Questions and Answers for Product Registrants on Management of Nitrosamine Impurities in Therapeutic Products

As part of the regulatory approach to manage the risk of nitrosamine impurities in therapeutic products, the Health Sciences Authority (HSA) has required all product registrants of therapeutic products containing chemically synthesised drug substances to conduct risk assessments of the products to identify any potential risk of nitrosamine impurities. Where potential risk is identified, confirmatory testing should be done, and the necessary risk mitigation measures must be implemented.

The review consists of 3 steps:

- Step 1: Perform risk assessment to identify potential risk of nitrosamine impurities.
- Step 2: Conduct detailed assessment to identify all potential sources of the nitrosamine impurities, conduct confirmatory testing and develop risk mitigation measures.
- Step 3: Implement risk mitigation measures.

Refer to the webpage on the Guidance for Product Registrants on the actions required by product registrants to manage the risk of nitrosamine impurities in therapeutic products and the associated timelines.

This document clarifies HSA's current approach, recommendations, and regulatory requirements in the management of nitrosamine impurities in therapeutic products. It will be updated as new information becomes available. Product registrants should keep up to date with the latest information and evolving international regulatory requirements on this topic.

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Acronyms

AI	Acceptable Intake
CAPA	Corrective Action and Preventive Action
CEP	Certificate of Suitability (Ph. Eur. Monograph)
CPCA	Carcinogenic Potency Categorisation Approach
CPDB	Carcinogenic Potency Database
CTD	Common Technical Document
DMF	Drug Master File
DNA	Deoxyribonucleic acid
EAT	Enhanced Ames Test
EMA	European Medicines Agency (EU)
FDA	Food and Drug Administration (US)
GDA	Generic Drug Application
GLP	Good Laboratory Practice
HSA	Health Sciences Authority (Singapore)
ICH	International Council for Harmonisation
LCDB	Lhasa Carcinogenicity Database
LTL	Less-than-lifetime
MDD	Maximum Daily Dose
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MIV	Minor Variation
NCTR	National Center for Toxicological Research
NDA	New Drug Application
NDSRI	Nitrosamine Drug Substance Related Impurity
OECD	Organisation for Economic Co-operation and Development
PRISM	Pharmaceutical Regulatory and Information System
SAR	Special Access Route
TD_{50}	Median Toxic Dose
TGA	Therapeutic Goods Administration (Australia)

TTC	Threshold of Toxicological Concern

Section A: Risk Assessment for Registered Therapeutic Products

1. Why are product registrants required to conduct a risk assessment for nitrosamines in all their products?

Nitrosamines are classified as probable human carcinogens based on animal carcinogenicity studies. They can form electrophilic alkylating agents via metabolism activation, which subsequently react with the DNA to induce mutations and genotoxic changes. Nitrosamines have been observed to be associated with the formation of tumours (liver, kidney, oesophagus, stomach) in various animal species (both rodent and non-rodent species). Hence, reasonable steps should be taken to prevent or minimise the risk of nitrosamines in all therapeutic products to prevent unnecessary exposure to patients.

2. What are the currently identified risk factors and potential root causes for nitrosamine impurities in therapeutic products?

Nitrosamines can be formed when an amine and nitrosating agent react under favourable conditions. They can also be formed via other non-classical reactions, such as oxidation of hydrazine compounds with oxygen/catalyst and hydrogen peroxide, or ozonolysis of hydrazone compounds.

The potential root causes for nitrosamine formation identified so far include:

<u>In the drug substance manufacturing process</u>

(a) Intrinsic properties of the drug substance or their intermediates
(b) Direct introduction of nitrosamines or nitrosamine precursors during manufacturing
(c) Use of recycled materials or raw materials containing nitrosamines or nitrosamine precursors
(d) Cross contamination of materials with nitrosamines or nitrosamines precursors in

multi-product facilities

(e) Carry-over of nitrosamines between process steps

(f) Poor operation/design of process steps resulting in inadequate purge of nitrosamines

In the drug product manufacturing process or during storage

Recent findings have highlighted the risk of nitrosamine formation via the nitrosation of vulnerable amine groups in the drug substance or their related impurities/degradants with traces of nitrites in the excipients during drug product formulation and/or storage. These nitrosamines are known as nitrosamine drug substance related impurity (NDSRI) and have been found at levels that could exceed acceptable limits, even if the nitrite levels in the excipients are very low. Hence, the risk assessment should be revisited if this risk was not considered previously, and confirmatory testing should be performed where needed. The stability of the drug product should also be considered to ensure that the nitrosamine level remains within the acceptable limit throughout the product shelf life.

