QUESTIONS AND ANSWERS

REQUEST TO EVALUATE THE RISK OF THE PRESENCE N-NITROSAMINE IMPURITIES IN HUMAN PHARMACEUTICAL PRODUCTS

(OCTOBER 2, 2019 LETTER FROM HEALTH CANADA TO MARKET AUTHORIZATION HOLDERS)

(dated 2019-11-26)

Questions and Answers

Request to evaluate the risk of the presence N-nitrosamine impurities in human pharmaceutical products

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The document represents Health Canada's current thinking and recommendations on this topic and may be subject to change as new information becomes available.

Q1. Are all drug products to be reviewed?

The request to evaluate the risk of the presence of nitrosamine impurities outlined in the October 2, 2019 letter applies to human pharmaceutical products containing chemically synthesized active pharmaceutical ingredients (APIs), including prescription and non-prescription (over the counter) drug products. It also includes chemically synthesized excipients and raw materials used in the manufacturing of drug products. Drug products that have been approved but are not yet marketed are also considered to be within the scope of this review.

Products that are not currently in scope include radiopharmaceuticals, biologicals/biotech products, disinfectants, veterinary products, natural health products and cosmetics.

Q2. When determining the priorities and order in which products should be reviewed, what factors should be considered?

Market Authorization Holders (MAHs) should use a risk-based approach to determine the order in which their drug products containing chemically synthesized APIs are reviewed. In order to prioritize the sequence in which products should be reviewed, MAHs should consider factors including, but not limited to, the following:

- Principles set out in the ICH's Q9 guideline on Quality Risk Management;
- Maximum daily dose of the drug product;
- Route of administration;
- Duration of use;
- Indication and considerations of special populations such as pregnant women and children;
- Toxicological profile of the API. As an example, evaluating the risk of presence of nitrosamine impurities in cancer therapies in which the API is a potent mutagen could be considered lower priority and sequenced for review after higher priority APIs;

- Market considerations such as the availability of product for sale on the Canadian market, number of patients being treated with the drug product;

- Emerging international or domestic information that one or more nitrosamine impurities has been identified in an API (or a structurally similar API) or drug product; and

- The presence of structural elements in the API or conditions in the manufacturing processes for the API or drug product, which are conducive to nitrosamine formation (e.g. presence of secondary or tertiary amine groups in the API). Available literature should be consulted for APIs known to contain nitrosamine impurities (e.g., M.K. Parr, J.F. Joseph, *Journal of Pharmaceutical and Biomedical Analysis* 164 (2019) 536–549).

Q3. Is Health Canada open to MAHs cooperating with the API and drug product manufacturers to perform risk assessments?

MAHs are responsible for the safety, efficacy and quality of their products and for carrying out the risk assessment. MAHs are advised to work with API and drug manufacturers to review their API and drug product manufacturing processes to conduct risk assessments, taking into account their knowledge of the manufacturing processes, potential sources of contamination and any other root causes of formation and presence of nitrosamine impurities. The information necessary for conducting the risk assessment should be made available to the MAHs by the API and drug product manufacturers. If the risk of nitrosamine impurity formation has been assessed during the development phase of the API or drug product manufacturing processes, the information from the assessment can be used to support the evaluation.

Q4: How should MAHs proceed when information necessary to complete risk assessments is not provided by the API or drug product manufacturer?

MAHs have the responsibility of ensuring the safety, efficacy and quality of products on the Canadian market. When information from manufacturers which is deemed to be essential to complete the risk assessment has not been provided to the MAH due to confidentiality concerns or other reasons, MAHs may qualify and engage a third party (e.g., a consultant) to work directly with manufacturers to complete the risk assessment on behalf of the MAH (Note: The use of a third party may also be an appropriate approach when the MAH has all of the required information to conduct the risk assessment from the manufacturers, but does not have personnel with the necessary qualifications (e.g. relevant training and practical experience) on staff to conduct the risk assessment).

Alternatively, the MAH should consider delegation of the risk assessment to the API and drug product manufacturers. In this scenario, the MAH continues to have the responsibility of ensuring the safety, efficacy, and quality of the medicines and should ensure through internal or third party audit that:

- Risk assessments have been conducted by personnel with acceptable qualifications (e.g., relevant training and practical experience);

- Manufacturers have considered all possible origins of nitrosamine impurities (including the examples of potential sources summarized in the October 2, 2019 Health Canada letter to MAHs).

Q5: Which nitrosamine impurities should be considered in the risk assessment and confirmatory testing?

