QUESTIONS AND ANSWERS

REQUEST TO EVALUATE THE RISK OF THE PRESENCE OF *N*-NITROSAMINE IMPURITIES IN HUMAN PHARMACEUTICAL, BIOLOGICAL AND RADIOPHARMACEUTICAL PRODUCTS

dated: 2020-12-15 (Update 2)

Questions and Answers

Request to evaluate the risk of the presence *N*-nitrosamine impurities in human pharmaceutical, biological and radiopharmaceutical products

This Questions and Answers (Q&A) document represents Health Canada's current thinking and recommendations on issues related to N-nitrosamine impurities (herein also referred to interchangeably as nitrosamine impurities or nitrosamines) and may be subject to change as new information becomes available.

The original Nitrosamines Q&A document was issued to Market Authorization Holders (MAHs) on November 26, 2019 and subsequently updated on June 12, 2020 (Update 1).
The Q&A document has now been updated to provide further details and guidance to Active Pharmaceutical Ingredient (API) manufacturers, drug product manufacturers, MAHs, and importers (Update 2).

Updates to the June 12, 2020 version of the Q&A document are identified below with the descriptors "NEW" or "UPDATED" (as applicable).

Multiple questions that provide information on a similar theme have been grouped together (i.e., under the headings of General, Safety, and Quality). Consequently, the questions have been re-numbered from the previous edition of this Q&A document.

Queries relating to Health Canada's letter dated October 2, 2019 or this related Q&A document from Health Canada can be directed to hc.bps.enquiries.sc@canada.ca.

Queries relating to Health Canada's letter entitled "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" can be directed to hc.brdd.ora.sc@canada.ca.

GENERAL (e.g., Scope, Responsibilities, Communications)

Q1: Are all drug products to be reviewed? (UPDATED)

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. This includes those drug products containing angiotensin II receptor blockers (also known as sartans). 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.

The current request for conducting risk assessments for the potential presence of nitrosamine impurities has now been extended to all biological and radiopharmaceutical products for human use. Refer to Question 2 for expected timelines for conducting risk assessments (and subsequent steps, as necessary) for biological and radiopharmaceutical products.

Please refer to Health Canada's letter entitled *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* for further details.

Products that are not currently within the scope of the October 2, 2019 letter include cosmetics that have not received a Drug Identification Number (DIN) and the following categories of drug products: antimicrobial agents, veterinary health products, and natural health products.

Q2: What are the current timelines for the completion of risk assessments (Step 1) and confirmatory testing/changes to the market authorization (Steps 2 and 3)? (NEW)

As communicated to MAHs on August 10, 2020, for drug products containing chemically synthesized APIs, the steps for actions relating to nitrosamines are expected to be completed as follows:

- Step 1 - Completion of risk assessments by March 31, 2021;
- Step 2 - Confirmatory testing by October 1, 2022;
- Step 3 - Changes to the market authorization by October 1, 2022.

As outlined in Health Canada's letter entitled *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*, for biological and radiopharmaceutical products, the steps for actions relating to nitrosamines are expected to be completed as follows:

- Step 1 - Completion of 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.

Q3: Do the outcomes of the risk assessments (Step 1) need to be 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 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.

For Canadian importers that received terms and conditions on their Drug Establishment Licence (DEL) for nitrosamine testing of angiotensin II receptor blockers (also known as sartans), Health Canada is providing an opportunity for importers to provide supporting information to modify or remove the terms and conditions by submitting the API and drug product risk assessments and testing results completed as per Steps 1 and 2 to hc.foreign.site-etranger.sc@canada.ca for consideration.

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

Q4: When determining the priorities and order in which products should be reviewed, what factors should be considered? (UPDATED)

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 and packaging 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).

Q5: Is Health Canada open to MAHs co-operating 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 product 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.

Q6: What are the responsibilities of API manufacturers, excipient manufacturers, drug product manufacturers, MAHs, and importers?

Following receipt of authorization to market in Canada, MAHs have the responsibility to ensure the ongoing safety, efficacy, and quality of pharmaceuticals, which would include implementation of an ongoing monitoring programme to detect trends in quality. This programme should be based on appropriate controls for raw materials, all processing steps, critical process parameters, and critical quality attributes.

In response to the request to complete risk assessments for the potential presence of nitrosamine impurities, MAHs should complete robust risk evaluations using a holistic approach with a detailed assessment of all stages of the product life cycle. This would include an appropriate level of documented root cause analysis, evaluation of manufacturing controls and conditions for the medicinal ingredients, non-medicinal ingredients (excipients) and the 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 for the drug product. MAHs are responsible to ensure that the risk assessments have been conducted by personnel with acceptable qualifications and expertise (e.g., relevant training, knowledge, and practical experience). To enable this robust risk assessment, information should be made available by API, excipient, and drug product manufacturers to the MAH.