The collaboration of quality technical experts of international regulatory agencies, including from HSA, has led to the development of the scientific paper 'Regulatory Experiences with Root Causes and Risk Factors for Nitrosamine Impurities in Pharmaceuticals' which provides an insight on the current scientific information from a quality perspective on risk factors and potential root causes for nitrosamine impurities. Manufacturers and product registrants can refer to the publication to better understand the risk factors and the recommendations for risk mitigation and control strategies. Product registrants can also refer to information published by other regulatory agencies as a reference - See Question 33.

Additional risk factors and potential root causes are likely to be discovered as the issue of nitrosamine impurities in therapeutic products continues to evolve. Product registrants should remain updated on the developments and revisit their risk assessments when new information becomes available to ensure that the quality of your product is maintained throughout its lifecycle.

3. Is risk assessment required for all products, and how should the products be prioritised for risk assessment if there are many registered products to be assessed?

A risk assessment is required for all products containing chemically synthesised drug substance. Product registrants should apply a risk-based approach to prioritise the evaluations and confirmatory testing if there are many registered products to be assessed.

The risk assessments should start with the products that may pose higher risk if found to contain nitrosamines. Some factors that can be considered include:

(a) Duration of treatment: Chronic use will have higher risk versus acute use.
(b) Maximum daily dose: The higher the dose, the lower will be the acceptable limit, and hence there is a higher chance to exceed the limit.
(c) Volume of distribution or usage: Higher volumes of distribution will have more significant public impact.
(d) Number of nitrosamines: Products with multiple nitrosamines will have a higher risk.
(e) Structural elements in the drug substance: Drug substances with structural elements that are prone to nitrosation (e.g., secondary, or tertiary amine group) will have higher risk of nitrosamine formation.

4. Is there a template to be used for the risk assessments?

Product registrants can refer to the following as a guide in identifying risks of nitrosamine formation and in conducting the risk assessment:

- Appendix 2: Assessment aid for assessing nitrosamine risk
- Appendix 3: Guidance on submission of nitrosamine risk assessment where a risk is identified

The risk assessment may be documented in any format as long as all the information

required in the assessment aid is included. The same risk assessment that is submitted to other regulatory agencies can be used, provided that the information is relevant to the locally registered products (e.g., with the same registered manufacturers, product formula, storage conditions and specifications).

5. Does HSA need to be informed of the outcome of the risk assessments?

If a potential risk of nitrosamine is identified, HSA is to be notified via email at HSA_ProductDefect@hsa.gov.sg or via the Product Defect Reporting Form, with submission of the risk assessment documents. The risk assessment documents can be submitted directly by the drug substance or drug product manufacturer instead of by the product registrant as a closed part of the submission if there are concerns on the proprietary nature of the documents. However, the documents must refer to the product using the name that is registered locally.

HSA does not need to be notified if no risk of nitrosamine is identified. However, the risk assessment documents must be retained and be made readily available for submission when requested.

6. Is conducting one risk assessment for products with multiple strengths that use the same manufacturing processes and the same drug substance and drug product manufacturers sufficient?

One risk assessment can be used for products with multiple strengths if all the following conditions are met:

(a) Same drug substance manufacturing processes;
(b) Same qualitative formula; and
(c) Same drug substance and drug product manufacturers.

7. Can only one risk assessment be submitted for products with multiple strengths with different coating excipients?

One risk assessment for all strengths is acceptable if the excipients in the coating do not increase the risk of nitrosamine formation. An assessment on whether the excipients in the coating would result in nitrosamine formation in the drug product must be conducted and included as part of the nitrosamine risk assessment report.

8. If there are multiple drug product manufacturers registered, but the product supplied in Singapore only comes from 1 of these drug product manufacturers, can the risk assessment be conducted on this manufacturer only?