Given that each drug substance and drug product manufacturing process is unique, it should be noted that the list of nitrosamines included in Annex 1 of the October 2, 2019 letter may not represent all nitrosamines potentially present in drug substances and drug products. Therefore, MAHs should ensure that the risk assessments consider and identify the possibility of any nitrosamine impurity which may be formed. All nitrosamines that have been determined to be potentially formed should be included within the program for confirmatory testing (Step 2 of the October 2, 2019 letter). For nitrosamines not included in Annex 1, MAHs should follow the principles outlined in the ICH M7(R1) guideline on mutagenic impurities to establish an interim acceptable intake.

Q6: Do the outcomes of the risk assessments (Step 1 of the October 2, 2019 letter) need to be provided to Health Canada?

Risk assessment documentation should be retained by the MAH, unless nitrosamine impurities are detected in the drug substance, drug product, or both, during the confirmatory testing. If any nitrosamine impurity is detected at any level, Health Canada should be informed immediately and the available details of the risk assessment should be submitted at the same time that Health Canada is informed of the detection. Please note that Health Canada may request to review the MAH's risk assessment report for all products and will request this information directly from the MAH, as necessary.

Q7. Are companies required to use the testing methodologies provided by Health Canada?

No. Testing methodologies have been published and shared by several regulators including Health Canada, Europe's network of Official Medicines Control Laboratories (OMCLs), and the US Food and Drug Administration (FDA). These methods may be used; however, there is no requirement to use only these published methods. In any case, appropriately sensitive, validated analytical methods must be used and the testing must be conducted at a GMP compliant facility. If other methodologies are used, there is no need to verify the method with Health Canada prior to use.

Q8. In cases where a risk assessment concludes there is no risk of nitrosamine contamination, is confirmatory testing required?

MAHs are required to conduct a thorough, robust risk assessment. In the October 2, 2019 letter, Health Canada shared some potential sources of nitrosamine impurities and noted that attention must be given to APIs as well as drug product manufacturing processes. For example, MAHs should evaluate whether secondary amines or nitrites coexist during the manufacturing processes and the potential of contamination through bulk raw materials and potable water.

MAHs should prepare a report including considerations, steps and conclusions. If it is concluded that a risk does not exist, then confirmatory testing is not expected.

In the event that a risk of formation or presence of nitrosamines is identified, confirmatory testing should be carried out using appropriately validated and sensitive methods. If one or more nitrosamine impurities are detected in an API or drug product, Health Canada must be informed immediately.

Q9: During confirmatory testing (Step 2), should the API or the drug product be tested?

During confirmatory testing, MAHs should test the drug product to determine the levels of nitrosamine impurities. Testing of the API is also recommended if the risk assessment indicated that the drug substance is a potential source of nitrosamine impurities in the drug product. In such cases, the results of API testing may be used to support root cause investigations and the development of a justified control strategy for nitrosamine impurities in the API.

Q10: When should a MAH contact Health Canada?

MAHs must inform Health Canada immediately, and provide a copy of the risk assessment report and confirmatory testing results, if nitrosamine impurities are detected at any level in the drug substance, drug product, or both. These communications should be directed as follows:

Location of firm	Reporting address
New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island, Québec	Health Products Compliance Unit East 1001 Rue St-Laurent Ouest, Longueuil, Québec, J4K 1C7 Phone : 450-646-1353 Toll free : 1-800-561-3350 E-mail : HC.qoc-cog.SC@canada.ca
Ontario	Health Products Compliance Unit Central 2301 Midland Ave., Toronto, Ontario, M1P 4R7 Phone: 416-973-1600 Toll free: 1-800-267-9675 E-mail: HC.insponoc-coon.SC@canada.ca
Manitoba, Saskatchewan, Alberta, British Columbia, Yukon, Northwest Territories, Nunavut	Health Products Compliance Unit West Suite 400 – 4595 Canada Way, Burnaby, British Columbia, V5G 1J9 Phone: 604-666-3350 Toll free: 1-800-267-9675 E-mail: insp_woc-coo@hc-sc.gc.ca

If nitrosamines are not detected during confirmatory testing (i.e. less than the appropriate limit of detection of the validated test method), no communication to Health Canada is necessary and the risk assessment report, analytical testing results, and the analytical method validation documentation should be retained by the MAH and should be made available to Health Canada upon request.

Q11. How will Health Canada respond to notifications of the detection of one or more nitrosamine impurities that are below interim acceptable limit(s)?