In the context of control for nitrosamine impurities, manufacturers and importers are required to comply with any Terms and Conditions specified in their Drug Establishment License (DEL). This could include restrictions or additional specific testing and investigational requirements for nitrosamine impurities.

Q7: How should a MAH proceed if they are unable to meet the specified timelines for risk assessment (Step 1)? (UPDATED)

Given the potential risks associated with nitrosamines in pharmaceuticals, MAHs should take action to complete the risk assessments as soon as possible and within the designated timelines.

If an MAH is unable to meet the Step 1 deadline due to exceptional circumstances, a request for extension should be submitted to Health Canada. This request for extension should be submitted as soon as possible. The request should contain relevant information, including the progress to date, the reasons for not meeting the deadline, the remaining work and the expected timelines for completing the risk assessments. To prioritize APIs and drug products for the completion of risk assessments, MAHs are reminded to use quality risk management principles (refer to ICH's Q9 guideline, Health Canada's GMP Guides 0001 (GMP Guide for Drug Products) and 0104 (GMPs for APIs)), together with additional considerations found under the answer to Question 4 in this Q&A document.

Requests for extensions will be considered on a case-by-case basis and should be directed to hc.bps.enquiries.sc@canada.ca (for drug products containing chemically synthesized APIs) or to hc.brdd.ora.sc@canada.ca (for biological and radiopharmaceutical products).

Q8: Is it acceptable to rely solely on statements or declarations by manufacturers and suppliers in lieu of completing risk assessments?

No. Statements and declarations provided by manufacturers and/or suppliers are not a substitute for an overall robust risk assessment by the MAH. While the provision of 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.

Q9: Is it acceptable to skip the risk assessment step (Step 1) and proceed directly to confirmatory testing (Step 2)?

No. 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 otherwise introduced into the API or drug product. If a risk of one 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 can also be useful for the establishment of a suitable control strategy and changes which can be introduced to prevent the presence of nitrosamines.

Q10: Is it acceptable to apply the results of a risk assessment and confirmatory testing for a drug product that is marketed outside of Canada to a drug which is authorized for sale in Canada?

In all instances, MAHs are responsible to ensure that risk assessments and (if applicable) confirmatory testing are relevant to the drug product which has been authorized for sale in Canada. If a risk assessment and confirmatory testing have been completed for a drug product which is approved for use outside of Canada, then it may be possible to utilize that information for the risk assessment and confirmatory testing of the drug product which is authorized for sale in Canada. In this scenario, the two drug products must be identical (e.g. composition, strength, manufacturing process, API and excipient sources, site(s) of manufacture, etc.). MAHs should prepare a written justification when the risk assessment and confirmatory testing results of a foreign product will be relied upon and should be prepared to provide this

justification to Health Canada upon request.

Q11: In cases where a risk assessment concludes that there is no risk for the presence of nitrosamines, is confirmatory testing required? (UPDATED)

MAHs are required to conduct a thorough, robust risk assessment. In the October 2, 2019 letter and in the letter entitled "*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*, 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 co-exist 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 with rationale. If it is concluded that a risk for the presence of nitrosamines 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 at any level in an API or drug product, Health Canada must be informed immediately using the reporting addresses provided in Question 13 (below).

Q12: How should changes to the market authorization be submitted? (NEW)

Regarding Step 3 (changes to the market authorization), changes should be submitted in a timely manner in eCTD format via the Common Electronic Submission Gateway (CESG) or in non-eCTD electronic-only format to the Office of Submissions and Intellectual Property, Therapeutic Products Directorate, Finance Building, 101 Tunney's Pasture Driveway, Address Locator 0201A1, Ottawa, Ontario K1A 0K9.

Health Canada's *Post-Notice of Compliance (NOC) Changes: Quality Document* and *Post-Drug Identification Number (DIN) Changes Guidance Document* provide information concerning change classification, reporting, and supporting data recommendations.

Given that these changes are the result of potential safety concerns, changes for new drugs should be submitted as Level 1 – Supplement (SNDS or SANDS, as appropriate) as described in Health Canada's *Post-Notice of Compliance (NOC) Changes: Quality Document.*

Q13: 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 API, 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 & Enforcement 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-coq.SC@canada.ca
Ontario	Health Products Compliance & Enforcement 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 & Enforcement 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.

