Health Canada Santé Canada

Guidance on nitrosamine impurities in medications

Evaluating and managing the risks of N-nitrosamine impurities in human pharmaceutical, biological and radiopharmaceutical products

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Canada

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

Également disponible en français sous le titre :
Lignes directrices sur les impuretés de nitrosamine dans les médicaments

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Background

This guidance represents Health Canada's current thinking and recommendations on issues related to *N*-nitrosamine impurities (nitrosamine impurities or nitrosamines). This guidance may be subject to change as new information becomes available and if further guidance is needed for applicants and market authorization holders (MAHs).

A questions-and-answers (Q&A) document on nitrosamines was issued to MAHs on November 26, 2019. This document has undergone a number of revisions and has been further updated as a guidance and to provide additional details to active pharmaceutical ingredient (API) manufacturers, drug product manufacturers, MAHs and importers of APIs and drug products.

In this guidance, changes from the previous version are identified with the descriptors "new" or "updated" (as applicable). Information on a similar theme is grouped together under general headings (for example, General, Safety and Quality).

Queries about the Health Canada letters noted below can be directed as follows:

- "Information to MAHs of Human Pharmaceutical Products Regarding Nitrosamine Impurities: Request to evaluate the risk of the presence of nitrosamine impurities in human pharmaceutical products containing chemically synthesized active pharmaceutical ingredients" (October 2, 2019)
    - Email to bpsenquiries@hc-sc.gc.ca

- "Information to MAHs of Human Pharmaceutical Products Regarding Nitrosamine Impurities: Request to evaluate the risk of the presence of nitrosamine impurities in biologics and radiopharmaceuticals" (December 15, 2020)
    - Email to brdd.nitrosamines.dmbr@hc-sc.gc.ca

If you have queries about this guidance, you may send an email to bpsenquiries@hc-sc.gc.ca.

General

Scope and responsibilities

1. Drug products that are within the scope of Health Canada's call for review

The request in Health Canada's call for review to evaluate the risk of the presence of nitrosamine impurities outlined in the October 2, 2019, letter applies to human pharmaceutical products with a drug identification number (DIN) containing chemically synthesized and semi-synthetic APIs. This includes:

- prescription and non-prescription (over-the-counter) drug products
- chemically synthesized excipients and raw materials used in the manufacturing of drug products

Also considered to be within the scope of Health Canada's call for review are:

- drug products that have been approved but are not yet marketed
- approved drug products with a DIN status reported as "dormant"

The request for conducting risk assessments for the potential presence of nitrosamine impurities was extended to all biological and radiopharmaceutical products for human use. This was outlined in Health Canada's letter dated December 15, 2020.

All human plasma proteins, vaccines and cell-based fermentation products are classified as biologics. They are, therefore, within the scope of the request for risk assessment.

Please refer to Health Canada's letter dated December 15, 2020, for further details.

All non-prescription products with a DIN, such as topical antiseptic products, grooming and personal hygiene products and sunscreens, are within the scope of products for assessment if they contain a chemically synthesized or semi-synthetic API. This is irrespective of the route of administration or any cosmetic properties.

Products that are **not** within the scope of the October 2, 2019 and December 15, 2020 letters include cosmetics (which do not have a DIN). The following categories of drug products are also excluded at this time: antimicrobial agents, veterinary products (including veterinary health products) and natural health products. Disinfectant products for use on hard surfaces are also not within the scope of products for assessment at this time.

2. Timelines for completing risk assessments (Step 1), confirmatory testing (Step 2) and changes to the market authorization (Step 3) (updated)

For drug products containing chemically synthesized and semi-synthetic APIs, the steps for actions relating to nitrosamines are expected to be completed as follows:

- Step 1: risk assessments by March 31, 2021
- Step 2: confirmatory testing by October 1, 2022
- Step 3: changes to the market authorization by October 1, 2023

For biological and radiopharmaceutical products, the steps for actions relating to nitrosamines are expected to be completed as follows:

- Step 1: risk assessments by November 30, 2021
- Step 2: confirmatory testing by November 30, 2023
- Step 3: changes to the market authorization by November 30, 2023

3. Outcomes of risk assessments (Step 1) and what is provided to Health Canada

Risk assessment documentation should be retained by the MAH, unless nitrosamine impurities are detected in the API, drug product or both during confirmatory testing. If any nitrosamine impurity is detected at any level, Health Canada must be informed immediately. 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 for all products and will request this information directly from the MAH, as necessary.

Canadian importers that received terms and conditions (T&C) on their drug establishment licence (DEL) for nitrosamine testing of angiotensin II receptor blockers (known as sartans) may provide supporting information to modify or remove the terms and conditions. They should submit the API and drug product risk assessments and testing results completed as per Steps 1 and 2 for consideration. Email to foreign.site-etranger@hc-sc.gc.ca.

MAHs may be requested by Canadian importers for a copy of the MAH's risk assessment and testing results to facilitate this request. Alternatively, MAHs may provide the requested risk assessment and related information to Health Canada on behalf of the Canadian importer. In this case, the MAH should specify on whose behalf the risk assessment and related information is being submitted.