Reasonable steps should be taken to prevent or minimise the risk of nitrosamines in all therapeutic products to prevent unnecessary exposure of these nitrosamines to patients. For products identified with risk of nitrosamines, HSA will require the necessary corrective action and preventive action (CAPA) to be implemented.

As such, a risk assessment for all the registered manufacturers must be conducted. This is to allow time to address the issues if a risk of nitrosamine is identified (e.g., conducting root cause analysis, developing CAPA plan, preparing variation for submission, and for approval of the variation application). Failure to perform risk assessment for the other registered manufacturers may lead to a delay in subsequent marketing of the product from these other manufacturers. Otherwise, a variation application should be submitted to delete these additional manufacturers for the product.

9. Is a risk assessment still required if the product was never marketed, and there is no plan to market the product soon?

Reasonable steps should be taken to prevent or minimise the risk of nitrosamines in all therapeutic products to prevent unnecessary exposure of these nitrosamines to patients. For products identified with risk of nitrosamines, HSA will require the necessary CAPA to be

implemented.

As such, a risk assessment must be conducted for all registered products irrespective of the marketing status. This is to allow time to address the issues if a risk of nitrosamine is identified (e.g., conducting root cause analysis, developing CAPA plan, preparing variation for submission, and for approval of the variation application). Failure to perform a risk assessment may lead to a delay in subsequent marketing of the product, particularly if the risk of nitrosamine in other similar products has already been mitigated.

10. Is a risk assessment still required if there is no information on the drug substance manufacturing process because the product was registered before 2004?

A risk assessment must be conducted for all registered therapeutic products irrespective of the time of registration. Product registrants are responsible for the quality, efficacy, and safety of their registered products throughout their lifecycle. Hence, product registrants should work with the drug substance and drug product manufacturers to evaluate the risk of nitrosamines in their products. For registered products that are lacking in information on the drug substance manufacturing process, please refer to Question 17 on the updating of drug substance manufacturer information in PRISM.

11. Is a risk assessment still required if there is no information on the drug substance manufacturing process because the application was supported by a Certificate of Suitability?

A risk assessment is still required for products for which the registration was supported by a Certificate of Suitability (CEP). Product registrants are responsible for the quality, efficacy, and safety of their registered therapeutic products throughout their lifecycle. Hence, product registrants should work with the drug substance manufacturer or CEP holder to ensure that adequate risk assessment is conducted for the drug substance.

12. Are therapeutic products containing inorganic active pharmaceutical ingredients exempted from risk assessment?

Although inorganic active pharmaceutical ingredients inherently have a low risk of nitrosamine formation, the risk assessment must still be conducted as nitrosamines can be from other sources (e.g., excipients and cross contamination).

13. Does the risk assessment exercise apply to biological therapeutic products?

Product registrants are responsible for the quality, efficacy, and safety of their registered therapeutic products throughout their lifecycle. While HSA has yet to request for risk assessments for biological therapeutic products, product registrants are advised to conduct a risk assessment if there is a potential risk of nitrosamines based on known risk factors and root causes.

14. Does the risk assessment exercise apply to unregistered therapeutic products brought in via Special Access Route?

Special Access Route (SAR) is specifically for unregistered therapeutic products intended to address an unmet medical need in Singapore, and where the healthcare institutions and clinicians assume full responsibility on the product's quality, efficacy, and safety. These products are not evaluated by HSA. Hence, a risk assessment will not be required at the point of SAR application. Nonetheless, applicants should ensure that the products supplied in Singapore are of acceptable quality, and to check with the manufacturers on the risk of nitrosamine where feasible. HSA may request for information relevant to our investigations and if deemed necessary, request for market actions to recall the product if the product is found to contain nitrosamines above the acceptable limit.

As with all unregistered therapeutic products imported via the SAR, HSA should be notified if there are any quality or safety issues detected with the products supplied locally, including

the risk of nitrosamines, particularly if the nitrosamines are detected above the acceptable limit.

15. When a risk of nitrosamines is detected in the drug substance from a particular manufacturer, will HSA alert other affected product registrants who are using the same source of drug substance (i.e., same drug master file)?

Product registrants will be contacted to conduct a risk assessment if it is suspected that their products could be at risk of nitrosamines. Information that is considered non-proprietary in nature will be shared where appropriate.

