15 January 2024

EMA/409815/2020 Rev.2.0

Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products

CHMP 关于法规 (EC) No 726/2004 第 5(3) 条关于人用药品中亚硝胺杂质意见针对上市许可持有人/申请人问题回答

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Revision History

Rev.	Summary of changes made	Date
0	Replace obsolete Q&A published in 2019 to support the initial "call for review" with a new version reflecting the main principles agreed as part of the Article 5(3) referral which concluded in July 2020.	03rd August 2020
1	Update to Q&A 3 in order to clarify products in scope of the call for review. Update to Q&A 4 in order to add the link to the outcome of the referral under article 3 of Directive 2001/83/EC for ranitidine.	29th January 2021
2	Update to Q&A 3 on indicating testing timeline at the time of step 1 "risk identified" reporting.	24th February 2021
3	Update to Q&A 3 on the approach for non-marketed medicines. New Q&A 19 on the requirements for line extensions and variation applications.	15th April 2021
4	Update to Q&A 3 on combining step 2 response for multiple products from the same MAH.	18th May 2021
4*	Updates to Q&A 3 on when to perform step 2 confirmatory testing in order to meet the established deadline for step 3. Update and Q&A 10 to add an AI for NMOR.	29th June 2021
5	Update to Q&A 10 to add an AI for NNV.	21st September
6	Guidance on confirmatory testing requirements for marketed (Q&A 8) and on-going applications (Q&A 14) to include cases where a potential nitrosamine impurity cannot be synthesised, and when a product is available in multiple strengths of the same dosage form.	14th October 2021
7	Inclusion of additional guidance on control strategies for products containing more than one nitrosamine impurity including examples (Q&A 10) and a decision tree (Annex I).	31st January 2022
8	Update to guidance on root causes and risk factors for nitrosamine contamination (Q&A 4) and on policy for confirmatory testing (Q&A 8) and dossier requirements (Q&A 15) to allow testing of intermediates, raw materials or API under certain circumstances.	24th March 2022
9	New Q&A 20 providing clarifications on what are the regulatory steps for dealing with scenario A cases and update Q&A10 with new AIs (N-nitrosomethylphenidate, N-nitrosopiperidine, N-nitrosorasagilene, 7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3- a]pyrazine, N-nitroso-1,2,3,6-tetrahydropyridine, N-nitrosonortriptyline, N-methyl-N-nitrosophenethylamine) and guidance on use of Ames test.	20th May 2022
10	Update to Q&A 5 to provide clarifications on the expectation for MAHs to continue to re-visit risk evaluations when new information becomes available with specific reference to API-nitrosamine risk. Update to Q&A 10 to include newly adopted AI for N- nitrosodabigatran and to indicate APIs where related nitrosamines have been identified. Clarification of how to set limits for products containing salt, hydrate or solvate forms of the API. Update to Q&A 14 to reference the new risk evaluation template for use in marketing authorisation applications.	23rd June 2022
11	Update to Q&A 3 on submission of amended step 1 response and extension of Step 3 deadline for chemical medicines.	29th July 2022
12	Update of Q&A 10 to add nitrosoduloxetine and introduction of Q&A 21 on approach to control presence of nitrosamine while the AI is being established.	10th October 2022
13	Update of Q&A 10 to add N-nitrosofluoxetine, N-nitrosoparoxetine, N-nitrosodiphenylamine, N-nitroso-mefenamic acid, N-nitrosopyrrolidine and N-nitrosodiethanolamine.	5th December 2022

14	Introduction of Q&A 22 on approach to control presence of N-nitrosamine exceeding the AI while CAPAs are being implemented. Update of Q&A 20 to consider the possibility of an interim limit based on the LTL approach during CAPA implementation. Update of Q&A 21 for increased clarity on the application of the temporary universal limit.	22nd December 2022
15	Amendment of Q&A 22 to indicate that no variation should be submitted to implement temporary above AI limits in specifications.	30th March 2023
16	Amendment to Q&A 10 to include the Carcinogenic Potency Categorization Approach (CPCA) and the enhanced Ames test (EAT) for establishing AIs for N-nitrosamines. Addition of Appendix 1, listing the nitrosamines for which AI have been established by the Nonclinical Working Party (NcWP), including new AIs for N-nitrosamines determined using the CPCA. Addition of Annex 2, describing the Carcinogenic Potency Categorization Approach for N-nitrosamines. Addition of Annex 3, describing the Enhanced Ames Test Conditions for N-nitrosamines.	7th July 2023
17	Amendment of Q&A 22 on approach to control presence of N-nitrosamine exceeding the AI while CAPAs are being implemented to extend the scope to authorised products for chronic use and clarify the applicable limits and exemptions. Amendment of Q&A 20 and Q&A 21 on approach to control presence of nitrosamine while the AI is being established to clarify that as the AIs can be established with the new carcinogenic category approach (CPCA) the approach for a universal temporary AI (t-AI) while a formal AI is established is no longer considered necessary.	28th July 2023
18	Update of Q&A 3 to highlighting the responsibilities of MAH(s) to control, report and mitigate the detection of Nitrosamine impurities throughout the product life-cycle, by using the established procedure.	2nd October 2023
19	Update of Q&A 10 to allow referral to other sources for CPCA categorisation, change reference from ICH M7(R1) to ICH M7(R2) guideline and removal of information in Annexes 2 and 3 to Appendices 2 and 3, respectively.	12th October 2023
20	Update of Q&A 3 and Q&A 10 to include guidance on non-mutagenic nitrosamine impurities (NMI) handling. Update to Q&A 9 to clarify sensitivity requirements for analytical methods. Update to Q&A 10 to include Ames test acceptability timelines.	15th January 2024

Introduction 介绍

The assessment report of the CHMP's Article 5(3) of Regulation (EC) No 726/2004 opinion on nitrosamine impurities in human medicinal products provides general guidance and recommendations on mitigating and preventing the presence of nitrosamines in human medicinal products. In this context all MAHs/Applicants of human medicinal products should work with the manufacturers of their Active Pharmaceutical Ingredients (APIs) and finished products (FPs) in order to ensure that the presence of nitrosamine impurities in their medicinal products is mitigated as much as possible and controlled at or below a limit defined based on ICH M7(R1) principles for substances of the "cohort of concern" reflected in this guideline and calculated considering a lifetime daily exposure and kept as low as possible and that appropriate risk mitigating measures are taken.

CHMP 法规 (EC) No 726/2004 第 5(3) 条评估报告中，关于人类医药产品中亚硝胺杂质的意见为减轻和预防人类医药产品中亚硝胺的存在提供了一般指导和建议。在这种情况下，所有 MAHs/人类医药产品的申请人应与其活性药物成分 (API) 和成品 (FP) 的制造商合作， 以确保尽可能减少其医药产品中亚硝胺杂质的存在，并根据 ICH M7(R1) 原则，将此类控制在或低于本指南中反映的“关注群体”物质定义的限度， 计算时考虑终生每日暴露并保持尽可能低水平，同时，还要采取适当的风险控制措施。

While the review by CHMP under Article 5(3) was ongoing, the regulatory authorities established in September 2019 a specific framework (hereinafter 'call for review')[1],[2] for medicinal products containing chemically synthesised APIs, to provide details on the reporting to the authorities by the MAHs and set expectations regarding risk evaluation (step 1), risk assessment/confirmatory testing (step 2) and risk mitigation measures (step 3) to be carried out. Following the CHMP's Article 5(3) opinion, a similar exercise is launched for medicinal products containing a biological API, as further explained in this document. Further details are provided in Q&A 2 below.

在 CHMP 根据第 5(3) 条进行审查的同时，监管机构于 2019 年 9 月为含有化学合成 API 的医药产品建立了一个具体框架（以下简称 “审查请求”）[1,2]，以提供有关报告的详细信息由 MAH 向当局报告，并制订有关风险评估的期望（第 1 步）、风险评估/确认测试（第 2 步）和风险降低措施（第 3 步）。根据 CHMP 第 5(3) 条的意见，针对含有生物 API 的医药产品开展了类似的工作，如本文件中进一步解释的那样。 下面的问答 2 中提供了更多详细信息。

1 https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing- authorisation-holders en.pdf

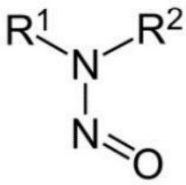
2 https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation en.pdf

The published CHMP Article 5(3) opinion, supplemented by the current Question and Answer document on its implementation, will replace the previous letter entitled 'Information on nitrosamines for marketing authorisation holders' (EMA/189634/2019, published on 19 September 2019).

已发布的 CHMP 第 5(3) 条意见，通过当前关于其实施的问答文件进行补充，将取代之前题为“上市许可持有人关于亚硝胺的信息”的信函（EMA/ 189634/2019，2019 年 9 月 19 日发布）。

The terms "nitrosamine" and "W-nitrosamine" are used interchangeably within this Q&A and related documents and should both be understood to refer to the following structure:

术语“亚硝胺”和“N-亚硝胺”在本问答和相关文件中可互换使用，均应理解为指代以下结构：



For the purpose of this Q&A please see definitions below:

出于本问答的目的，请参阅以下定义

Risk evaluation: all activities in step 1.