4. Determining the priorities and order in which products should be reviewed

MAHs should use a risk-based approach to determine the order in which their drug products are reviewed. In order to prioritize the sequence in which products should be reviewed, MAHs should consider a number of factors, including the following:

- principles set out in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9 guideline on quality risk management
- maximum daily dose of the drug product
- route of administration
- duration of use
- indication and consideration of special populations, such as pregnant women and children
- toxicological profile of the API
    - for 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 and number of patients being treated with the drug product
- emerging international or domestic information that 1 or more nitrosamine impurities has been identified in an API (or a structurally similar API) or drug product
- the presence of structural elements in the API or conditions in the manufacturing and packaging processes for the API or drug product, which are conducive to nitrosamine formation (for example, presence of secondary or tertiary amine groups in the API)

Available literature should be consulted for APIs known to contain nitrosamine impurities (for example, M.K. Parr, J.F. Joseph, *Journal of Pharmaceutical and Biomedical Analysis* 164 (2019) 536–549).

5. MAHs co-operating with API and drug product manufacturers to perform risk assessments

After receiving authorization to market in Canada, MAHs are responsible for the safety, efficacy and quality of their drug products and for carrying out the risk assessments. They should:

- work with API and drug product manufacturers to review their API and drug product manufacturing processes to conduct risk assessments
- take into account the API and drug product manufacturers' knowledge of the manufacturing processes, potential sources of contamination and other root causes of the formation and presence of nitrosamine impurities

API and drug product manufacturers should make available to the MAHs the information necessary for conducting the risk assessments.

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.

6. Responsibilities of API manufacturers, excipient manufacturers, drug product manufacturers, MAHs and importers

After receiving authorization, MAHs are responsible for ensuring the ongoing safety, efficacy and quality of drug products on the Canadian market. This would include implementing an ongoing monitoring program to detect trends in quality. Such a program should be based on appropriate controls for raw materials, all processing steps, critical process parameters and critical quality attributes.

To complete risk assessments for the potential presence of nitrosamine impurities, MAHs should complete robust risk evaluations using a holistic approach. A detailed assessment of all stages of the product's life cycle should be done and would include the following:

- an appropriate level of documented root cause analysis
- evaluation of manufacturing controls and conditions for the APIs, non-medicinal ingredients (excipients) and drug product
- the potential interactions with the container closure system and
- the potential of increased risks over the retest period for the API or the shelf life of the drug product

MAHs are responsible for ensuring that personnel with acceptable qualifications and expertise (for example, relevant training, knowledge and practical experience) have conducted the risk assessments. Information should be made available to the MAH by API, excipient and drug product manufacturers.

In the context of control for nitrosamine impurities, manufacturers and importers must comply with any terms and conditions specified on their DEL. This could include restrictions or additional specific testing and investigational requirements for nitrosamine impurities.

7. Inability to meet specified timelines for risk assessment (Step 1), confirmatory testing (Step 2) or changes to the market authorization (Step 3)

Given the potential risks associated with nitrosamines in drug products, MAHs should take all necessary measures to complete the 3 steps as soon as possible and within the designated timelines.

In a follow-up letter issued to MAHs of drug products containing chemically synthesized active pharmaceutical ingredients on April 14, 2021, Health Canada requested that affected MAHs indicate their status for completing Step 1, risk assessments. MAHs should provide a completed Annex 1, Annex 2 or Annex 3, as applicable, as per the instructions in the April 14, 2021, follow-up letter. If risk assessments have **not** been completed for all marketed, approved and dormant products or have been partially completed, Annex 3 should be completed.

MAHs unable to meet the Step 2 or 3 deadlines due to exceptional circumstances may submit a request for extension to Health Canada. This should be done as soon as possible. The request should contain relevant information, including the progress to date, the reasons for not meeting the deadline(s), the remaining work and the expected timelines for completion.

To prioritize APIs and drug products for the completion of risk assessments, confirmatory testing or changes to the market authorization, MAHs are reminded to use quality risk management principles. Consult ICH's Q9 guideline, Health Canada's good manufacturing practices (GMP) guides 0001 (for drug products) and 0104 (for APIs). Also consult the information in number 4.

Requests for extensions will be considered on a case-by-case basis. Direct such requests as follows:

- for drug products containing chemically synthesized or semi-synthetic APIs: bpsenquiries@hc-sc.gc.ca
- for biological and radiopharmaceutical products: brdd.nitrosamines.dmbr@hc-sc.gc.ca

8. Statements or declarations by manufacturers and suppliers in lieu of completing risk assessments

Statements and declarations provided by manufacturers and/or suppliers are not a substitute for an overall robust risk assessment by the MAH. While the knowledge and expertise offered by manufacturers is valuable and is encouraged to support the risk assessment process, manufacturer/supplier statements or declarations do not replace a documented risk assessment by the MAH.

9. Skipping the risk assessment step (Step 1) and proceeding directly to confirmatory testing (Step 2)

The risk assessment step (Step 1) is necessary to identify possible root causes and the scope of nitrosamine impurities that have the potential to be formed or introduced into the API or drug product. If a risk of 1 or more nitrosamine impurities is identified, this knowledge is used to guide the development and validation of appropriate test methods required for the confirmatory testing stage (Step 2).

This knowledge may also be useful for the establishment of a suitable control strategy and changes introduced to prevent the presence of nitrosamines.

As such, it is not appropriate to proceed directly to confirmatory testing (Step 2) without completing the risk assessment step (Step 1).

10. Applying the results of a risk assessment and confirmatory testing for a drug product marketed outside Canada to a drug product authorized for sale in Canada

MAHs are responsible for ensuring that risk assessments and, if applicable, confirmatory testing are relevant to the drug product authorized for sale in Canada.