16. Will HSA share product-specific evaluation/investigation report/data of products with risk of nitrosamines?

HSA is unable to share product-specific evaluation reports as they may contain proprietary information. Drug substances that are known to potentially contain nitrosamines are listed in Appendix 1: HSA recommended acceptable intake for certain known nitrosamines and the common root causes of nitrosamine formation are detailed in Question 2. Product registrants should keep abreast of new information and developments on this topic and conduct reassessments for the risk of nitrosamines in their products where appropriate.

17. The drug substance manufacturer information for a product registered before 2004 is not captured in PRISM. Is it required to update this information in PRISM?

An update of the drug substance manufacturer information in PRISM is required for products where a risk of nitrosamine is identified because more information about the manufacturing process will be required for assessment.

All product registrants are encouraged to update the drug substance manufacturer information even though a risk is not identified in the product so that complete information is

available to facilitate subsequent variation applications, as well as post-market follow-ups on the product.

To update the drug substance manufacturer information in PRISM, please submit a MIV-2 with the following documents:

(a) Declaration that this is an update of an existing drug substance manufacturer information in PRISM and not a change to add a new drug substance manufacturer. Please state the date of first use of this drug substance manufacturer in your declaration letter as the existing drug substance manufacturer may differ from the one in the initial product registration.
(b) Complete CTD Section S or both the open and closed portions of the DMF; or
(c) CEP (Certificate of Suitability from EDQM), S.2.1 (Drug substance manufacturer(s)), S.4.1 (Drug substance specification from drug product manufacturer), S.4.4 (Certificate of Analysis from drug substance manufacturer) and S.7* (Stability data).
**If re-test period or shelf life is not stated in CEP, the stability data in Section 3.2.S.7 should be submitted.*

18. Is it required to update the drug substance intermediate manufacturer information in PRISM if it is not found in S.2.1?

It is not mandatory to update the drug substance intermediate manufacturer in PRISM unless the identified risk for nitrosamine formation is with the drug substance intermediate.

Section B: Acceptable Intake

19. How should the acceptable intake of nitrosamines in products be established?

Appendix 1 lists the acceptable intakes (AI) that is accepted by HSA for certain known nitrosamines. The list will be updated as more information becomes available. As there are different ways to manufacture a drug substance and drug product, the nitrosamines listed in Appendix 1 are not exhaustive and do not represent all nitrosamines that could potentially be present in a drug substance or drug product. Conversely, the nitrosamines may not be present in all drug products containing the same drug substance.

For nitrosamines that are not identified in Appendix 1, an AI based on the approaches mentioned below should be proposed. Alternatively, the AI published by HSA's reference agencies (Australia TGA, EMA, Health Canada, Swissmedic, UK MHRA, US FDA) can be proposed for evaluation – See Question 33.

The AI for nitrosamines can be established using the following approaches:

A. If the nitrosamine has sufficient substance-specific animal carcinogenicity data, the TD_{50} should be calculated and used to derive a substance-specific limit for lifetime exposure as recommended in the International Council for Harmonisation (ICH) M7 guideline.

B. If there is insufficient substance-specific animal carcinogenicity data, the following approaches can be used:

   i. The Carcinogenic Potency Categorisation Approach (CPCA) should be used to establish the AI, unless other robust data are available to justify a higher AI. Additional details on the CPCA can be found in Appendix 4: Carcinogenic potency categorisation approach (CPCA) for nitrosamines.

ii. A negative result in an GLP-compliant Enhanced Ames Test (EAT) will allow control of the nitrosamine at 1.5 µg/day. For nitrosamines with a positive EAT result, the AI should be determined using options (i) or (iii). Additional information on the EAT can be found in Appendix 5: Enhanced Ames test (EAT) conditions for nitrosamines.

All Ames tests initiated after August 2023 must adhere to the EAT protocol for acceptance. For Ames tests initiated before August 2023, acceptance will be considered on a case-by-case basis, with assessment based on the EAT protocol requirements.

iii. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the TD_{50} from the surrogate substance can serve as a point of departure for derivation of AI by structure-activity relationship and read across.

iv. A negative result in a relevant well-conducted in-vivo mutagenicity study will allow control of the nitrosamine as a non-mutagenic impurity (i.e., controlled according to ICH Q3A/B guideline, irrespective of the AI obtained through the above options). For nitrosamines with a positive in-vivo mutagenicity result, the AI should be established using options (i) or (iii).

