guidance document.

- Considering the risk profiles of nitrosamines and the possibility of an additive biological effect, the AI limits published in Appendix 1 are considered appropriate by Health Canada for lifetime and less-than-life (LTL) administration of a drug product, including during the 3 year CAPA implementation timeline.

It should be noted that despite the 3 year CAPA implementation timeline, it is Health Canada's expectation that MAHs implement risk mitigation measures to reduce the levels of nitrosamine impurities to below the AI limits as soon as possible.

Health Canada recognizes the challenges faced by MAHs to decrease levels of nitrosamine impurities in their drug products while maintaining drug supply to Canadians. To minimize the impacts on drug supply within the Canadian market, MAHs are requested to engage Health Canada prior to taking any market action for a drug product due to a nitrosamine impurity issue.

Health Canada's [Guidance on Nitrosamine Impurities in Medications](#) provides the Department's current thinking and recommendations on issues related to *N*-nitrosamine impurities. This guidance document will soon be updated to reflect the expectations described above relating to the Step 3 timeline.

If you have any nitrosamine-related enquiries for drug products containing chemically synthesized and semi-synthetic APIs, please email bpsenquiries@hc-sc.gc.ca.

If you have any nitrosamine-related enquiries for biological and radiopharmaceutical drug products, please email brdd.nitrosamines.dnbr@hc-sc.gc.ca.

Sincerely,



Kelly Robinson
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Health Products and Food Branch

Cc

Kim Godard, Director General, Health Product Compliance Directorate, Regulatory Operations and Enforcement Branch

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