If a risk assessment and confirmatory testing have been completed for a drug product approved for use outside Canada, it may be possible to use that information for the risk assessment and confirmatory testing of the drug product authorized for sale in Canada. In this scenario, the 2 drug products must be identical (for example, composition, strength, manufacturing process, API and excipient sources, manufacturing sites).

MAHs should prepare a written justification when the risk assessment and confirmatory testing results of a foreign product will be relied upon. MAHs should be prepared to provide this justification to Health Canada upon request. This justification should be included in communications to Health Canada if nitrosamine impurities are detected at any level in the API, drug product or both. Refer to the information in number 15.

11. Nitrosamine risk assessment applicable to a drug product brought into Canada under the Special Access Program (SAP)

Companies may need to conduct nitrosamine risk assessments for drug products not authorized for sale in Canada that are being made available in Canada through SAP. Refer to the approaches described in Health Canada's October 2, 2019, and December 15, 2020, letters and in this document.

If the nitrosamine risk assessment or confirmatory testing results (if applicable) indicate the risk of presence of a nitrosamine impurity, notify SAP by email at sapd-pasm@hc-sc.gc.ca.

To protect the health and safety of patients accessing unauthorized drug products, significant new information on the safety, efficacy and quality of drug products released under SAP should be made available to practitioners and SAP.

12. Confirmatory testing where the risk assessment concludes there is no identified risk for the presence of nitrosamines

MAHs are expected to conduct a thorough, robust risk assessment. In Health Canada's letters dated October 2, 2019, and December 15, 2020, Health Canada shared some potential sources of nitrosamine impurities. Refer to number 29 for more information on risk factors and potential root causes for nitrosamine impurities.

MAHs should prepare a report that includes considerations, steps, conclusions and a rationale. The report should clearly identify which nitrosamine(s) is (are) at risk of formation, if applicable. If it is concluded that a risk for the presence of nitrosamines is not identified, then confirmatory testing is not expected.

If a risk of formation or presence of nitrosamines is identified, confirmatory testing should be carried out using appropriately validated and sensitive methods. If 1 or more nitrosamine impurities are detected at any level in an API or drug product, Health Canada must be informed immediately. The reporting addresses are provided in number 15.

13. Submitting changes to the market authorization

For Step 3 (changes to the market authorization), changes should be submitted in a timely manner in eCTD or non-eCTD format using the Common Electronic Submission Gateway (CESG).

For information on change classification, reporting and supporting data recommendations, consult the following documents:

- Post-Notice of Compliance (NOC) Changes: Quality Document
- Post-Drug Identification Number (DIN) Changes Guidance Document

These changes are the result of potential safety concerns. Therefore, changes for new drugs should be submitted as a Level I - Supplement (for pharmaceuticals) or as a Level I – Supplement or Level II - Notifiable Change, as applicable (for biologicals and radiopharmaceuticals).

When filing a Supplement or a Notifiable Change for the market authorization, applicants should clearly indicate in the covering letter that the changes are for issues associated with nitrosamines.

14. Selling a drug product if changes (specifications, controls) to the market authorization (Step 3) submitted as a Supplement or Notifiable Change are still under review

The ongoing marketing of a drug product depends on the impurity levels and the risk of nitrosamine impurities that are detected upon notification to the Regulatory Operations and Enforcement Branch (ROEB). Some of the outcomes of the ROEB assessment may include recalls or stop sale requests until the risks are mitigated and suitable corrective and preventive actions are in place to ensure that all lots being released to market meet the acceptance criteria for each nitrosamine impurity (and multiple nitrosamines, if relevant). Both outcomes would affect the ongoing marketing of the product while the Supplement or Notifiable Change is being reviewed. Refer to the information in number 13.

15. Contacting Health Canada if nitrosamine impurities are detected

MAHs must inform Health Canada immediately if nitrosamine impurities are detected at any level in the API, drug product or both. MAHs must provide a copy of the risk assessment and confirmatory testing results.

Communications should be directed as follows:

Table 1. Addresses and contact information

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

If nitrosamines are not detected during confirmatory testing (for example, less than the appropriate limit of detection of the validated test method), MAHs do not need to communicate to Health Canada. However, they should keep the risk assessment, analytical testing results and analytical method validation documentation on hand in case Health Canada requests them.

16. When information necessary to complete risk assessments is not provided by the API or drug product manufacturer

MAHs are responsible for ensuring the ongoing safety, efficacy and quality of products on the Canadian market. When manufacturers do not provide information that is essential for MAHs to complete the risk assessment due to confidentiality or other reasons, MAHs may engage a third party (such as a consultant) to work directly with the manufacturer to complete the risk assessment.

The third-party approach may also be appropriate when the MAH:

- has all of the required information to conduct the risk assessment from the manufacturer **but**
- does not have staff with the necessary qualifications (for example, relevant training and practical experience) to conduct the risk assessment

For additional guidance on outsourced activities, consult the:

- section C.02.012, interpretation 3 to 12 of the Good Manufacturing Practices Guide for Drug Products (GUI-0001)

Alternatively, MAHs should consider delegating the risk assessment to the API and drug product manufacturers. In this scenario, MAHs would continue to be responsible for ensuring the safety, efficacy and quality of their drug products.