20. How should the acceptable limit for a single known nitrosamine in a product be calculated?

The acceptable limit (in ppm) is determined by dividing the AI of the nitrosamine (in ng/day) by the maximum daily dose (MDD) of the product (in mg) in the approved local product labels (i.e., product insert or patient information leaflet). A clinical justification for the MDD used in the calculation of the acceptable limit should be provided if the information on the MDD is not available in the product labels.

21. How should the acceptable limit be calculated when there is more than one nitrosamine that is present at ≥ 10% of its acceptable intake in the same product?

If more than one nitrosamine is present at ≥10% of its AI in the product, there are two approaches that are considered acceptable to derive the acceptable limit in order not to exceed the acceptable risk level of 1:100,000 as outlined in the ICH M7 guideline:

1. The total nitrosamine level does not exceed the AI of the most potent nitrosamine; or

2. The overall risk level for all identified nitrosamines does not exceed 1 in 100,000. With reference to EMA's question-and-answer document, two different approaches can be used to achieve this:

    i. Fixed approach: Fixed acceptable limits (in ppm/ppb) are set for individual nitrosamines and no limit for total nitrosamines is needed. The acceptable limit for each nitrosamine should be set at a percentage of its acceptable limit such that the sum of the percentage acceptable limit for each specified nitrosamine does not exceed 100%.

    ii. Flexible approach: Each nitrosamine should be specified at its acceptable limit (in ppm/ppb) and an additional limit for total nitrosamines is required. The calculation for total nitrosamines could be written as:

$$\sum_{i=2}^{n} \frac{Xi}{AIi} \; x \; 100\% \; \leq 100\%$$

    Where Xi is the amount of each single nitrosamine i in ppm and AIi is the acceptable limit of each nitrosamine i in ppm.

    For each batch, to determine whether the limit for total nitrosamines is met, the

amount of each nitrosamine present (in ppm/ppb) should be converted to a percentage of its respective acceptable limit. The sum of the percentage acceptable limit of specified nitrosamines should not exceed 100%.

Example to illustrate the above control options

Two nitrosamines, NDMA and NDEA, are detected at or above 10% of their respective AI in a drug product with a maximum daily dose of 300 mg.

Calculation of the acceptable limit for each of the nitrosamines

- NDEA: $\frac{26.5\ \text{ng/day}}{300\ \text{mg/day}}$ = 0.088 ppm or 88 ppb → This is the more potent nitrosamine.
- NDMA: $\frac{96\ \text{ng/day}}{300\ \text{mg/day}}$ = 0.32 ppm or 320 ppb

Specification possibilities for the different control options

Nitrosamine	Option 1	Option 2 – Fixed approach (Using 20:80 ratio[2])	Option 2 – Flexible approach
NDMA	Not needed	NMT 64 ppb (320 ppb x 20%)	NMT 320 ppb
NDEA	Not needed	NMT 70 ppb (88 ppb x 80%)	NMT 88 ppb
Total nitrosamines	NMT 88 ppb	Not needed	NMT 100%[1]

[1] $(\frac{[NDMA]\ ppb}{320\ ppb} + \frac{[NDEA]\ ppb}{88\ ppb})\ x\ 100\% \leq 100\%$

NMT 100% = 1:100,000 theoretical excess cancer risk

[2]*The ratio of 20% NDMA to 80% NDEA (20:80) is used as an example only. Different ratios could be used in different situations dependent on relative amounts present, provided that the sum of the % acceptable limit for each specified nitrosamine does not exceed 100%.*

Example of acceptable batch test results for the different control options

Assuming the following data from one batch was obtained:

- NDMA found at 38 ppb
- NDEA found at 44 ppb

	Option 1		Option 2 – Fixed approach (Using 20:80 ratio[2])		Option 2 – Flexible approach	
Nitrosamine	**Limit**	**Results**	**Limit**	**Results**	**Limit**	**Results**
NDMA	Not needed	-	NMT 64 ppb	38 ppb	NMT 320 ppb	38 ppb (12% of the limit)
NDEA	Not needed	-	NMT 70 ppb	44 ppb	NMT 88 ppb	44 ppb (50% of the limit)
Total nitrosamines	NMT 88 ppb	82 ppb	Not needed	-	NMT 100%	62%

The approach chosen needs to be justified by the product registrant.