风险评估：步骤 1 中的所有活动

Risk assessment: all activities in step 2.

风险评估：步骤 2 中的所有活动

1. Should the risk of presence of nitrosamines be considered for all human medicinal products?

所有人类医药产品都应考虑存在亚硝胺的风险吗？

MAHs/Applicants of all human medicinal products should ensure that the presence of nitrosamines is controlled and kept as low as possible, irrespective of marketing status or the type of product (e.g. generics and over the counter (OTC) products).

所有人类医药产品的 MAH/申请人应确保亚硝胺的存在受到控制并保持在尽可能低的水平，无论上市状态或产品类型如何（例如仿制药和非处方药 (OTC) 产品）。

For details on the approach required, please refer to Q&A 10 on the limits for nitrosamines and Q&A

12 on the measures to mitigate the risk of presence of nitrosamines.

有关所需方法的详细信息，请参阅关于亚硝胺限度的问答 10 和关于降低亚硝胺存在风险的措施的问答 12。

MAHs/Applicants are reminded of their obligations to ensure that, in accordance with Article 23 and Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, their medicinal products are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress.

提醒 MAHs/申请人，他们有义务确保根据指令 2001/83/EC 的第 23 条和附件 I 以及第 726/2004 号法规 (EC) 第 16 条，他们的医药产品是通过以下方式制造和控制的：符合最新科学技术进步的过程和方法。

Therefore, MAH/ Applicants shall:

因此，MAH/申请人应：

- design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of W-nitrosamines in their API and FP(s);
  设计他们的制造流程和控制措施，以尽可能防止或尽可能降低他们的 API 和 FP 中可能存在 N-亚硝胺。
- assess the risk of presence nitrosamine impurities in their API(s) and FP(s) and introduce any resultant changes to the dossier as needed (e.g. changes to their manufacturing processes);
  评估其 API 和 FP 中存在亚硝胺杂质的风险，对任何由此产生的结果，根据需要对注册资料进行变更（例如，对其制造工艺的变更）。
- ensure that active substances and excipients used in their FPs are manufactured in compliance with good manufacturing practices in line with Article 46(f) of Directive 2001/83/EC.
  确保其 FP 中使用的活性物质和赋形剂的生产符合 2001/83/EC 指令第 46(f) 条的良好生产规范。

Compliance of the MAHs/Applicants with the above-mentioned obligations is subject to regular controls by competent authorities including during GMP inspections.

MAHs/申请人履行上述义务的情况受到主管当局的定期监管，包括在 GMP 检查期间。

While the Article 5.3. recommendations on controlling nitrosamine impurities apply to all human medicinal products, the call for review applies only to human medicines containing chemically synthesised APIs or biological APIs, as further explained in Q&A 2 below.

而第 5.3 条法规关于控制亚硝胺杂质的建议适用于所有人类医药产品，审查要求仅适用于含有化学合成 API 或生物 API 的人类药物，如下面的问答 2 中进一步解释。

2. What is the 'call for review'?

什么是“审查要求”

In September 2019, a 'call for review' was launched for medicinal products containing chemically synthesised APIs to request MAHs to review their manufacturing processes in order to identify and, if necessary, mitigate the risk of presence of nitrosamine impurities and report the outcome back to authorities. This exercise was started while the review by CHMP under Article 5(3) for Nitrosamine impurities in human medicinal products was ongoing.

2019 年 9 月，针对含有化学合成 API 的医药产品发起了“审查要求”，要求 MAH 审查其制造工艺，以确定并在必要时降低亚硝胺杂质存在的风险， 并将结果报告给当局。这项工作是在 CHMP 根据第 5(3) 条对人用药品中的亚硝胺杂质进行审查时开始的。

Following the conclusion of the review under Article 5(3), the CHMP considered that there is also a risk of presence of nitrosamines in biological medicinal products, in particular for the biological medicines with the following risk factors:

审查结束后根据第 5 条第 3 款，CHMP 认为生物医药产品中也存在亚硝胺的风险，特别是具有以下风险因素的生物药品：

- biologicals containing chemically synthesised fragments, where risk factors similar to chemically synthesised active substances are present;
  含有化学合成片段的生物制品，存在类似于化学合成活性物质的风险因素；
- biologicals using processes where nitrosating reagents are deliberately added;
  使用故意添加亚硝化试剂的工艺的生物制品；
- biologicals packaged in certain primary packaging material, such as blister packs containing nitrocellulose.
  用某些内包装材料包装的生物制品，例如含有硝化纤维。

For the above reasons the current call for review has been extended to cover also all biological medicinal products for human use. For further reference on what is considered to be a biological medicinal product for the purpose of this exercise, please consult the CMDh Questions & Answers on Biologicals.

由于上述原因，目前的审查要求已扩大到涵盖所有供人类使用的生物医药产品。如需进一步了解什么被认为是本操作目的的生物医药产品，请参阅 CMDh 关于生物制品的问答。

The call for review consists of 3 steps: 审查要求包括 3 个步骤

- Step 1: MAHs to perform a risk evaluation to identify if APIs and/or FPs could be at risk of presence of nitrosamine;

第 1 步：MAH 执行风险评估以确定 API 和/或 FP 是否存在存在亚硝胺风险；

- Step 2: if a risk is identified, MAHs to proceed with confirmatory testing in order to confirm or refute the presence of nitrosamines. MAHs should report outcomes as soon as possible;

  第 2 步：如果发现风险，MAH 将进行验证性测试以确认或否认亚硝胺的存在。 MAH 应尽快报告结果；

- Step 3: if the presence of nitrosamine(s) is confirmed, MAHs should implement effective risk mitigating measures through submission of variation.

  第 3 步：如果确认存在亚硝胺，MAH 应实施提交变更申请，采取有效风险控制措施；

Please refer to Q&A 3 for further details on the 'call for review' including the timelines for chemicals and the timelines for biologicals.

请参阅问答 3，了解有关“审查要求”的更多详细信息，包括化学品的时间表和生物制品的时间表。

For the specific case of sartans with a tetrazole ring that have been subject to a review under Article 31 of Directive 2001/83/EC, further guidance will be published soon.

对于根据指令 2001/83/EC 第 31 条接受审查的带有四唑环的沙坦类具体案例，进一步的指南将很快发布。

3. For the 'call for review' for chemically synthesised and biological medicinal products, when and how should MAHs report steps 1 and 2 to competent authorities? (Updated)

对于化学合成和生物医药产品的“审查要求”，MAHs 应何时以及如何向主 管部门报告步骤 1 和 2？（更新）

Submission of step 1 outcome 提交第一步结果

Products that have been approved after 26 September 2019 but for which a risk evaluation was not assessed within the MAA procedure should comply with the call for review deadlines, if not already done so.

对于在 2019 年 9 月 26 日之后获得批准，但未在 MAA 程序中进行风险评估评估的产品，如果尚未这样做，则应遵守审查截止日期的要求。

For product containing **chemically** synthesised APIs, the step 1 risk evaluation should be concluded and reported at the latest by **31st March 2021**.

对于含有**化学**合成 API 的产品，第一步风险评估最迟应在 **2021 年 3 月31日**前完成并报告。

For product containing **biological** APIs, step 1 risk evaluation should be concluded and reported at the latest by **01st July 2021**.

对于含有**生物** API 的产品，第一步风险评估应最迟在 **2021 年 7 月 1 日**前完成并报告。

The risk assessment has to be performed for all products for which a potential risk has been identified in step 1, irrespective of the marketing status of the product or whether any registered manufacturers are actively used in supply. However, it is recognised that step 2 may not be possible for medicines that are not marketed, including the case of manufacturers not actively used in supply, since there may be no finished product batches available for confirmatory testing. In these cases, i.e. where no batches of finished products are available, it would be acceptable to submit a written commitment that step 2 confirmatory testing will be conducted once finished product has been manufactured and/or the product is launched. The outcome of step 2 testing as well as any necessary variation(s) as part of step 3 will therefore need to be submitted and approved before the product can be placed on the market or the manufacturer can be actively used in supply, even if this is after the step 2 and 3 deadlines. MAHs'/Applicants' compliance with the above-mentioned obligations is subject to regular controls by competent authorities including during inspections.