MAHs should ensure through internal or third-party audit that:

- risk assessments have been conducted by personnel with acceptable qualifications (relevant training and practical experience)
- manufacturers have considered all possible risk factors and potential root causes of nitrosamine impurities (including those in the December 15, 2020, letter concerning biologics and radiopharmaceuticals, and those identified in number 29)

17. Additional expectations of MAHs if nitrosamine impurities are detected in the API and/or drug product

Where 1 or more nitrosamine impurities are detected (for multiple nitrosamines, refer to number 27), in addition to notifying Health Canada, MAHs should provide:

- a health risk assessment posed by the presence of the nitrosamine(s) along with intentions related to any actions, as necessary, for the batches on the Canadian market
    - where product recalls are warranted, consult the Drugs and Natural Health Products Recall Guide (GUI-0039) for procedures
- indicate if the product is considered to be medically necessary and if any disruption to product supply is expected
- a detailed investigation report assessing all possible root causes of the detected nitrosamine impurity (or impurities) and describing corrective and preventive actions
    - perform investigations in accordance with written procedures
    - evaluate all potential changes to facilities, materials, equipment and/or process intended to reduce the levels of the nitrosamine impurities through a formal change control system
- a risk mitigation plan to ensure that, moving forward, nitrosamine impurity levels will be consistently below the AI at the end of the retest period for the API or the shelf-life for the drug product

Remember to submit changes to the market authorization as per Step 3 of the October 2, 2019 letter. Refer to number 13 on how changes should be submitted.

Health Canada may use such notifications to request additional actions and/or information. 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 the ICH M7 guideline.

We may request additional actions by other MAHs of the same products to mitigate any risks identified and protect people's health and safety if necessary.

For more information on the establishment of specifications and controls, refer to number 34 and number 35, respectively.

18. Assessing progress with the request to review the risk of presence of nitrosamine impurities

On April 14, 2021, Health Canada issued a follow-up letter to the October 2, 2019, letter. In the letter, we asked MAHs with drug products containing chemically synthesized and semi-synthetic APIs to provide their progress towards completing Step 1 (risk assessments).

Health Canada may also:

- verify progress during inspections, proactive risk management projects and compliance verification upon receipt of a complaint and/or notification or
- request information at such time as changes are made to either the existing market authorization for a product or for the drug establishment licence

We appreciate the significance of this request. We will continue to engage with stakeholders to consider all options to address the potential risks associated with nitrosamines.

19. Approach for drug products that are planned for submission or are already filed with Health Canada (updated)

Whenever possible for APIs and drug products that are under development, manufacturing processes should ensure that the formation/introduction of nitrosamine impurities is avoided at the outset.

If the formation or introduction of nitrosamine impurities is unavoidable, manufacturing processes should demonstrate process capability to routinely reduce the levels of nitrosamine impurities below the AI. A control strategy, based on product and process understanding, should be established for each nitrosamine impurity present in the API and/or drug product.

For drug products that are planned for submission or have already been submitted, MAHs and applicants should proactively undertake a risk assessment for the potential presence of nitrosamine impurities in the drug product (if this has not already been undertaken) using the considerations and steps provided for marketed products in Health Canada's communications. For planned submissions, the relevant sections of the Common Technical Document (CTD) in the drug application should include information on these risk assessments.

A summary and discussion of the risk assessment for nitrosamine impurities in the drug product should be placed in section 3.2.P.2 of the CTD. Confirmatory testing results and updated control strategy (where warranted) should also be included in the drug application (for example, under sections 3.2.S.2, 3.2.S.4, 3.2.S.7, 3.2.P.3, 3.2.P.4, 3.2.P.5, 3.2.P.8).

For submitted applications currently under review, MAHs and applicants may be asked to provide the risk assessment and confirmatory testing results as part of the assessment procedure. For further information, refer to number 20.

20. Risk assessments for the potential presence of nitrosamine impurities as part of the expected content for new submissions (updated)

Risk assessments for nitrosamine impurities should be conducted routinely during API and drug product development. The outcome of the risk assessment for nitrosamine impurities in the drug product and the justification for the proposed control strategy for nitrosamine impurities should be made available for assessment in New Drug Submissions (NDSs), Abbreviated New Drug Submissions (ANDSs), Supplements and Notifiable Changes (refer to number 13). For more information on mutagenic impurity considerations and quality risk management principles, consult the following:

- Good Manufacturing Practices Guide for Drug Products (GUI-0001)
- Good Manufacturing Practices Guidelines (GMP) for Active Pharmaceutical Ingredients (GUI-0104)
- ICH's M7 guideline
- ICH's Q9 guideline

All NDSs, ANDSs, Supplements and Notifiable Changes (for quality changes that may impact the potential presence of nitrosamine impurities in the API or drug product) should include a summary and discussion of the risk assessment for the potential formation/presence of nitrosamine impurities in the drug product. This was required as follows:

- as of April 1, 2021, for pharmaceutical products containing chemically synthesized and semi-synthetic APIs
- as of November 30, 2021, for biologics and radiopharmaceutical products

For Clinical Trial Applications (CTAs) (as described in section 9.1 of ICH's M7 guideline):

- For Phase 1 clinical trials of 14 days or less, include a description of efforts to mitigate risks of mutagenic impurities focused on Class 1 and Class 2 impurities and those in the cohort of concern (for example, nitrosamine impurities).
- For Phase 1 clinical trials greater than 14 days and for Phase 2 and 3 clinical trials, also include Class 3 impurities that require analytical controls.

Failure to include this information could result in requests for additional information, delays in the review process, and potentially the issuance of negative decisions.