Q14: How should MAHs proceed when information necessary to complete risk assessments is not provided by the API or drug product manufacturer? (UPDATED)

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).

For additional guidance, refer to Health Canada's GMP Guide 0001, C.02.012, Interpretation 3-12[1], regarding outsourced activities.

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 their medicines and should ensure through internal or third party audit that:

- Risk assessments have been conducted by personnel with acceptable qualifications

[1] https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001/document.html#a5.23

(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, the letter entitled *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*, and within this Q&A document).

Q15: How will Health Canada respond to notifications of the detection of one or more nitrosamine impurities that are present in the API or drug product? (UPDATED)

In the case where one or more nitrosamine impurities are detected (refer also to Question 23 below concerning the detection of multiple nitrosamines), in addition to notifying Health Canada (refer to Question 13 regarding appropriate contacts within Health Canada), the Department 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; in cases where product recall actions are warranted, Health Canada's GUI-0039 (Drugs and natural health products recall guide) should be consulted for procedures;
- Perform quality investigations in accordance with written procedures;
- Assess possible root cause(s), describe and carry out corrective and preventive actions (CAPAs);
- 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;
- Establish a risk mitigation plan to ensure that level(s) will be consistently below the acceptable intake(s) at the end of the retest period for the API or the shelf-life for the drug product moving forward;
- Further, measures should be initiated to introduce changes or controls in 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)). Health Canada may request additional actions by other MAHs of the same products to mitigate any risks identified and protect the health and safety of Canadians if deemed necessary.

In situations where a nitrosamine is detected above the AI, refer also to Question 29 concerning establishment of specifications.

Q16: 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 license.

Q17: What approach should be taken 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 be designed to ensure that the formation/introduction of nitrosamines is avoided at the outset.

If the formation or introduction of nitrosamines is unavoidable, manufacturing processes should demonstrate process capability to routinely reduce the levels of nitrosamine impurities below the acceptable intake. 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 which are planned for submission or have already been submitted, MAHs should 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 communications. For planned submissions, the relevant sections of the Common Technical Document (CTD) in the drug application should include information on these risk assessments.

The risk assessment should be placed in section 3.2.P.2, and confirmatory testing results and updated control strategy (where warranted) should also be included in the drug application (e.g., 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, etc.). For submitted applications that are currently under review, the sponsor may be requested to provide the risk assessment and confirmatory testing results as part of the assessment procedure.

Please refer to Question 18 for further information.

Q18: Will a risk assessment for the potential presence of nitrosamines become part of the expected content for new submissions? (UPDATED)

As for all impurities, and especially for highly potent, mutagenic carcinogens, risk assessments for nitrosamines should be conducted routinely during API 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 New Drug Submissions (NDSs), Abbreviated New Drug Submissions (ANDSs), and Supplements. ICH's M7(R1) guideline, and ICH Q9 guidelines together with Health Canada's GMP Guides 0001 and 0104, should be consulted for further information concerning mutagenic impurity considerations and quality risk management principles, respectively.

As of April 1, 2021, all NDSs, ANDSs, and Supplements (for Quality changes that may impact

the potential presence of nitrosamines in the drug substance or drug product) for pharmaceutical products containing chemically synthesized APIs should include a summary of risk assessments for the potential formation/introduction of nitrosamines in the API and drug product. Applicants should complete and should include a discussion on the risk assessments as well as any supporting information. Failure to include this information could result in requests for additional information, delays in the review process, and potentially the issuance of negative decisions.

Q19: How is Health Canada planning to engage stakeholders and ensure ongoing communication with industry? (UPDATED)

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, root causes and new findings. Health Canada has hosted an information session with stakeholders in January 2020 and may host additional sessions in future as necessary. Health Canada has also established a dedicated webpage for information regarding nitrosamine impurities in medications, including summaries of analytical testing results of several products for levels of nitrosamine impurities. The Health Canada website with information on nitrosamines can be accessed at:

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html

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.

Q20: How is Health Canada working with global regulators around the issue of nitrosamine impurities in drug products? (UPDATED)

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 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.

SAFETY

Q21: What are the acceptable intakes for nitrosamine impurities that are considered acceptable to Health Canada? (NEW)

In addition to the limits for nitrosamine impurities outlined in Annex 1 of the October 2, 2019 letter, acceptable intakes have been derived for *N*-nitrosodibutylamine (NDBA) and 1-methyl-4-

nitrosopiperazine (MNP).