必须对在步骤 1 中识别出潜在风险的所有产品进行风险评估，无论产品的市场状态如何或是否有任何注册制造商的产品在使用。然 而，人们认识到，对于未上市的药品，包括制造商产品未使用的情况，步骤 2 可能是不可能的，因为可能没有可用于确认测试的成品批次。在这些情况下，即在没有可用批次的成品的情况下，可以提交一份书面承诺，即在成品制造和/或产品投放市场后将进行第 2 步确认测试。因 此，第 2 步测试的结果以及作为第 3 步一部分的任何必要变更，需要在产品投放市场或制造商可以用于供应之前提交并获得批准，即使这在第 2 步和第 3 步的截止日期之后。MAH/申请人遵守上述义务的情况受到主管当局的定期监管，包括在检查期间。

All MAHs should inform the concerned Competent Authorities of the outcome of their risk evaluation (step 1) using the dedicated templates.

所有 MAH 都应使用专用模板将风险评估（步骤 1）的结果告知相关主管部门。

If a risk has been identified, the expected timeline for the testing activities should also be provided as foreseen in the dedicated template. No additional documentation is required at this stage. However, the risk review should be adequately documented, and related documentation should be made available upon request.

如果已识别风险，还应按照专用模板提供测试活动的预期时间表。在这个阶段不需要额外的文件。但是，应充分记录风险审查，并应要求提供相关文件。

Step 2 should be started as soon as a risk is identified in API and/or FP and in accordance with

product prioritisation (see Q&A 6).

一旦在 API 和/或 FP 中识别出风险并根据产品优先级（参见问答 6），应立即开始第 2 步。

If a risk has been identified for the API, the MAH is advised to report this outcome by using step 1 response template and to proceed directly to step 2 confirmatory testing of the FP. If no risk has been identified in the API, the MAH is advised to proceed with the risk evaluation of the FP and to present the result of Step 1 when a final conclusion has been reached on both the API and the FP. MAHs should inform the concerned Competent Authorities of the outcome of their risk evaluation (step 1) even if no risk has been identified in the API or FP.

如果已确定 API 存在风险，建议 MAH 使用步骤 1 按照模板报告此结果，并直接进行 FP 的步骤 2 确认测试。如果 API 中没有发现风 险，建议 MAH 继续对 FP 进行风险评估，并在对 API 和 FP 达成最终结论时提交第 1 步的结果。 MAHs 应该将风险评估（步骤 1）的结果通知有关主管当局，即使没有 API 或 FP 中已识别风险。

It is acceptable for the submission of the outcome of step 1 to submit one email notification grouping products with identical outcome under the following provisions:

提交步骤 1 的结果可以按照以下规定提交一封电子邮件通知，将结果相同的产品分组：

- For those Member States that have a dedicated portal, the MAH should submit the notification via this portal;

  对于那些拥有专用门户网站的成员国，MAH 应通过这个门户网站提交通知

- If the outcome of step 1 is "risk identified", it is possible to provide a response by grouping these products. MAHs are still required to indicate the expected testing timeline on the related "Step 1 risk identified response template" excel file.

  如果步骤 1 的结果是“已识别风险”，则可以通过对这些产品进行分组来提供回复。 MAH 仍然需要在相关的“第 1 步风险识别回复模板”excel 文件中指 明预期的测试时间表。

In specific cases it may be possible to correct a former step 1 outcome from "risk" to "no risk" by using the "Step 2 no nitrosamine detected response template". This template now contains a tick box for such cases. The possibility to amend the step 1 outcome may only be used in those cases where data was missing at the March 2020 deadline and is now available.

在特定情况下，可以使用“第 2 步未检测到亚硝胺回复模板”将之前第 1 步的结果从“风险”更正为“无风险”。该模板现在包含针对此类情况的勾选框。只有 在 2020 年 3 月截止日期时数据缺失且现在可用的情况下，才能使用修改步骤 1 结果的可能性。

Submission of step 2 outcome

提交第 2 步结果

The step 2 confirmatory testing should be conducted in accordance with product prioritisation (see Q&A 6).

第 2 步确认测试应根据产品优先顺序进行（参见问答 6）

For nitrosamine impurities that are classified as non-mutagenic in Appendix 1 based on in-vivo mutagenicity studies, the submission of step 2 confirmatory testing is not required, and these mpurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines. For all other nitrosamine impurities the submission of step 2 confirmatory testing is required using the dedicated response templates.

对于附录 1 中根据体内致突变性研究归类为非致突变性的亚硝胺杂质，不需要提交步骤 2 确认试验，这些杂质应根据 ICH Q3A（R2）和 ICH Q3B（R2）指南进行控制。对于所有其他亚硝胺杂质，需要使用专用回复模板提交步骤 2 确认测试。

For product containing **chemically** synthesised APIs, confirmatory testing activities at Step 2 are expected to be finalised at the latest by **26th September 2022.** MAHs should refrain from submitting incomplete step 2 outcomes.

对于含有**化学**合成 API 的产品，第 2 步的确认测试活动预计最迟将**于 2022 年 9 月26日**完成。MAH 应避免提交不完整的第 2 步结果。

The deadline for the submission of any changes required to Marketing Authorisations (Step 3, see Q&A 13) is by **1st October 2023**.

提交上市授权所需的任何更改的截止日期（第 3 步，参见问答 13）是在 **2023 年 10 月1日**之前。

For product containing **biological** APIs, confirmatory testing activities at Step 2 and submission of any changes required to Marketing Authorisations (Step 3, see Q&A 13), are expected to be finalised at the latest by **1st July 2023.**

对于含有**生物** API 的产品，第 2 步的确认测试活动和提交上市许可所需的任何变更（第 3 步，参见问答 13）预计最迟将于 **2023 年 7 月1日**完成。

In order to meet the above deadlines for submission of any changes required to Marketing Authorisations at Step 3 for products containing chemically synthesised or biological APIs, it would be expected that confirmatory testing activities at Step 2 are finalised in advance of these deadlines.

为了在上述截止日期前提交包含化学合成或生物 API 的产品的第 3 步上市许可所需的任何变更，建议第 2 步的确认测试活动在这些截止日期之前完成。

MAHs should forthwith inform the competent authorities if tests confirm the presence of nitrosamine, irrespective of the amount detected and by utilising the dedicated reporting templates. The immediate risk to patients should be assessed based on the limits defined in Q&A 10 and appropriate action

proposed to avoid or minimise the exposure of patients to nitrosamines.

如果测试确认存在亚硝胺，则 MAH 应立即通知主管当局，无论检测到多少，并使用专用报告模板。应根据 Q&A 10 中定义的限制和建议的适当行动来评估对患 者的直接风险，以避免或尽量减少亚硝胺对患者产生的风险。

For the submission of the outcome of step 2 confirmatory testing several products can be combined when the outcome is "no nitrosamines detected". When the outcome is "nitrosamines detected" all strengths and pharmaceutical forms of one marketing authorisation can be combined in one response template when the supporting documentation is completely identical for all products concerned; if not the response has to be submitted separately.

为了提交第 2 步确认测试的结果，当结果是“未检测到亚硝胺”时，可以多个产品一起申报。当结果是“检测到亚硝胺”时，所有相关产品的支持文件完全相同时，可以将一个产品的所有规格和剂型组合在一个回复模板中；如果不是，则必须单独提交答复。

In case one or more nitrosamines are identified that exceed the limit defined in Q&A 10, the following supportive documentation is required at the time of reporting:

如果发现一种或多种亚硝胺超过问答 10 中定义的限度，则在报告时需要提供以下支持文件：

- testing results expressed in ng and ppm;

  测试结果以 ng 和 ppm 表示

- interim investigation report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment.

  中期调查报告，包括（初步）根本原因、风险缓解计划和收益/风险评估。

For their responses, MAHs are required to use dedicated templates and contact points as outlined on the EMA and CMDh websites.

对于他们的回复，MAH 必须使用专用模板和联系点，如 EMA 和 CMDh网站。

Please note the set deadlines of the Call For Review (Step 1, 2 and 3) as described above for medicines containing chemically synthesised and biological active substances have passed. Any MAHs that have not reported identified Nitrosamine impurities to the relevant Competent Authority, should do so as a matter of priority, including any updates to previous notifications.

请注意，上述含有化学合成和生物活性物质的药物审查要求（步骤 1、2 和 3）的截止日期已经过期。任何已确定的亚硝胺杂质但尚未向相关监管当局报告的，MAH 应优先报告，包括对以前通知的任何更新。

MAH(s) should report in accordance with the established limits and recommendations described in this guidance. MAH(s) should continue to use the response templates and available communication mechanisms previously established.

MAH 应按照指南中所建立的限度和建议进行报告。MAH 应继续使用以前建立的报告模板和可用的沟通机制。

MAH(s) are reminded of their responsibilities to ensure the quality, safety and efficacy of their medicines and to adhere to the Nitrosamines guidance outlined by the EU Network. MAHs and Manufacturers should work together and take precautionary measures to mitigate the risk of presence of nitrosamines during the manufacturing and storage of all authorised medicinal products and throughout the lifecycle of the product if any changes are made.