21. Controls for nitrosamines in APIs purchased for compounding

The Policy on Manufacturing and Compounding Drug Products in Canada (POL-0051) provides a policy framework to help distinguish between compounding and manufacturing activities of drug products in Canada. In Canada, the compounding of drugs is done mainly by pharmacists as an integral part of their profession. It's regulated by the respective regulatory authorities in each province/territory.

This policy indicates that compounded products should be either:

- produced from an authorized API used in an authorized drug product for use in Canada or
- listed in a recognized Pharmacopoeia (for example, USP/NF, Ph. Eur., Ph. Int., BP, Codex - Schedule B, *Food and Drugs Act*)

Health Canada recommends, therefore, that principles outlined in the October 2, 2019, letter and in this guidance should be considered when purchasing APIs and producing compounded products.

Health care professionals and compounding firms are encouraged to access the nitrosamines webpage to stay informed on affected medications and recalls due to the presence of nitrosamines. This page is updated regularly and also includes general information on nitrosamine impurities, what Health Canada is doing to address the issue and our testing results.

Communications

22. Engaging stakeholders and ensuring ongoing communication with industry

Health Canada is committed to sharing information with stakeholders and maintaining transparency as we continue to analyze and better understand this evolving, global situation.

To date, we have shared information openly with stakeholders, including information on the potential sources of nitrosamine impurities, root causes and new findings. We hosted stakeholder sessions in January 2020, February 2021 and October 2021, and may host more sessions in the future if necessary.

We also established a dedicated webpage on nitrosamine impurities in medications. The webpage includes the following:

- summaries of drug products that have been affected or recalled due to the presence of nitrosamines
- analytical testing results of several products for levels of nitrosamine impurities

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.

23. Health Canada works with global regulators relating to issues associated with nitrosamine impurities in drug products

Health Canada regularly collaborates with international regulatory partners, including those in Europe, the United States, Japan, Switzerland, Singapore, Australia and Brazil, as well as the World Health Organization. Through collaboration, we hope to increase the understanding of the issues associated with 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 AI limit in human drug products, individual jurisdictions must determine timelines and actions that will best protect patient safety and work within the relevant regulatory framework.

Safety

24. AI limits for nitrosamine impurities that Health Canada considers acceptable (updated)

AI limits have been derived for 21 nitrosamines (Table 2). These AI limits are considered appropriate for all routes of administration.

Table 2. Established AI limits for some nitrosamines

Nitrosamine	AI (ng/day)*
N-nitroso-methylphenidate	1300
N-nitroso-piperidine	1300
N-nitrosomorpholine (NMOR)	127.0
N-nitroso-duloxetine (NDLX)	100.0
4-(methylnitrosamino)-1-(3-pyridyl)-1-(butanone) (NNK)	100.0
N-nitroso-dimethylamine (NDMA)	96.0
N-nitroso-4-(methylamino)butyric acid (NMBA)	96.0
1-methyl-4-nitrosopiperazine (MNP)	96.0
N-nitroso-varenicline (NNV)	37.0
7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3-a]pyrazine (NTTP)	37.0
N-nitroso-1,2,3,6-tetrahydropyridine (NTHP)	37.0
N-nitroso-diethylamine (NDEA)	26.5
N-nitroso-diisopropylamine (NDIPA)	26.5
N-nitroso-ethylisopropylamine (NEIPA)	26.5
N-nitroso-dibutylamine (NDBA)	26.5
N-nitroso-dipropylamine (NDPA)	26.5
N-nitroso-rasagiline	18.0
N-nitroso-dabigatran	18.0
N-nitroso-tamsulosin	18.0
N-nitroso-nortriptyline (NNORT)	8.0
N-methyl-N-nitroso-phenethylamine (NMPEA)	8.0

* Limit to be applied to maximum daily dose (MDD) of the drug product

For NDMA and NDEA, sufficient carcinogenicity data were available to linearly extrapolate from the dose giving a 50% tumour incidence (TD_{50}) to a 1 in 10^5 excess cancer risk, using the most relevant TD_{50} value in the Carcinogenic Potency Database.

Insufficient carcinogenicity data were available to derive compound-specific limits for certain nitrosamines (for example, NMBA, NDIPA, NEIPA, NDBA and MNP). For this reason, a structure-activity relationship (SAR) assessment was performed to determine if sufficient carcinogenicity data were available for a structurally similar compound or, if not available, determine if the nitrosamine is anticipated to be chemically more or less potent than NDMA or NDEA.

For a nitrosamine impurity not included in the table, MAHs and applicants should refer to the ICH M7 guideline for recommendations on how to derive an AI limit. In cases where there is insufficient carcinogenicity data available for a nitrosamine impurity, MAHs and applicants may:

- apply the class-specific threshold of toxicological concern (TTC) of 18 ng/day for nitrosamine impurities as a default limit
- conduct a structure-activity relationship assessment with read-across to justify a limit higher than 18 ng/day

Consistent with international regulatory practices, Health Canada will continue to use, and expect applicants and MAHs to use, mass-based calculations (rather than molar-based) to derive AI limits for nitrosamine impurities when an analogue is selected for read-across.