Non-mutagenic nitrosamines can be controlled individually in accordance with the ICH Q3A/B guideline.

22. Can the "Less-Than-Lifetime" approach described in the ICH M7 guidelines be applied?

Product registrants are required to establish and implement the necessary CAPA to reduce the nitrosamine levels to at or below the AI. As this may require time, the use of an interim AI may be considered in cases where the AI is exceeded to avoid supply disruptions to patients.

The interim AI can only be used for a pre-defined period as agreed with HSA because it is only a temporary measure while the CAPA is being implemented. HSA may require additional monitoring measures during the period of the interim AI use. The use of an interim AI is not applicable to products with multiple nitrosamines. Please discuss with HSA on the approach to be taken for such products.

The interim AI can be calculated using the less-than-lifetime (LTL) approach described in the ICH M7 guideline as follows:

Treatment duration	Up to 12 months	>12 months
Interim AI	13.3 x AI*	6.7 x AI*

**In any case the AI should not exceed 1.5 µg/day unless the AI (in Appendix 1) is > 1.5 µg/day, or the nitrosamine is placed in Potency Category 5 according to CPCA, or the nitrosamine is shown to be negative in an enhanced Ames test (EAT).*

The use of an interim AI is only applicable under exceptional circumstances to ensure continual supply for currently registered products and is generally not considered for products in new or pending product registration applications. Hence, product registrants should ensure that the nitrosamine level is within the AI published in Appendix 1 for all new drug applications (NDA) and generic drug applications (GDA).

23. How should the acceptable intake for nitrosamines in products that fall within the scope of the ICH S9 guideline be determined?

Nitrosamines in products that fall within the scope of the ICH S9 guideline can be controlled according to the ICH Q3A/B guidelines.

24. Are nitrosamines in topical products known to have the same risk as those in oral products?

Nitrosamines in topical products are also at risk as they may be absorbed through the skin. The approach to risk assessment applies to all products regardless of their route of

administration. There are no corrections to the AI for topical products. Exceptions may include situations where route-specific differences are justified by data, which will be evaluated on a case-by-case basis.

Section C: Product Testing, Root Cause Analysis and CAPA Development

25. How should confirmatory testing be conducted where a risk of nitrosamine impurities has been identified?

Generally confirmatory testing should be done on the drug product. Testing may be conducted on the drug substance when the root causes are only linked to the drug substance manufacturing process. In such cases, the risk assessment conducted on the drug product should conclude that there are no additional risk factors for formation of nitrosamine impurities in the drug product. Products identified as high risk for nitrosamines should be tested as soon as possible.

Testing of the drug substance and/or drug product for the nitrosamines should be conducted on a representative number of batches using appropriately validated and sensitive methods.

Test methods for determining the presence of several types of nitrosamines in certain drug substances have been published by various regulatory agencies, including HSA. These methods can be used as the starting point for the development and validation of analytical methods for nitrosamine in other drug substances. Click here for the test methods published by HSA.

Product registrants should ensure the analytical methods developed are sufficiently sensitive to detect the specific nitrosamine with the limit of quantification minimally corresponding to the AI of the nitrosamine.

26. How many batches should be tested for confirmatory testing?

The number of batches to be tested should commensurate with the nitrosamine risk. Confirmatory testing should be conducted on at least 6 pilot batches or 3 commercial-scale batches.

Where possible, confirmatory testing should include both newly produced batches as well as retained samples or stability batches stored under the long-term storage conditions registered locally to ensure that the testing covers the entire product shelf life. The batches need not be consecutive batches. It is recommended that randomized batches be tested to achieve the objective of representative testing, particularly for drug product batches to ensure that the batches tested used different drug substance batches. The batches tested need not be those supplied locally but must be representative of the local batches.

Testing using bracketing approach is acceptable with appropriate justifications for products with multiple strengths.

27. Does the analytical method validation report need to be submitted to HSA?

Submission of the analytical method validation report is mandatory if routine or skip testing of the nitrosamine is proposed. HSA may also request for the report on a case-by-case basis after evaluation of the nitrosamine risk assessment.