请注意 MAH 他们有责任确保其药物的质量、安全性和有效性，并遵守欧盟网络概述的亚硝胺指南。MAHs 和制造商应共同努力，采取预防措施，在所有授权药品的生产和储存过程中以及在产品的整个生命周期中（如果发生任何变化）降低亚硝胺的存在风险。

Authorities in the EU will continue take all necessary measures to protect patients and ensure that medicines in the EU meet the required quality standards. The Authorities in the EU will also continue to collaborate with international partners on Nitrosamine to reflect scientific advances.

欧盟当局将继续采取一切必要措施保护患者，并确保欧盟的药品符合要求的质量标准。欧盟当局还将继续与国际伙伴在亚硝胺方面合作，以反映科学进步。

4. What are the currently identified risk factors for presence of nitrosamines?

目前已确定存在亚硝胺的危险因素有哪些？

W-Nitrosamines can be formed when an amine and nitrosating agent are combined under favourable conditions although other generation pathways are also possible, such as e.g. oxidation and reduction processes from hydrazine-type compounds and N-nitro derivatives.[3],[4] Root causes for N-nitrosamines in medicinal products identified to date can be grouped as risk factors linked exclusively with the manufacturing process and storage of active substance and/or as risk factors associated with manufacture and storage of the finished product. Moreover, there are risk factors specifically linked to GMP aspects. Currently identified risk factors for N-nitrosamine impurities in medicinal products are listed below, along with some identified in the literature. However, the list is not exhaustive and further root causes may also be applicable - it is up to MAHs to determine if there is a risk with their product:

当胺和亚硝化剂在有利条件下结合时，可以形成 N-亚硝胺，尽管其他生成途径也是可能的，例如肼类化合物和 N-硝基衍生物的氧化和还原过程。[3,4] 药品中 N-亚硝胺的根本原因迄今为止可归类为仅与活性物质的制造过程和储存相关的风险因素和/或与成品的制造和储存相关的风险因素。 此外，还有与 GMP 方面特别相关的风险因素。下面列出了目前已确定的药品中 N-亚硝胺杂质的风险因素，以及文献中确定的一些因素。但是，该列表并不详尽，可能还适用其他根本原因。

Risk factors related to the manufacture of the active substance:

与活性物质生产相关的风险因素

1. Use of nitrite salts and esters (e.g. NaNO2, alkyl nitrites), or other nitrosating agents (e.g. nitroso halides, nitrosonium salts, nitrogen oxides, nitro alkanes, halogenated nitro alkanes, Fremy's salt, nitroso sulfonamides),[3],[4] in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process. Sources for secondary or tertiary amines can also be starting materials, intermediates, reagents, solvents (e.g. DMF, DMAc and NMP) and catalysts, which contain amine functionality, amine impurities (e.g. quaternary ammonium salts) or which are susceptible to degradation to reveal amines.

   在制造过程的相同或不同步骤中存在仲胺或叔胺情况下，使用亚硝酸盐和酯（例如 NaNO2、亚硝酸烷基酯）或其他亚硝化剂（例如亚硝基卤化物、亚硝鎓盐、氮氧化物、硝基烷烃、卤化硝基烷烃、弗雷米盐、亚硝基磺酰胺)[3,4]。仲胺或叔胺的来源也可以是起始材料、中间体、试剂、溶剂（例如 DMF、DMAc 和 NMP）和催化剂，它们含有胺官能团、胺杂质（例如季铵 盐）或易于降解以释放胺。

2. Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process (see 1).[5]

   在制造过程的相同或不同步骤中，在存在仲胺或叔胺的情况下，通过羟胺氧化形成亚硝酸盐，或从硝基芳烃前体释放亚硝酸盐（例如通过氟脱硝）（参 见 1）[5]。

3. Use of disinfected water (chlorination, chloro-amination, ozonisation) in the presence secondary or tertiary amines within the same or different steps of the manufacturing process (see I).[6],[7],[8],[9]

   在制造过程的相同或不同步骤中使用存在仲胺或叔胺的消毒水（氯化、氯胺化、臭氧化）（参见 1）。[6、7、8、9]

4. Oxidation of hydrazines, hydrazides and hydrazones by hypochlorite, air, oxygen, ozone and peroxides in the manufacturing process or during storage.[4] Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts).

   次氯酸盐、空气、氧气、臭氧和生产过程或储存过程中的过氧化物。[4]在 API 生产过程中使用受污染的原材料（例如溶剂、试剂和催化剂）。

5. Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts).

   使用受污染的回收或循环使用材料（例如溶剂、试剂和催化剂）。

6. Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents.

   使用供应商提供的受污染的起始原料和中间体，供应商使用可能含有残留亚硝胺或亚硝化剂的工

艺或原材料。

7. Carry-over of nitrosamines deliberately generated (e.g. as starting materials or intermediates) during the manufacturing process.

在制造过程中有意产生的亚硝胺的残留（例如作为原料或中间体）。

3 Lessons learnt from presence of N-nitrosamine impurities in sartan medicines EMA/526934/2019.

4 Org. Process Res. Dev. 2020, **24** (9), 1558-1585

5 Chem. Rev. 2016, **116**, 422-518

6 Crit. Rev. in Environ. Sci. 2017, 47, (24), 2448-2489

7 J. Pharm. Biomed., 2019, **164**, 536-549

8 Water Research, 2011, **45** (2), 944-952

9 j.Org. Chem.2021,86,2037-2057

Risk factors also related to the finished product: 也与成品有关的风险因素

8. Reaction of nitrosatable nitrogen functionality in APIs or their impurities/degradants with nitrosating agents present in components of the FP during formulation or storage. A particular risk of formation of nitrosamines should be noted for active substances that contain a nitrosatable amine functional group. Several examples have been reported where the amine functionality was shown to be vulnerable to nitrosation and formation of the corresponding N- nitroso impurity (i.e. NO-API). Secondary amines appear particularly vulnerable to this reaction although some cases with tertiary amines have also been observed. Vulnerable amines could also be formed by degradation (e.g. hydrolysis) during formulation or storage. Nitrites have been identified as impurities in many common excipients.[10] MAHs and/or applicants should be aware that N-nitroso API impurities can form at levels exceeding the AI even if nitrite levels in the excipients are very low. The overall nitrite content will also depend on the relative composition in terms of the excipients. As it has been reported that N-nitroso impurities can form from APIs or their impurities/degradants (containing amine functionality or susceptible to degradation to reveal amines) during manufacture of the finished product, as well as during storage, MAHs should give consideration to the stability of the finished product and should ensure that the AI of any *N*-nitrosamine impurity is not exceeded until the end of shelf life of the FP. For further information, please refer to the assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

API 或其杂质/降解物中亚硝化氮官能团与在配制或储存过程中存在于 FP 组分中的亚硝化剂产生反应。应注意一个特定的含有亚硝基胺官能团活性物质形成亚硝胺的风险。已经报道了几个例子，其中胺官能团显示出易受亚硝化，并形成相应 N 亚硝基杂质（即 NO-API）。仲胺似乎特别容易受到这种反应的影响，尽管也观察到了一些叔胺的情况。易降解胺也可能在配制或储存过程中通

过降解（例如水解）形成。亚硝酸盐已被确定为许多常见辅料中的杂质。[10] MAH 和/或申请人应该意识到，即使辅料中的亚硝酸盐含量非常低，N-亚硝基 API 杂质的含量也可能超过 AI。总亚硝酸盐含量也将取决于赋形剂的相对组成。据报道，在成品制造和储存过程中，API 或其杂质/降解物（含有胺官能团或易于降解以释放 胺）可能会形成 N-亚硝基杂质，因此 MAH 应考虑成品的稳定性，并且应确保在 FP 的保质期结束之前不超过任何 N-亚硝胺杂质的 AI。如需更多 信息，请参阅 CHMP 关于人用药品中亚硝胺杂质的 Article 5(3) 意见的评估报告

9. Degradation processes of active substances, including those induced by inherent reactivity (e.g. presence of nitro-alkyl, oxime, or other functionality[3,11,4]) or by the presence of an exogenous nitrosating agent. This could potentially occur during both active substance and finished product manufacturing processes or during storage and could be influenced by crystal structure, crystal habit and storage conditions (temperature, humidity etc.). For more details, refer to page 6 of Referral under Article 31 of Directive 2001/83/EC for ranitidine and published literature.[11,12]

活性物质的降解过程，包括由固有反应性（例如硝基烷基、肟或其他功能性 [3,11,4] 的存在）或外源亚硝化剂的存在引起的降解过程。这可能发生在活性物质和成品制造过程中或储存过程中，并且可能受到晶体结构、晶体常态和储存条件（温度、湿度等）的影响。有关更多详细信息，请参阅关于雷 尼替丁的指令 2001/83/EC 第 31 条下的引荐第 6 页和已发表的文献。 [11,12]

10. Oxidation of hydrazine or other amine-containing functional groups present in active substances or their impurities/degradants (e.g. from hydrazones and hydrazides), either in active substance manufacturing processes or during storage.[4] This root cause has also been observed during manufacture and storage of finished products containing such functional groups. Potential oxidants include oxygen and peroxides (common impurities in some excipients).[10]

无论是在活性物质生产过程中还是在储存过程中，活性物质或其杂质/降解物（如腙和酰肼）中的肼或其他含胺官能团的氧化。[4] 这个根本原因在含有此类官能团成品生产和储存过程中也观察到。潜在的氧化剂包括氧气和过氧化物（某些赋形剂中的常见杂质）。 [10]

11. Use of certain packaging materials. Relevant nitrosamine contamination has been observed in primary packaging of finished products in blister with lidding foil containing nitrocellulose. During the blister heat-sealing process, nitrogen oxides can be generated thermally from nitrocellulose. Under these conditions, nitrosamines have been shown to form from low molecular weight amines present either in printing ink or in the finished product and to transfer to the product and/or to the cavity via evaporation and condensation.