In the case where one or more nitrosamine impurities are detected and are below the current interim acceptable limit(s), Health Canada expects that MAHs will:

- Initiate actions to determine the origin of the detected nitrosamine impurity(ies);
- Determine any actions, as necessary, for the batches on the Canadian market;
- Establish a risk mitigation plan to ensure that level(s) will be consistently below the current interim acceptable limit(s) at the end of the shelf-life for the drug product moving forward. Further, measures should be initiated to introduce changes or controls in the manufacturing processes, where possible, to reduce the levels of the nitrosamine impurities to levels below the detectable limits in the longer term.

Health Canada may use such notifications to request documentation describing the company's root cause investigation and risk mitigation plan for the detected nitrosamine impurities. Health Canada may also use such notifications to request additional actions. For example, the origin of nitrosamine impurities may be attributed to the type of process chemistry used and the risk mitigation plan may necessitate the establishment of a control strategy by manufacturers for each detected nitrosamine impurity according to ICH's guidance for mutagenic impurities (i.e. ICH M7(R1)).

Q12. How will Health Canada assess progress with this request to review the risk of the presence of nitrosamine impurities (for example during inspections or when applications are filed by the MAH)?

Health Canada has not yet determined which mechanisms may be most appropriate to address this request. Health Canada appreciates the nature of this request is significant and seeks to continue to engage with stakeholders to look at all options to meet their needs. Potential options include verification during inspections, proactive risk management projects to measure progress, verification or request for information at such time as changes are made to either the existing market authorization for a product or for the drug establishment licence.

Q13. If the interim acceptable limits are revised in the future, how will Health Canada communicate this information?

Health Canada continues to cooperate with international regulatory agencies to determine long-term acceptable limits for nitrosamine impurities. Health Canada intends to communicate any changes to the acceptable limits for nitrosamine impurities to MAHs in a timely manner. To minimize the impact of potential future tightening of acceptable limits for nitrosamine impurities, as a proactive measure, MAHs should use validated test methods that are capable of determining nitrosamine impurities at levels below the current interim acceptable limits.

Q14. What approach should be taken for drug products that are planned for submission or are already filed with Health Canada?

For drug products which are planned for submission or have already been submitted, it is recommended that MAHs proactively undertake a risk assessment for the potential presence of nitrosamine impurities (if this has not already been undertaken) using the considerations and steps provided for marketed products in Health Canada's communication to MAHs dated October 2, 2019. For planned submissions, the relevant sections of the Common Technical Document (CTD) in the drug application should be updated with the outcome of the risk assessment, as well as confirmatory testing results and updated control strategy (where warranted). For submissions under review, the sponsor may be requested to provide information on the risk assessment and confirmatory testing results as part of the assessment procedure.

Q15. Will a risk assessment for the potential presence of nitrosamines become part of the expected content for new submissions?

As for all impurities, and especially for highly potent, mutagenic carcinogens, risk assessments should be conducted routinely during drug substance and drug product development. The outcome of the risk assessment and the justification for the proposed control strategy with respect to such impurities should be made available for assessment in the drug submission. ICH's guidance documents M7(R1) and Q9 should be consulted for further information concerning mutagenic impurity considerations and quality risk management principles, respectively.

Q16. How is Health Canada planning to engage stakeholders and ensure ongoing communication with industry?

Health Canada's primary goal is to protect the health and safety of Canadians. We are committed to sharing information with stakeholders and maintaining transparency as we continue to analyse and better understand this evolving, global situation. To date, Health Canada has shared information openly with stakeholders including potential sources of nitrosamine impurities and new findings. Discussions are ongoing to determine the most appropriate and effective methods to continue to engage stakeholders as new information becomes available to ensure a coordinated and consistent approach in dealing with this complex issue.

Q17. How is Health Canada working with global regulators around the issue of nitrosamine impurities in drug products?

Health Canada is collaborating with international regulatory partners including those in Europe, the United States, Japan, Switzerland, Singapore, and Australia to understand the issue of nitrosamine impurities, align requirements and actions as appropriate and share information under the terms of our confidentiality agreements. When determining appropriate regulatory measures to address the presence of nitrosamine impurities that exceed the interim acceptable intake in human pharmaceuticals, individual jurisdictions must determine timelines and actions that are in the best interest of protecting patient safety and work within the relevant regulatory framework.

Questions relating to the October 2, 2019 letter from Health Canada or this related Questions and Answers document can be directed to hc.bps.enquiries.sc@canada.ca.