The derived AIs for seven nitrosamines are summarised in the table below:

Nitrosamine	Acceptable Intake (ng/day)*
N-nitrosodimethylamine (NDMA)	96.0
N-nitroso-4-(methylamino)butyric acid (NMBA)	96.0
1-methyl-4-nitrosopiperazine (MNP)	96.0
N-nitrosodiethylamine (NDEA)	26.5
N-nitrosodiisopropylamine (NDIPA)	26.5
N-nitrosoethylisopropylamine (NEIPA)	26.5
N-nitrosodibutylamine (NDBA)	26.5

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

Sponsors should refer to Health Canada's October 2, 2019 letter, and the ICH M7(R1) guideline, for information on how to propose an AI for a nitrosamine which is not included in the above table.

Please also refer to Question 23 concerning the presence of multiple nitrosamines, Question 24 concerning application of a less-than-lifetime limit, and to Question 26 concerning the nitrosamines which should be included in risk assessments and confirmatory testing.

Q22: If the acceptable intakes are revised in the future, how will Health Canada communicate this information? (UPDATED)

Health Canada continues to work with international regulatory agencies to determine 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.

The interim acceptable intakes which were originally communicated to MAHs for five nitrosamine impurities in angiotensin II receptor blockers (also known as "sartans") as being in place until September 30, 2020, will not be reduced to a lower level at this time.

Q23: If multiple nitrosamines are detected in an API or a drug product, what is the acceptable limit? (NEW)

If an API or drug product has the risk of containing more than one actual or potential nitrosamine impurity, the total (cumulative) daily exposure of the multiple nitrosamines should be limited to the acceptable intake of the most potent nitrosamine 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 two 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 two nitrosamines should be limited to 26.5 ng/day.

Q24: If a nitrosamine impurity is present in a drug product that is administered for less

than a lifetime, can a less-than-lifetime (LTL) limit be derived considering the principles outlined in ICH's M7(R1) guideline? (UPDATED)

As outlined in Annex 1 of the October 2, 2019 letter to MAHs, interim acceptable intakes were established for five nitrosamine impurities considering the principles outlined in ICH's M7(R1) guideline. Acceptable intakes for additional nitrosamine impurities have since been established and are provided in Question 21. These acceptable intakes are considered to be appropriate for all routes of administration.

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 incidence, using the most relevant TD_{50} value in the Carcinogenic Potency Database. Insufficient carcinogenicity data were available to derive compound-specific limits for NMBA, NDIPA, NEIPA, NDBA and MNP. For this reason, a structure-activity relationship analysis was performed to predict if each nitrosamine is chemically more similar to NDMA or NDEA. For a nitrosamine impurity that is not included in the table in Question 21, MAHs should follow the principles as outlined in ICH's M7(R1) guideline to derive and qualify an acceptable intake.

Considering the risk profiles of NDMA and NDEA, the limits outlined in the table in Question 21 are considered appropriate for lifetime and LTL administration of a drug product. If a nitrosamine impurity cannot be controlled at the acceptable intake, on a case-by-case basis, and only in exceptional circumstances, Health Canada will consider an interim acceptable intake of a nitrosamine based on LTL administration taking into account the medical necessity of the drug product and other risk management considerations (e.g., the availability of alternative medications on the Canadian market). In the case where an interim limit of a nitrosamine is proposed by a MAH based on LTL administration, this interim limit will be evaluated by Health Canada considering the approach described in Table 2 of the ICH M7(R1) guideline as well as levels observed in representative batches. Health Canada will consider an interim limit for a nitrosamine impurity based on LTL administration as a transitory measure only, until appropriate changes to reduce the level of the nitrosamine impurity below the acceptable intake have been implemented.

QUALITY

Q25: Should risk assessments include a consideration of all components of the drug product, including the API and excipients, as well as the container closure system?

Yes. 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[2] or reactive amines as part of their molecular structure which, under certain process or storage conditions, may lead to the formation of nitrosamine impurities. It is also important to note that the use of certain packaging components has been identified as a potential source of nitrosamine impurity formation during drug product packaging (e.g. a lidding foil

[2] Wu, Y. et al. AAPS PharmSciTech 2011, 12(4), 1246-1263

containing nitrocellulose printing primer may react with amines in printing ink to generate nitrosamines, which could be transferred to the drug product via vaporization and condensation onto the drug product during heat-sealing of the blister materials.

Q26: Which nitrosamine impurities should be considered in the risk assessment and confirmatory testing? (UPDATED)

Given that each API 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 (i.e. NDMA, NDEA, NMBA, NEIPA and NDIPA), Health Canada's letter regarding biologics and radiopharmaceutical products, and in this Q&A document is not exhaustive and does not represent all nitrosamines potentially present in APIs and drug products. Conversely, these nitrosamines may not be relevant potential impurities in all APIs and drug products. Therefore, MAHs should ensure that the risk assessments consider and identify the possibility of any nitrosamine impurity which 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 in the October 2, 2019 letter, Health Canada's letter regarding biologics and radiopharmaceutical products, and in this Q&A document, MAHs should follow the principles outlined in the ICH M7(R1) guideline on mutagenic impurities to establish an acceptable intake.