某些包装材料的使用。在带有含有硝化纤维素的盖箔的泡罩成品一级包装中观察到在泡罩热封过程中相关的亚硝胺污染，硝酸纤维素加热会产生氮氧化物。在这些条件下，已显示亚硝胺由印刷

油墨或成品中存在的低分子量胺形成，并通过蒸发和冷凝转移到产品和/或包装容器中。

[10] AAPS Pharm.Sci.Tech.2011，12(4),1248- 1263

[11] Org. Process Res. Dev.2020,24 (12),2915-2926

[12] Chem.Pharm.Bull., 2021，69，872-876

12. Reaction of amines leaching from quaternary ammonium anion exchange resins (e.g. used for purification steps) with nitrosating agents present in the liquid phase. A recent example of this was in the production of water for injections where residual chloramine used to disinfect incoming water reacted with dimethylamine leaching from the anion exchange resin used in the demineralisation step to form NDMA. In addition, disinfection procedures such as e.g. chlorination, chloro-amination and ozonisation can lead to significant N-nitrosamine generation as by-products in case vulnerable amines are present.[6],[7],[8],[9] Given the source of contamination, risk is related to the concentration of the reactive agent(s) and thus to the volume of water in or used to dilute a particular product. The same risks could be associated with active substances or finished products manufactured using water purified using similar resins

从季铵阴离子交换树脂（例如用于纯化步骤）中浸出的胺与存在于液相中的亚硝化剂的反应。最近的一个例子是注射用水的生产，其中用于对进水进行消毒的残留氯胺与脱盐步骤中使用的阴离子交换树脂中浸出的二甲胺发生反应，形成 NDMA。此外，消毒程序如如果存在易降解的胺，氯化、氯胺化和臭氧化会导致产生大量副产品 N-亚硝胺。[6,7,8,9] 考虑到污染源，风险与反应剂的浓度有关（ s)，因此与 特定产品中或用于稀释特定产品的水量相关。同样的风险可能与使用类似树脂纯化水生产的活性物质或成品有关。

Risk factors related to GMP aspects:

与 GMP 方面相关的风险因素

13. Cross-contamination due to different processes being run successively on the same manufacturing line.

同一生产线不同工序连续运行造成的交叉污染。

14. Carry-over of impurities between process steps due to operator-related errors or insufficiently detailed batch records such as inadequate phase separations during work-up procedures.

由于操作员相关错误或批记录不够详细（例如后处理过程中的相分离不充分）造成在工艺步骤之间存在残留杂质污染。

15. Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts) where the recovery is outsourced to third parties who are not aware of the content of the materials they are processing. Recovery processes carried out in non-dedicated equipment

should also be considered.

使用受污染的回收或循环使用材料（例如溶剂、试剂和催化剂），将回收工作外包给不知道他们正在处理的材料内容的第三方。在非专用设备中进行的回收过程也应该考虑风险。

5. What to do if after submission of step 1 and /or step 2 responses, new information (e.g. related to new potential risk factors or root causes) is identified?

如果在提交第 1 步和/或第 2 步回复后发现新信息（例如与新的潜在风险因素或根 本原因相关），该怎么办?

MAHs together with API and FP manufacturers are expected to maintain the quality of their product throughout its lifecycle. Therefore, once step 1 and/or 2 responses are submitted, MAHs are expected to continue to review and re-visit the outcome of the risk evaluation as and when new information becomes available. MAHs are advised to routinely check this Q&A document and in particular Q&A 4 which will be kept up to date as regards newly identified risk factors for formation of nitrosamines, and also Q&A 10 concerning limits for nitrosamines.

MAH 以及 API 和 FP 制造商应在其整个生命周期内保持其产品质量。因此，一旦提交了第 1 步和/或第 2 步的回复，MAH 应继续审查并在得到新信息时重新审视风险评估的结果。建议 MAH 定期查阅此问答文件，尤其是问答 4，其中关于新确定的亚硝胺形成风险因素会持续更新，以及问答 10 关于亚硝胺的限度规定会更新。

In particular, MAHs should note the risk of formation of nitrosamine impurities from active substances (or their related impurities) containing a vulnerable amine during finished product formulation and/or storage due to the presence of traces of nitrites. This has been recently elaborated as a risk factor to Q&A 4 (bullet 8) based on understanding gained during the call for review. MAHs that did not take into account this risk as part of step 1 response for their products containing active substances with vulnerable amines should reconsider their original step 1 risk evaluations in light of this new information and proceed to step 2 confirmatory testing as appropriate (see also Appendix 1).

特别是，MAHs 应注意，含有易降解胺的原料药（或其相关杂质）在成品配制和/或储存过程中，由于存在痕量亚硝酸盐而导致形成亚硝胺杂质的风险。最近，根 据在审查要求期间获得的知识，这已被详细阐述为问答 4（第 8 条）的风险因素。未将含有易降解胺活性物质的产品风险作为第 1 步回复的一部 分的 MAH 应根据此新信息重新考虑其最初的第 1 步风险评估，并酌情进行第 2 步确认测试（见附件 1）。

Appropriate timelines for reviewing the previous risk evaluation and for conducting confirmatory testing (if needed), should be followed depending on the risk identified.

应根据已识别的风险，遵循适当的时间表来审查以前的风险评估和进行确认测试（如果需要）。

The same approach should be followed for medicinal products granted a positive opinion and marketing authorisation during the call for review.

对于在审评期间获得肯定意见和上市许可的药品，应遵循相同的方法。

6. What factors should be considered in prioritising the risk evaluation?

优先考虑风险评估的因素有哪些?

When conducting the risk evaluation and risk assessment, MAHs should use a risk-based approach to prioritise products for evaluations and confirmatory testing. MAHs may consider factors such as the maximum daily dose taken for the concerned medicinal product, duration of treatment, therapeutic indication and number of patients treated. For example, medicinal products with higher daily dose and those for chronic use may take priority.

在进行风险评估和风险评估时，MAHs 应使用基于风险的方法来优先考虑产品进行评估和确认测试。

MAHs 可以考虑相关药品的最大日剂量、治疗持 续时间、适应症和接受治疗的患者人数。例如，日剂量较高的药品和长期使用的药品可能会优先考虑。

In order to undertake the analysis of the identified medicinal products at risk, MAHs can also use tools such as Failure Mode Effects Analysis (FMEA) and Failure Mode, Effects and Criticality Analysis (FMECA) as outlined in the ICH Q9 guideline on quality risk management.

为了对已识别的存在风险的医药产品进行分析，MAH 还可以使用ICH Q9 指南中概述的失效模式影响分析 (FMEA) 和失效模式、影响和关键 性分析 (FMECA) 等工具关于质量风险管理。

7. How should the risk evaluation be performed?

风险评估应该如何进行?

MAHs/Applicants in collaboration with API, FP manufacturers and their raw material suppliers are required to perform risk evaluations using quality risk management principles, as outlined in ICH Q9 guideline. The principles described in ICH M7 guideline and in the Assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products in relation to the toxicology assessment, control strategy and changes to the manufacturing processes for active substances

should also apply.

MAHs/申请人与 API、FP 制造商及其原材料供应商合作，需要使用质量风险管理原则进行风险评估，如 ICH Q9 指南中所述。 ICH M7 指南，以及 CHMP 关于人用药品中亚硝胺杂质的第 5(3) 条意见中与毒理学评估、控制策略和活性物质生产工艺变更评估报告描述相关意见的原则也应适用。

Manufacturers of active substances and FP and their raw material suppliers should provide MAHs/applicants with all information necessary for a comprehensive risk evaluation. If the risk of nitrosamine impurity formation was assessed during the development phase of the API/FP manufacturing processes, the information from this assessment can be used to support the risk evaluation.

活性物质和 FP 的制造商及其原材料供应商应向 MAHs/申请人提供全面风险评估所需的所有信息。如果在 API/FP 生产工艺的开发阶段评估了亚硝胺杂质形成的风险，则该评估的信息可用于支持风险评估。

MAHs/Applicants and manufacturers should consider as part of the risk evaluation all potential sources of contamination or formation of nitrosamine, notably the root causes listed under Q&A 4.