28. What are the actions required if testing confirms the presence of nitrosamine in the product?

If confirmatory testing confirms the presence of nitrosamine in the product, product registrants must investigate and identify the root cause, as well as determine and monitor the level of nitrosamine throughout the product's registered shelf life. Product registrants must provide a CAPA plan and include any market actions to address the nitrosamine risk where needed. Irrespective of the level detected, HSA must be informed via email at HSA_ProductDefect@hsa.gov.sg or via the Product Defect Reporting Form. The following information should be provided, where available:

- (Preliminary) root cause
- Confirmatory test results

- Interim/Final CAPA plan
- Health hazard assessment
- An assessment on whether the product is medically necessary or important
- Market action proposed (if any)
- An assessment on whether any disruption to product supply is expected

If nitrosamines are detected at significant levels (e.g., at >30% of the AI), all batches within expiry date in the local market may need to be tested to determine if market actions are needed. In general, batches tested with nitrosamine above the AI will not be allowed for supply in Singapore. However, the use of an interim AI may be considered where appropriate to inform market actions or to avoid supply disruptions before the CAPA can be implemented – See Question 22.

Thorough investigations on the root cause of nitrosamine formation in the product must be conducted and nitrosamine levels lowered as much as possible to be at or below the AI. The manufacturing process should be reviewed and adapted to prevent or mitigate nitrosamine formation wherever possible. In processes where there is no feasible alternative manufacturing method available to eliminate the risk of nitrosamine formation, it must be demonstrated that the process can purge the nitrosamines generated, and routine or skip testing for the nitrosamine may be required depending on the nitrosamine level found.

Routine testing for the nitrosamine in the product is warranted if nitrosamines are detected at >30% of the AI – See Question 29. Testing for nitrosamines is usually carried out on the drug product. However, if the root cause identified the source of the nitrosamine to be the drug substance manufacturing process, other control strategies such as those stated in the ICH M7 guideline could be used. Data should be provided to show that the nitrosamine will not be present above the AI in the drug product. Justification based on scientific principles alone (i.e., use of Option 4 outlined in the ICH M7 guideline) to conclude that nitrosamine is not formed is generally considered inadequate. Such cases will be evaluated on a case-by-case basis and needs to be supported by actual experimental data (e.g., spiking/purging data).

Testing of raw materials (e.g., excipients) should also be considered where appropriate.

Further investigations on whether the nitrosamine level will increase with time, temperature and humidity needs to be conducted, and testing of stability batches should be done where appropriate (e.g., when a risk was identified that nitrosamine levels could increase over time, or the potential for increase over time is unclear). Some NDSRIs have been observed to increase during long-term storage or stressed testing. Additional data may be required to justify the limit of the nitrosamine used at release and at the end of shelf life, considering the rate of increase in the nitrosamine over time.

Appropriate interim and final CAPAs (e.g., change of manufacturing process, change of raw material quality, and introduction of appropriate specifications) to minimise the risk of nitrosamine formation and to control the nitrosamine level at or below the AI should be implemented.

The risk of nitrosamine will also need to be reassessed with any applicable change that may impact the risk (e.g., change of excipient, change of manufacturer, change of manufacturing process, and change of packaging).

29. When should a test for nitrosamines be included in the specification?

A. Routine testing for the nitrosamine should be done when the:

- Risk of nitrosamine formation is high (e.g., during the manufacturing process and/or during storage), or
- Level of the nitrosamine is found to be at significant levels (e.g., at >30% of the AI), or
- Nitrosamine is detected in the drug product and the root cause is unknown, regardless of the level detected. In such cases, routine testing should be continued until the root cause is identified and alternative appropriate control are

implemented.

A test and acceptance criteria in the release and shelf-life specifications should be included where appropriate and all new batches should be tested for the nitrosamine. Only batches that meet the acceptance criteria can be distributed. Product registrants must ensure that the analytical methods developed is sufficiently sensitive to detect the specific nitrosamine with the limit of quantification minimally corresponding to the AI of the nitrosamine in this case.