Q27: 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 all cases, 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.

Analytical methods should be quantitative in nature (as opposed to limit-based tests) and should be fully validated prior to the commencement of the confirmatory testing. If employed, the use of limit-based tests should be accompanied by appropriate scientific justification in the risk assessment documentation (e.g., demonstration that the limit test is well below the acceptable intake limit, supporting evidence that indicates no increase in the concentration of nitrosamine impurities over time).

Unless otherwise justified, method validation should be performed using the drug product which is authorized for use in Canada. Where multiple strengths of a drug product exist and the validation is intended to cover multiple strengths, the justification for the choice of product strength used for validation should be described in the validation protocol.

Q28: What are the limits of quantitation (LOQ) that should be validated for nitrosamine impurity analytical procedures? (NEW)

The limit of quantitation (LOQ) for analytical procedures which are intended for quantitation of

nitrosamine impurities should be equal to or less than the acceptable limit for the most potent nitrosamine detected in an API or drug product. Analytical procedures may need to be validated with LOQs well below the acceptable limit for the most potent nitrosamine present, if proposals for a reduced testing programme or absence of testing of the drug product are anticipated.

Q29: When should routine testing for nitrosamine impurities be included in the API and/or drug product specification? (NEW)

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 when the concentration of any nitrosamine is found to be at significant levels (e.g. greater than 30% of the acceptable intake) during confirmatory testing. The late-stage formation/introduction of a nitrosamine impurity in the manufacturing process, the presence of nitrosamine precursor functional groups in the API, and the potential for nitrosamine formation on storage are some examples where the risk for nitrosamines is considered to be high. Where multiple nitrosamines are potential and/or detected in an API, a cumulative limit for nitrosamines based on the acceptable intake for the most potent nitrosamine 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 when 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 criterion for both release and shelf life specifications should be included. Where multiple nitrosamines are potential, a cumulative limit for nitrosamines based on the acceptable intake for the most potent nitrosamine should also be included in the specifications for release and shelf life. MAHs should test all new lots of drug product for nitrosamines and only release lots which meet the acceptance criteria for individual (and cumulative nitrosamines, if relevant). Routine testing of all drug product lots should continue until such time that root cause is fully understood and alternative controls/risk mitigation measures (e.g. process controls, raw material specifications, etc.) have been implemented such that nitrosamine impurities can be assured to be routinely below the acceptable limit in the future.

Q30: What are the potential control options for nitrosamine impurities in the API? (NEW)

Control options for nitrosamine impurities include routine testing in the API (ICH M7(R1) Option 1) or control in upstream intermediate specifications at the acceptable limit (ICH M7(R1) Option 2) when the root cause (or causes) of nitrosamine presence have been established unequivocally. In addition, the control of nitrosamine impurities in upstream intermediate specifications at acceptance criteria which exceed the acceptable limit (ICH M7(R1) Option 3) may be proposed when the root cause (or causes) have been established unequivocally and justification of the proposed limit is supported by demonstrated process capability (e.g. spike and purge studies).

Q31: 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 API 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.

Q32: How many batches and what type of drug product batches should be tested as part of confirmatory testing for marketed products and new product submissions? (NEW)

For marketed products, all drug product batches on the Canadian market within expiry should be subjected to confirmatory testing when a risk of nitrosamines is identified. The test data should span the approved shelf life of the drug product to ascertain if nitrosamine levels could increase over time due to degradation or other root causes. As such, the need to test every lot is important in cases where the root cause for nitrosamines is uncertain or unknown, or where the root cause is linked to drug product manufacturing or stability. All drug product lots should be tested as levels may vary from lot to lot.

For NDSs, ANDSs, and Supplements (for Quality changes that may impact the potential presence of nitrosamines in the drug substance or drug product), at least six pilot or three commercial scale batches should be subjected to confirmatory testing where a risk of nitrosamines has been identified. However, where the risk of nitrosamine contamination is high (e.g. 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 etc.), a higher number of batches should be submitted for assessment. Testing results of stability batches for a nitrosamine impurity should be submitted where there is an identifiable risk that nitrosamine levels could increase in the drug product over time or where the potential for increases over time is unclear. A minimum of six months of accelerated and long-term stability data in the proposed container closure system(s) should be provided.