MAH/申请人和制造商应在风险评估中考虑所有潜在的污染源或亚硝胺的形成，特别是问答 4 中列出的根本原因。

As MAHs/Applicants and manufacturers for products containing biological APIs should consider the following aspects that may increase the risks of nitrosamine presence in their products:

作为含有生物 API 的产品的 MAH/申请人和制造商，应考虑以下可能增加其产品中存在亚硝胺风险的方面：

- biologicals containing chemically synthesised fragments, where risk factors similar to chemically synthesised active substances are present;

  含有化学合成片段的生物制品，其中存在类似于化学合成活性物质的风险因素

- biologicals using processes where nitrosating reagents are deliberately added;

  使用故意添加亚硝化试剂的工艺的生物制品

- biologicals packaged in certain primary packaging material, such as blister packs containing nitrocellulose.

  用某些内包装材料包装的生物制品，例如含有硝化纤维的泡罩包装

For further information on root causes, please refer also to the assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

有关根本原因的更多信息，另请参阅 CHMP 关于人用药品中亚硝胺杂质的第 5(3) 条意见的评估报告。

If, after completion of the risk evaluation, a risk is identified in the API and/or the FP, MAHs/applicants

must notify the competent authorities of the identified risk, proceed without further delay with confirmatory tests (see Q&A 8) and introduce any necessary changes to the dossier.

如果在完成风险评估后，在 API 和/或 FP 中识别出风险，MAHs/申请人必须将识别出的风险通知主管当局，立即进行确认测试（见问答 8）并 引入任何对注册资料进行必要的修改。

All MAHs should inform the concerned Competent Authorities of the outcome of their risk evaluation (step 1) even if a risk has not been identified, please see Q&A 3 for further details.

即使尚未确定风险，所有 MAH 也应将其风险评估（步骤 1）的结果告知相关主管当局，请参阅问答 3 了解更多详情。

8. How should confirmatory tests be conducted by MAHs and manufacturers?

MAHs 和制造商应如何进行确认性试验？

For the purpose of confirmatory testing as part of step 2 of the call for review to MAHs, testing should generally be carried out on the FP. Testing of the API, its intermediates, starting materials, solvents, reagents, excipients or any other raw materials for nitrosamines, amines, nitrites or other compounds with potential to generate nitrosamines is also recommended, if the risk assessment indicates that they are a potential source of nitrosamine impurities in the FP. In such cases, the results of testing API, intermediates or other relevant materials may be used to support root cause investigations and the development of a justified control strategy for nitrosamine impurities.

为了作为 MAH 审查要求的第 2 步的一部分，通常应在 FP 上进行确认测试。如果风险评估表明它们是 FP 中亚硝胺杂质的潜在来源，API、中间体，溶剂，试剂，辅料或其他相关材料建议进行测试。在这种情况下，测试结果可用于支持根本原因调查和制定合理的亚硝胺杂质控制策略。

However, some root causes may only be linked to the API manufacturing process (see Q&A 4). In these cases, testing of the API or intermediates upstream of the active substance could be used as a surrogate for testing the finished product, provided that the risk assessment performed on the FP concluded no additional risk factors for formation of nitrosamine impurities in the finished product (see Q&A 4, risk factors related to the finished product). If testing is carried out on an intermediate, then there should also be no risk factors associated with subsequent steps in the API manufacturing process or the finished product. The confirmatory testing strategy is the responsibility of the MAH and should be justified based on the risk assessment for the finished product and documented in the MAH's pharmaceutical quality system. It should be clearly justified why testing of the active substance or intermediate is appropriate and why further risk of nitrosamine formation in the finished product or subsequent API manufacturing steps can be excluded. If nitrosamines are detected, then an

appropriate control strategy should be implemented in the dossier.

然而，一些根本原因可能只与 API 生产过程有关（见问答 4）。在这些情况下，API 或活性物质上游中间体的测试可用作测试成品的替代品，前提是对 FP 进行的风险评估得出的结论是成品中没有形成亚硝胺杂质的其他风险因素（参见问答 4，与成品相关的风险因素）。如果对中间体进行测试，那么也不应该有与 API 生产过程或成品中的后续步骤相关的风险因素。确认测试策略是 MAH 的责任，应根据对成品的风险评估进行论证，并记录在 MAH 的药品质量体系中。应该清楚地说明为什么对活性物质或中间体进行测试是合适的，以及为什么可以排除成品或后续 API 生产步骤中进一步形成亚硝胺的 风险。如果检测到亚硝胺，则应在注册资料中实施适当的控制策略。

In any case, if the control point of nitrosamines is not in the finished product, the responsibility for quality lies with the MAH.

无论如何，如果亚硝胺的控制点不在成品中，那么质量的责任就在 MAH身上。

The number of batches to be tested should be commensurate with the risk. MAHs and manufacturers should test a representative number of batches of FP and the relevant starting materials, intermediates, API or raw materials as applicable. If the source of risk has been identified and is well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch, testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. This includes testing not only of newly produced batches but also retained samples of batches still within expiry date. If fewer than 3 batches are manufactured annually, then all batches should be tested.

测试的批次数量应与风险相称。 MAH 和制造商应测试代表性批次的 FP 和相关的起始材料、中间体、API 或适用的原材料。如果风险源已被识别并被充分理解（例如通过加标和清除研究），预计批次之间的杂质水平是一致的，则应对年度批次的 10% 或每年 3 次进行测试，以最高者为准。这不仅包括对新生产批次的检测，还包括对仍在有效期内的批次的留样进行检测。如果每年生产的批次少于 3 批，则所有批次应该进行测试。

If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, (or were used historically for batches still within expiry date), then testing of additional batches would be necessary to cover these risk factors.

如果使用了多个制造商、制造工艺和/或有风险原材料的来源（或历史上对仍在有效期内的批次使用过），则有必要对其他批次进行测试以涵盖这些风险因素。

If a product is available in multiple strengths of the same dosage form with the same risk factors

applicable to each, then testing could be rationalised by testing only the worst-case scenario strength. The worst-case approach should be justified by the MAH on a case-by-case basis. The justification should be documented in the risk assessment in the MAH's pharmaceutical quality system.

如果一种产品有多种规格的相同剂型，且每种规格都适用相同的风险因素，则可以通过仅测试最差情况下的规格来测试。MAH 应根据具体情况对最坏情况的方法进行论证。理由应记录在 MAH 药品质量体系的风险评估中。

During development of an analytical method, a reference standard of the relevant nitrosamine impurity is generally needed. If, despite extensive efforts, it becomes apparent that the relevant nitrosamine impurity cannot be synthesised, then this could be an indication that the nitrosamine either does not exist or that there is no risk of it being formed. In such cases, it may not be necessary to conduct confirmatory testing. This should be justified thoroughly on a case-by-case basis according to appropriate scientific principles. The justification could include relevant literature, information on structural/stereo-electronic features and reactivity of the parent amine, stability of the nitrosamine and experimental data to illustrate the efforts made to synthesise and to analyse the impurity. The justification should be documented in the risk assessment in the MAH's pharmaceutical quality system.

在分析方法的开发过程中，通常需要相关亚硝胺杂质的标准品。如果尽管付出了广泛的努力，但很明显无法合成相关的亚硝胺杂质，那么这可能表明亚硝胺不存在或没有形成亚硝胺的风险。在这种情况下，可能没有必要进行确认测试。这应该根据适当的科学原则在个案的基础上进行彻底的论证。理由可以包括 相关文献、关于母体胺的结构/立体电子特征和反应性的信息、亚硝胺的稳定性和实验数据，以说明为合成和分析杂质所做的努力。理由应记录在 MAH 药品质量体系的风险评估中。

Methods for determination of various nitrosamines in sartans with a tetrazole ring, metformin and ranitidine have already been developed by the Official Medicines Control Laboratories and are available for reference on the European Directorate for the Quality of Medicines & HealthCare (EDQM) website.

带有四唑环的沙坦类、二甲双胍和雷尼替丁的各种亚硝胺的测定方法已经由官方药物控制实验室开发，并可在欧洲药物和保健质量理事会 (EDQM) 网站上提供参考。

These may serve as a starting point for the development and validation of analytical methods for testing other APIs/FPs.

这些可以作为开发和验证用于测试其他 API/FP 的分析方法的起点。

Appropriately sensitive analytical methods for determination of specific nitrosamines in other medicinal products should be developed and validated accordingly before testing. The limit of

quantification (LoQ) should be at or below the acceptable limit for the respective nitrosamine impurity. If the same analytical method is used to test for multiple nitrosamines, then the selectivity of the method should be demonstrated at the LoQ for each nitrosamine.