B. Skip testing according to the ICH Q6A guideline definition may be accepted if the root cause of the nitrosamine formation is known, and the nitrosamine level is consistently below 30% of the acceptable limit. A test and acceptance criteria in the release and shelf-life specifications should be included where appropriate and all new batches should be tested for the nitrosamine. Only batches that meet the acceptance criteria can be distributed. Product registrants must ensure that the analytical methods developed is sufficiently sensitive to detect the specific nitrosamine with the limit of quantification minimally corresponding to 30% of the AI of the nitrosamine in this case.

C. Testing for the nitrosamine can be omitted if it is consistently present at <10% of the acceptable limit, and the root cause for its formation is understood such that appropriate controls can be established to ensure that the level of the nitrosamine will consistently be at <10% of its acceptable limit throughout the product shelf life. Product registrants must ensure that the analytical methods developed is sufficiently sensitive to detect the specific nitrosamine with the limit of quantification minimally corresponding to 10% of the AI of the nitrosamine in this case.

Section D: New and Pending Applications

30. Is a risk assessment for nitrosamines required for all new product applications (NDAs and GDAs)?

A nitrosamine risk assessment is required for all products containing chemically synthesised drug substance. A failure to provide the necessary nitrosamine risk assessment would result in requests for additional information during the evaluation stage and delay the evaluation process as any outstanding issues will have to be addressed before the application can be approved. Hence, the risk assessment should be submitted at the point of application submission to avoid any unnecessary delays in the registration process.

Appendices 2 & 3 have been developed to help product registrants identify the risk for nitrosamine formation and to guide the risk assessment. The risk assessment may be documented in any format as long as all the information required in the assessment aid is included. The same risk assessment that is submitted to other regulatory agencies can be used, provided that the information is relevant to the locally registered products (e.g., with the same registered manufacturers, product formula, storage conditions and specifications).

For products with high risk of nitrosamine formation, confirmatory test data is expected to be available before the application can be accepted for evaluation.

31. Will HSA require nitrosamine testing to be included in the specifications for all new product registrations? Will the current registration guidelines be updated?

At present, there are no plans to mandate nitrosamine testing in the specifications for all new product registrations. As with all other impurities, the requirement for testing is dependent on the risk and level of nitrosamines found as part of the risk assessment. Please refer to Question 29 for the testing requirements.

The principles of ICH M7 guideline is applicable to the control of nitrosamines that are mutagenic impurities. Appendix 2 is designed to help applicants identify the risk of nitrosamine formation while an international guideline is being developed in the longer term. Nitrosamine risk assessments should be submitted as part of the CTD sections for impurities (3.2.S.3.2 for Drug substance and 3.2.P.5.5 for Drug product).

32. Is a risk assessment for nitrosamines required for all new and pending MIV applications?

An impact assessment for nitrosamine formation should be performed when changes are made to the manufacturing process. The risk of nitrosamine formation needs to be reassessed with any applicable changes (e.g., change of excipient, change of manufacturer, change of manufacturing process, and change of packaging) to determine if the change may impact the risk. For changes that will result in additional risks of nitrosamine formation, the risk assessment should be provided at the point of application submission. A failure to provide the necessary nitrosamine risk assessment would result in requests for additional information during the evaluation stage and delay the evaluation process as any outstanding issues will have to be addressed before the application can be approved.

Section E: International Collaboration and Guidelines

33. Is HSA working with other drug regulatory agencies to align the requirements across the different jurisdictions to facilitate the response by manufacturers?

HSA has been collaborating with other international regulatory agencies including those in Australia, Brazil, Canada, Europe, Japan, Switzerland and the United States as well as the World Health Organization to discuss and share information relating to the root causes of nitrosamine formation and management of the risk of nitrosamine impurities. This international collaboration aims to coordinate and align the regulatory approach for the risk assessment exercise, the scientific principles in the determination of the AI for nitrosamines, and risk mitigation measures where appropriate.

Further information on the management of nitrosamine impurities in some of these countries can be found in the links below:

(a) Australia TGA: Nitrosamine Impurities in Medicines webpage
(b) EMA: Nitrosamine Impurities webpage
(c) Health Canada: Nitrosamine Impurities in Medications webpage
(d) Swissmedic: Potential Nitrosamine Contamination webpage
(e) UK MHRA: Nitrosamines Impurities in Medicines webpage
(f) US FDA: Information about Nitrosamine Impurities in Medications webpage