MAHs and applicants should also refer to the following items for more information:

- number 27 on the presence of multiple nitrosamines
- number 28 on applying a less-than-lifetime limit
- number 31 on which nitrosamines should be included in risk assessments and confirmatory testing

25. AI limits for nitrosamine impurities in drug products that fall within the scope of the ICH S9 guideline or where the API is genotoxic

If a nitrosamine impurity is identified in a pharmaceutical, biologic or radiopharmaceutical product that is intended for advanced cancer indications (defined in the scope of the ICH S9 guideline), the impurity can be controlled per the recommendations in the ICH S9 questions-and-answers document.

If a nitrosamine impurity is identified in a drug product where the API is genotoxic at therapeutic concentrations, the impurity can be controlled at limits for non-mutagenic impurities. Refer to the ICH Q3A and Q3B guidelines.

26. Communicating if AI limits are revised in the future

Health Canada continues to work with international regulatory agencies to determine acceptable limits for nitrosamine impurities. We will communicate any changes to the acceptable limits for nitrosamine impurities to MAHs and applicants in a timely manner.

Interim AI limits were originally communicated to MAHs for 5 nitrosamine impurities in angiotensin II receptor blockers (also known as "sartans"). These were in place until September 30, 2020, and will not be reduced to a lower level.

27. Acceptable limit if multiple nitrosamines are detected in an API or a drug product

If an API or drug product has the risk of containing more than 1 actual or potential nitrosamine impurity, total (cumulative) daily exposure should be limited to the nitrosamine with the most conservative AI limit at the maximum daily dose of the drug product.

Examples:

- If a drug product contains both NDMA and NMBA, the total/cumulative daily exposure of the 2 nitrosamines should be limited to 96.0 ng/day.
- If a drug product contains both NDMA and NDEA, the total/cumulative daily exposure of the 2 nitrosamines should be limited to 26.5 ng/day.

If an applicant or MAH proposes to control multiple nitrosamine impurities in an API or drug product using an alternative methodology, Health Canada will assess the acceptability of the approach on a case-by-case basis. Any proposed alternative methodology should ensure that excess cancer risk does not exceed 1 in 100,000.

28. Application of a less-than-lifetime (LTL) limit by considering the principles in ICH's M7 guideline if a nitrosamine impurity is present in a drug product that is administered for less than a lifetime

Considering the risk profiles of nitrosamines and the possibility of an additive biological effect, the limits outlined in Table 2 are considered appropriate for lifetime and LTL administration of a drug product.

If a nitrosamine impurity cannot be controlled at the AI, Health Canada will consider an interim limit higher than the AI. We will do so on a case-by-case basis and only in exceptional circumstances (for example, to avoid a drug shortage of a drug product that is considered medically necessary).

Where an applicant or MAH proposes an interim limit higher than the AI for a nitrosamine impurity, Health Canada will consider:

- the medical necessity of the drug product
- levels of impurity observed in representative batches
- other risk management considerations (for example, the availability of alternative medications on the Canadian market)

We will consider an interim limit higher than the AI for a nitrosamine impurity as a transitory measure only, until appropriate changes to reduce the level of the nitrosamine impurity to at or below the AI have been implemented.

Quality

29. Risk factors and potential root causes to be considered for the presence of nitrosamine impurities in human pharmaceuticals when performing a risk assessment

Knowledge of risk factors and potential root causes for nitrosamine impurities continues to evolve. Applicants and MAHs should stay up-to-date on risk factors and potential root causes that Health Canada and other regulators have identified. The formation or introduction of nitrosamines may occur during the API or drug product manufacturing process. It may also occur through degradation mechanisms over the retest period of the API and the shelf-life of the drug product.

Inadequate process design and/or process controls, as well as gaps in quality and compliance oversight, may contribute to the presence of nitrosamine impurities in APIs and drug products above acceptable intake (AI) limits. Applicants and MAHs should consider both intrinsic and extrinsic factors when conducting risk assessments for nitrosamine impurities.

Potential and confirmed root causes for the presence of nitrosamines in drug products include the following:

- Nitrosation of a secondary or tertiary amine during API or drug product manufacturing, with insufficient downstream purge of the nitrosamine formed, and/or during API or drug product storage (common nitrosation conditions involve the combination of amines and nitrite ion under acidic conditions)
    - Sources of amines include APIs, API intermediates, starting materials, reagents, solvents, catalysts, reaction by-products and degradation products. Certain non-medicinal ingredients may also contain amines as part of their structure. Amines leading to stable nitrosamines include secondary amines and tertiary amines. Quaternary ammonium salts are also potential precursors to nitrosamines. Primary and tertiary amines may contain secondary amines as impurities. Amines may be present as impurities in amides or formed through the degradation of amides (for example, via hydrolysis). Tertiary amines may be nitrosated by a dealkylative pathway to produce one or more secondary amines, which may subsequently undergo nitrosation to produce multiple nitrosamines.
    - Nitrosating agent precursors and sources include:
        - nitrite ion intentionally used in a manufacturing process (for example, as used in diazotization chemistry or as a reducing agent for azide ion)
        - nitrite present as an impurity in reagents (for example, sodium azide), common non-medicinal ingredients (for example, microcrystalline cellulose, magnesium stearate)
        - nitrogen oxides (for example, NO, N_2O_3)
        - nitric acid
        - nitrosyl halides