应在测试前相应地开发和验证用于测定其他医药产品中特定亚硝胺的适当敏感的分析方法。定量限 (LoQ) 应等于或低于相应亚硝胺杂质的可接受限度。如果使用相同的分析方法测试多种亚硝胺，则应在每种亚硝胺的 LoQ 下证明该方法的选择性。

Given the trace levels of nitrosamines to be measured, the following technical aspects should be considered when developing analytical methods:

鉴于要测量的痕量亚硝胺，在开发分析方法时应考虑以下技术方面：

- Interference caused by presence of trace amounts of nitrosamines in testing materials utilised (e.g. water, airborne sources, plastics products and rubber/elastomeric products);
  所用测试材料中存在痕量亚硝胺引起的干扰（例如水、气源、塑料产品和橡胶/弹性体产品）
- Contamination during sample preparation (avoiding cross contaminations from gloves, membranes, solvents etc.) which could lead to false positive results;
  样品制备过程中的污染（避免手套、膜、溶剂等），可能导致假阳性结果
- *In situ* formation of nitrosamines during analysis;
  分析过程中原位形成亚硝胺
- Use of accurate mass techniques are required (MS/MS or high-resolution accurate mass systems) in order to overcome interference in the identification of the specific peak of a certain nitrosamine (e.g. false positives have been observed from DMF co-eluting with NDMA).
  需要使用精确质量技术（MS/MS 或高分辨率精确质量系统）以克服对特定亚硝胺特定峰鉴定的干扰（例如从 DMF 与 NDMA 共洗脱中观察到假阳性）

As a result of the above considerations, control experiments should be conducted such as analysing samples by orthogonal analytical methods.

基于上述考虑，应进行对照实验，例如通过正交分析方法分析样品

Further details in relation to analytical methodology can be found on EDQM website and in the CHMP assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

有关分析方法的更多详细信息，请访问 EDQM 网站并在 CHMP 评估报告中 CHMP 关于人用药品中亚硝胺杂质的第 5(3) 条意见。

9. What are the requirements of the analytical method(s)?（Updated）

分析方法有何要求（更新）

The analytical methods need to be sufficiently sensitive in order to adequately detect and quantify trace levels of nitrosamine impurities. When developing the analytical method, the required sensitivity should derive from the appropriate acceptable intake determined in line with the approaches described in Q&A 10. Appropriate development of the analytical method and the required sensitivity are the responsibility of the MAH/applicant.The following principles apply:

分析方法需要足够灵敏，以便充分检测和定量痕量亚硝胺杂质。在开发分析方法时，所需的灵敏度应来自根据问答 10 中描述的方法确定的适当的可接受摄入量。开发合适的分析方法和所需的灵敏度是 MAH/应用者的责任。以下原则适用：

- The limit of quantification (LoQ) provides the minimum level at which an analyte can be quantified with acceptable accuracy and precision and should thus be used for impurity testing and decisionmaking;

  定量限(LoQ) 提供了分析物可以以可接受的准确度和精密度进行定量的最低水平，因此应用于杂质检测和决策制定

- If quantitative testing is performed as a routine control, the LoQ should be < of the acceptable limit based on the relevant acceptable intake (AI) for the respective nitrosamine impurity;

  如果定量检测作为常规控制进行，LoQ 应＜基于相应亚硝胺杂质的相关可接受摄量 (AI) 的可接受限度；

- If quantitative testing is performed to justify skip testing, the LoQ of the analytical procedure employed should be < 30% of the acceptable limit based on the AI;

  如果执行定量测试以证明挑批检测的合理性，则所用分析程序的 LoQ 应＜基于 AI 的可接受限度的 30%；

- If quantitative testing is performed to justify omission of specification, the LoQ of the analytical method employed should be < 10% of the acceptable limit based on the AI;

  如果进行定量测试以证明不制定标准是合理的，则分析的 LoQ 采用的方法应＜基于 AI 的可接受限度的 10%；

- Exceptions are anticipated for medicinal products used at high daily doses (AI may be below technical feasibility of the method), or in case more than one nitrosamine is anticipated or identified in a given medicinal product.

  预计每日高剂量使用的医药产品会有例外情况（AI 可能低于该方法的技术可行性），或者在给定医药产品中预计或鉴定出超过一 种亚硝胺的情况。

Different analytical methods may be used for determination of multiple nitrosamines. If the same analytical method is used for multiple nitrosamines, the selectivity of the method should be demonstrated for each nitrosamine.

可以使用不同的分析方法来测定多种亚硝胺。如果对多种亚硝胺使用相同的分析方法，则应证明该方法对每种亚硝胺的专一性。

10. Which limits apply for nitrosamines in medicinal products? (updated)

医药产品中的亚硝胺什么限度适用？ （更新）

ICH M7(R2) guideline defines N-nitrosamines as substances of the "cohort of concern" for which limits in medicinal products refer to the so-called substance-specific acceptable intake (AI) (the Threshold of Toxicological Concern, TTC, value of 1.5 ug/day cannot be applied) which is associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure). The calculation of AI assumes a lifelong daily administration of the maximum daily dose of the medicinal product and is based on the approach outlined in the ICH M7(R1) guideline as well as the principles described in relation to the toxicological evaluation in the assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

ICH M7(R1) 指南将 N-亚硝胺定义为“关注人群”的物质，其在医药产品中的限度指的是所谓的特定物质可接受摄入量 (AI)（毒理学关注阈值，TTC，值不 能应用 1.5 微克/天），这与可忽略不计的风险相关（在一生的暴露过程中，理论上的超额癌症风险 < 100,000 分之一）。 AI 的计算是依据假设终生每天服用最大日剂量的医药产品，并基于 ICH M7(R1) 指南中概述的方法，以及 CHMP 关于人用药品中亚硝胺杂质的第 5(3) 条 意见评估报告中与毒理学评估相关的原则。

The 'less than lifetime' (LTL) approach should not be applied in calculating the limits as described above but can only be considered after consultation with competent authorities as a temporary measure until further measures can be implemented to reduce the contaminant at or below the limits defined above.

如上所述，“小于寿命”(LTL) 方法不应应用于计算限度，而只能在与主管当局协商后作为临时措施考虑，直到可以采取进一步措施将污染物减少到 限度或低于上面定义限度。

For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, N-nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines, as specified in the Q&A document to ICH S9 guideline. In addition, limits according to ICH Q3A(R2) and ICH Q3B(R2) apply to any impurities in Appendix 1 considered to be a non-mutagenic impurity (NMI) based on negative results from a well-conducted in vivo mutagenicity study.

对于 ICH S9 指南范围内定义的仅用于晚期癌症的产品，N-亚硝胺杂质应根据 ICH Q3A（R2）和 ICH Q3B（R2）指南进行控制，如 ICH S9 指南问答文件中所述。此外，根据 ICH Q3A（R2）和 ICH Q3B（R2）的限度适用于附录 1 中根据良好进行的体内诱变性研究的阴性结果被视为非诱变性杂质（NMI）的任何杂质。

If the active substance itself is mutagenic or clastogenic at therapeutic concentrations, N-nitrosamine impurities should be controlled at limits for non-mutagenic impurities according to ICH M7(R2). The same risk approach is applicable to all routes of administration. Corrections to limits are generally not acceptable unless route-specific differences are justified by data.

如果活性物质本身在治疗浓度下具有致突变性或致裂性，则根据 ICH M7（R2），N-亚硝胺杂质应控制在非诱变杂质的限度内。相同的风险方法适用于所有给药途径。除非特定路线的差异有数据证明，否则对限度的修正通常是不可接受的。

Establishment of the AIs

AI 的建立

Two scenarios are foreseen for detection of new nitrosamines:

对于新亚硝胺的检测，预计有两种情况：

A. If N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data, the TD50 should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline.

A.如果某些 N-亚硝胺具有足够的动物致癌性数据被确定为特定物质，则应计算并使用 TD50 得出特定物质的终生接触限度，如下所示 ICH M7（R2）指南中推荐。

B. If N-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline,

B.如果按照 ICH M7（R2）指南中建议，N-亚硝胺没有足够的具体数据来确定终生接触特定限度，

1.The Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines (Appendix 2) should be used to establish the AI, unless other robust data are available that would override this AI.

N-亚硝胺致癌效力分类方法（附录 2）应该用来建立 AI，除非有其他可靠的数据可以覆盖这个 AI。

2. A negative result in an GLP-compliant enhanced Ames test (EAT, Appendix 3) allows control of the N-nitrosamine at 1.5 µg/day. For substances testing positive, the AI should be established using options 1 or 3. For reporting requirements see Q&A 3 above.

符合 GLP 的增强型 Ames 试验（EAT，附录 3）的阴性结果允许 N-亚硝胺控制在 1.5 g/天。对于检测呈阳性的物质，应使用选项 1 或 3 建立 AI。有关报告要求，请参见上文问答 3。

3. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the TD50 from the surrogate substance can serve as a point of departure for derivation of AI by SAR and read across.