        - alkyl nitrites and nitro compounds (for example, nitromethane)
        - potable and/or purified water containing nitrite
- Using a nitrosamine as a starting material or synthetic intermediate, with incomplete conversion of the nitrosamine and/or insufficient downstream purge
- Reaction of nitrite ion and an amine under process conditions with pH >7 under catalysis by a carbonyl compound, with insufficient downstream purge
- Oxidation of a hydrazine functional group in an API, starting material, intermediate or a reagent to produce a nitrosamine, with insufficient downstream purge
- Using certain materials in container closure components, such as:
    - nitrocellulose, found in certain lidding foils used for blister packaging
    - certain types of vulcanisation accelerators (for example, dithiocarbamate, thiourea, thiruams) which are used in rubber manufacturing
- Using recycled materials (for example, solvents, reagents, catalysts) contaminated with nitrosamines and/or nitrosamine precursors
- Cross-contamination of materials with nitrosamines/nitrosamine precursors in multi-product facilities (for example, through the use of shared equipment)
- Poor operation of a process step (for example, during liquid-liquid phase separations), which is intended to purge nitrosamines
- Using certain manufacturing operations that could facilitate contact between nitrosamine precursors (for example, wet granulation) or introduce nitrosating agents/precursors (for example, nitrogen oxides during fluid bed drying)

30. Components of drug products to consider in risk assessments

All components of the finished drug product should be considered as potential sources of nitrosamine impurities, or their precursor nitrosating agents and amines, in the context of the designated process and storage conditions. For example, some excipients may contain residual levels of nitrite (Wu, Y. et al. AAPS PharmSciTech 2011, 12(4), 1246-1263) or reactive amines as part of their molecular structure. Under certain manufacturing process or storage conditions, this may lead to the formation of nitrosamine impurities.

Refer to number 29 for more information on risk factors and potential root causes to take into consideration.

31. Nitrosamine impurities to consider in the Step 1 risk assessment and Step 2 confirmatory testing

Each API and drug product manufacturing process is unique. Thus, the nitrosamines listed in Table 2 of this guidance (refer to number 24) are not exhaustive and do not represent all nitrosamines potentially present in APIs and drug products. Conversely, the nitrosamines listed in Table 2 may not be potential impurities in all APIs and drug products.

MAHs and applicants should ensure that the risk assessments consider and identify the possibility of any nitrosamine impurity that may be formed or introduced. All nitrosamines that have been determined to be potentially formed or introduced should be included within the program for confirmatory testing (Step 2).

For nitrosamines not included Table 2, MAHs and applicants should follow the principles outlined in the ICH M7 guideline on mutagenic impurities to establish an AI limit. Refer to number 24 for more information.

32. Testing methodologies provided by Health Canada

Several regulators, including Health Canada, Europe's network of Official Medicines Control Laboratories (OMCLs) and the U.S. Food and Drug Administration (FDA), have published and shared testing methodologies. These methods may be used, although there is no requirement to do so.

In all cases, companies should use appropriately sensitive, validated analytical methods and conduct the testing at a GMP-compliant facility. If other methodologies are used, there is no need to verify the method with Health Canada prior to use.

Analytical methods should be quantitative in nature (as opposed to limit-based tests) and should be fully validated before confirmatory testing begins. If limit-based tests are used, ensure that the appropriate scientific justification is provided in the risk assessment documentation. For example:

- demonstration that the limit test is valid at or lower than the AI limit
- supporting evidence that indicates there is no increase in the concentration of nitrosamine impurities over time

Unless otherwise justified, method validation should be performed using the drug product that is authorized for use in Canada.

Where multiple strengths of a drug product exist and the validation is to cover multiple strengths, the justification for the choice of product strength used for validation should be described in the validation protocol.

33. Validating the limit of quantitation (LOQ) for nitrosamine impurity analytical procedures

The LOQ for analytical procedures that are intended for quantitation of nitrosamine impurities should be equal to or less than the most conservative AI limit of the nitrosamines detected in an API or drug product. Analytical procedures may need to be validated with LOQs well below the most conservative AI limit of the nitrosamines present, if proposals for a reduced testing program or absence of testing of the drug product are anticipated.

34. Including routine testing for nitrosamine impurities in the API and/or drug product specification (updated)

The API specification should include a test and acceptance criterion for each nitrosamine impurity when:

- the risk for nitrosamine presence is considered to be high and/or
- the concentration of any nitrosamine is found to be at significant levels (for example, greater than 30% of the AI limit) during confirmatory testing

Examples where the risk for nitrosamines is considered high:

- potential for nitrosamine formation on storage
- presence of nitrosamine precursor functional groups in the API
- late-stage formation/introduction of a nitrosamine impurity in the manufacturing process

Where multiple nitrosamines are potential and/or detected in an API, a cumulative limit using the most conservative AI limit of the nitrosamines present should also be included in the specification.

Routine testing for nitrosamine impurities should be included in the drug product specification when:

- the potential for nitrosamine introduction during drug product manufacturing, packaging and storage is identified and/or
- a nitrosamine impurity is detected in the drug product during confirmatory testing and the root cause is unknown

Where such a risk is identified, a test and acceptance criteria for both release and shelf life specifications should be included. Where multiple nitrosamines are potential and/or detected, control for total nitrosamines using the most conservative AI limit of the nitrosamines potential and/or detected should be included in the specification. Alternatively, control limits expressed on an individual impurity basis (for example, a limit for each nitrosamine set at a percentage of its AI limit such that the sum of the % AI limits for each specified nitrosamine does not exceed 100%) may be proposed with appropriate justification. Other approaches for establishing a suitable specification when multiple nitrosamines are concerned may be acceptable if appropriately justified.

MAHs should test all new lots of drug product for nitrosamines and only release lots that meet the acceptance criteria for individual (and multiple nitrosamines, if relevant). Continue routine testing of all drug product lots until the root cause is identified and alternative controls/risk mitigation measures (such as process controls, raw material specifications) have been implemented. Ensure that nitrosamine impurities will be routinely below the AI limit in the future.

35. Potential control options for nitrosamine impurities in the API

Control options for nitrosamine impurities include:

- routine testing in the API (ICH M7 option 1)
- control in upstream intermediate specifications at the acceptable limit (ICH M7 option 2) (when the route cause, or causes, of nitrosamine presence have been established unequivocally)
- control in upstream intermediate specifications at acceptance criteria that exceed the acceptable limit (ICH M7 option 3) (when the root cause, or causes, have been established unequivocally and justification of the proposed limit is supported by demonstrated process capability (for example, spike and purge studies)

Proposals for an ICH M7 option 4 control strategy for nitrosamine impurities in a new market authorization application will be evaluated on a case-by-case basis. An option 4 control strategy proposal may not be appropriate when the concentration of any nitrosamine impurity in an API is greater than 30% of the AI limit. However, such a strategy may be acceptable when process understanding has been demonstrated by fate-purge studies, identification of process parameters that impact nitrosamine impurity levels and when supported by appropriate analytical data. Predicted purge factor calculations should be supported by appropriate analytical data.

This information should be provided along with copies of analytical procedures and method validation reports in the new market authorization application.

Refer also to number 34 for information on routine testing for nitrosamine impurities in the API and/or drug product specification.

36. Confirmatory testing expectations (Step 2)

During confirmatory testing, MAHs should test the drug product to determine the levels of nitrosamine impurities.

Testing the API is also recommended if the risk assessment indicated that the API is a potential source of nitrosamine impurities in the drug product. The API testing results may be used to support root cause investigations and the development of a justified control strategy for nitrosamine impurities in the API.

37. Analytical laboratories conducting nitrosamine testing and listing on the DEL

The analytical lab used for nitrosamine confirmatory testing (Step 2) does not have to be listed on the DEL at this time. However, in all cases, the confirmatory testing must be conducted at a GMP-compliant facility. A foreign analytical lab, if used for conducting the nitrosamine confirmatory testing, must either:

- have been deemed GMP-compliant by Health Canada or
- have a valid GMP inspection by a competent or qualified regulatory authority demonstrating compliance with current GMP standards

Ethical drugs are those that do not require a prescription, but are generally prescribed by a medical practitioner as professional use products (for example, hemodialysis solutions, nitroglycerine). For testing ethical and over-the-counter drugs, if no inspection reports by regulatory/qualified authorities are available, a corporate or consultant audit report to demonstrate GMP compliance is acceptable.

For more information about acceptable GMP evidence and regulatory requirements, refer to the following guidance:

- How to Demonstrate Foreign Building Compliance with Drug Good Manufacturing Practices (GUI-0080)

However, analytical labs must be listed on the applicable annex of the DEL if they are conducting:

- nitrosamine testing used to release APIs and drug products for the Canadian market or
- tests that are part of the API or drug product specification
    - includes testing imposed through the sartan terms and conditions

For guidance on Health Canada's expectations for testing facilities or for other related questions, please send an email to foreign.site-etranger@hc-sc.gc.ca.

38. Number and types of drug product batches as part of confirmatory testing for marketed products and new market applications

For marketed products, the number of batches to be tested should be commensurate with the risk. Examples of high risk include:

- late-stage formation/introduction of a nitrosamine impurity in a manufacturing process
- presence of nitrosamine precursor functional groups in the API
- potential for nitrosamine formation on storage

MAHs and manufacturers should test a representative number of batches of the drug product as appropriate based on the risk assessment (for example, batches that are representative of sources of components, manufacturing processes/sites, manufacturing dates).

If the root cause for nitrosamine risk has been identified and scientifically demonstrated, and impurity levels are expected to be consistent from batch-to-batch (for example, as demonstrated by spike-purge studies), testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. Testing should include both newly produced batches as well as retained samples of batches still within the expiry date. If fewer than 3 batches are manufactured annually, then all batches within the expiry date should be tested.

Testing plans or protocols (for example, a protocol for the number and type of batches to be tested) do not need to be submitted to Health Canada for assessment and approval before initiating confirmatory testing.

If nitrosamine impurities are detected at significant levels (approaching, at or above AI limits), additional batches of the drug product on the Canadian market and within the expiry date should undergo confirmatory testing. In such cases, MAHs may be requested to test all lots on the Canadian market that are within the expiry date.

For NDSs, ANDSs, Supplements and Notifiable Changes (for quality changes that may impact the potential presence of nitrosamines in the drug substance or drug product, refer to number 13), at least 6 pilot or 3 commercial-scale batches should undergo confirmatory testing where a risk of nitrosamines has been identified. A higher number of batch results should be submitted for assessment where the risk of nitrosamine presence is high. Examples include:

- the late-stage formation/introduction of a nitrosamine impurity
- nitrosamine precursor functional groups in the API
- stability concerns exist for nitrosamine formation over the retest period/shelf life

Testing results of stability batches for a nitrosamine impurity should be conducted where:

- a risk has been identified that nitrosamine levels could increase in the API or drug product over time or
- the potential for increases over time is unclear

A minimum of 6 months of accelerated and long-term stability data in the proposed container closure system(s) should be provided in the drug application.