如果替代亚硝胺具有足够可靠的致癌性数据，替代物质的 TD50 可以作为 SAR 推导 AI 的出发点，并

进行交叉读取。

4. A negative result in a relevant well-conducted in vivo mutagenicity study can allow control of the N-nitrosamine as a non-mutagenic impurity (NMI), i.e. according to ICH Q3A(R2) and ICH Q3B(R2) limits, irrespective of the limit calculated through option 1, 2 or 3. For substance testing positive, the AI should be established using options 1 or 3. For reporting requirements see Q&A 3 above.
相关的良好体内致突变性研究的阴性结果可以控制作为非致突变杂质（NMI）的 N-亚硝胺，即根据 ICH Q3A（R2）和 ICH Q3B（R2）限值，而不考虑通过选项 1、2 或 3 计算的限值。对于物质检测呈阳性，应使用选项 1 或 3 建立 AI。有关报告要求，请参见上文问答 3。

The risk approach is applicable to all routes of administration. Corrections to limits are generally not acceptable unless data justify route-specific differences.
风险方法适用于所有给药途径。对限度的修正一般不可接受，除非数据证明有特定给药途径的差异。

Appendix 1 lists the nitrosamines for which acceptable intakes have been established by the Non-clinical Working Party.
附录 1 列出了非临床工作组已确定亚硝胺可接受的摄入量。

If the nitrosamine is not included in Appendix 1, MAH/MA applicants can also refer to a CPCA category from another source e.g. CPCA categories published by other regulatory authorities, but this will need confirmation to allow control of the substance at the level corresponding to that category.
如果亚硝胺不包括在附录 1 中，MAH/MA 申请人也可以参考其他来源的 CPCA 类别，例如其他监管机构公布的 CPCA 类别，但这需要确认，以允许在与该类别相对应的水平上控制该物质。

All Ames assays initiated after August 2023 must comply with the EAT or they will not be accepted. Ames assays initiated before August 2023 may be accepted on a case by case basis, and assessed according to the requirements of the EAT protocol, but they must be submitted before January 31st 2024.
2023 年 8 月后开始的所有 Ames 检测必须符合 EAT，否则将不被接受。2023 年 8 月前启动的 Ames 检测可根据具体情况接受，并根据 EAT 协议的要求进行评估，但必须在 2024 年 1 月 31 日之前提交.

Calculation of the limit when a single known nitrosamine is identified：

当识别出单一已知亚硝胺时的限度计算：

The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective AI in Appendix 1 (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC.
特定药品转换为标准限度（ppm）的计算方法是将附录 1 中的相关 AI（ng）除以 SmPC 中反映的给定产品的最大每日剂量（mg）。

The maximum daily dose is defined in line with the definition of the product strength in the Guideline on the SmPC. Therefore, the limit in ppm should usually be expressed per active moiety (free base, free acid or anhydrous/non-solvated material) for control point in the FP. Exceptions to this are active

substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate and active substances present in the formulation as ester or pro-drug.

每日最大剂量的定义与 SmPC 指南中产品强度的定义一致。因此，以 ppm 为单位的限值通常应以 FP 中控制点的每个活性部分（游离碱、游离酸或无水/非溶剂化物质）表示。例外情况是医药产品中的活性物质，其规格传统上以盐或水合物的形式表示，活性物质在制剂中以酯或前药的形式存在。

For a control point in the API only, the limit should be expressed in general per drug substance (i.e. relating to form of salt, hydrate, solvate etc. where relevant).

仅对于原料药中的控制点，限度应以每种原料药进行表示（即与盐、水合物、溶剂化物等的形式有关）。

Calculation of limit when more than one nitrosamine is identified in the same product

在同一产品中鉴定出一种以上亚硝胺时的限量计算

Please also refer to the decision tree in Annex 1 for further guidance.

请参考附件 1 中的决策树，以获得进一步的指导。

For determining limits in the case of presence of more than one nitrosamine, two approaches are considered acceptable in order not to exceed the acceptable risk level of 1:100,000 as outlined in ICH M7(R2) guideline:

在含有一种以上亚硝胺的情况下，为了不超过 ICH M7（R2）指南中概述的 1:10 0,000 的可接受风险水平，有两种方法被认为是可接受的：

1. The total daily intake of all identified N-nitrosamines not to exceed the AI of the most potent N-nitrosamine identified, or

   所有已识别的 N-亚硝胺的每日总摄入量不得超过已识别的毒性最强的 N-亚硝胺的摄入量，或

2. Total risk level calculated for all identified N-nitrosamines not to exceed 1 in 100,000.

   所有确定的 N-亚硝胺计算的总风险水平不超过 100,000 分之一。

The approach chosen needs to be duly justified by the MAH/Applicant.

所选择的方法需要由 MAH/申请人充分证明。

Specifications for individual N-nitrosamines should generally include an AI limit expressed in ppm or ppb. The conversion to an AI limit in ppm/ppb for a particular medicinal product is calculated by dividing the respective above AI (in ng/d) by the maximum daily dose (in mg) of a given product as reflected in the SmPC. The calculation of the specification limit does not take into account the molecular weight of the N-nitrosamine.

单个 N-亚硝胺的规格通常应包括以 ppm 或 ppb 表示的 AI 限度。特定药品的 AI 限度（ppm/ppb）的转换计算方法是将上述 AI（ng/d）除以 SmPC 中反映的给定产品的最大每日剂量（mg）。标准限度的计算没有考虑 N-亚硝胺的分子量。

It is considered that the presence of one or more N-nitrosamines at <10% of their respective AI constitutes a negligible toxicological risk, and as such, they do not need to be specified. N-Nitrosamines present below 10% of their respective AI do not need to be factored into the calculation of limits for individual or total N-nitrosamine(s).

据认为，一种或多种 N-亚硝胺在其各自 AI<10%时的存在构成可忽略的毒理学风险，因此，不需要对其进行规定。在计算单个或总 N-亚硝胺的限度时，不需要考虑低于其各自 AI 10%的 N-亚硝胺。

However, the overall principle of the Article 5(3) referral should still be considered, notably that "the presence of N-nitrosamines in human medicinal products shall be mitigated as much as possible." Therefore, manufacturers are encouraged to improve their processes, even if they result in only very small amounts (<10% AI) of multiple nitrosamines, as processes and controls should be designed to prevent if possible or mitigate as much as possible the presence of N-nitrosamines in APIs and FPs (see Q&A 1).

然而，仍应考虑第 5（3）条提及的总体原则，特别是"应尽可能减少人类医药产品中 N-亚硝胺的存在。"因此，鼓励制造商改进他们的工艺，即使他们只产生非常少量（<10%AI）的多种亚硝胺，因为工艺和控制应设计为尽可能防止或尽可能减少原料药和 FPs 中 N-亚硝胺的存在（见问答 1）。

For option 1, the AI limit for total N-nitrosamines should be set in ppm/ppb according to the most potent N-nitrosamine present at ≥ 10% of its AI. The most potent nitrosamine is the one with the lowest AI (see Appendix 1). Limits for individual N-nitrosamines can be defined but are not necessarily needed. However, it should be clearly stated which N-nitrosamines are included in the calculation of total N-nitrosamines.

对于方案 1，总 N-亚硝胺的 AI 限度应根据其 AI≥10%时存在的最大毒性 N-亚硝胺设定为 ppm/ppb。最大毒性的亚硝胺是 AI 最低的亚硝胺（见附录 1）。可以定义单个 N-亚硝胺的限度，但不一定需要。但是，应该明确说明哪些 N-亚硝胺包括在总 N-亚硝胺的计算中。

For option 2, the limits for N-nitrosamines should ensure an overall risk of not more than 1 in 100,000. Different approaches can be employed to achieve this risk requirement:

对于备选方案 2，N-亚硝胺的限度应确保总体风险不超过 10 万分之一。可以采用不同的方法来实现这一风险要求：

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

固定方法：为单个亚硝胺设定固定的 AI 限度（ppm/ppb），不需要对总的 N-亚硝胺设定限度。每种 N-亚硝胺的限度应设置为其 AI 限度的百分比，以便每种指定亚硝胺的%AI 限度之和不超过 100%。

Flexible approach: each N-nitrosamine should be specified at its AI limit in ppm/ppb and an additional limit for total N-nitrosamines is required. The calculation for total N-nitrosamines could be written as:

灵活的方法：每种 N-亚硝胺应以 ppm/ppb 为单位规定其 AI 限度，并要求对总 N-亚硝胺进行额外规定限度。总 N-亚硝胺的计算可写成：

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

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

其中 Xi 是以 ppm 为单位的每个单个 N-亚硝胺 i 的量，AIi 是以 ppm 为单位的每个 N-亚硝胺 i 的 AI 限度。

For each batch, to determine whether the limit for total N-nitrosamines is met, the amount of each N

nitrosamine present (in ppm/ppb) should be converted to a percentage of its respective AI limit. The sum of % AI limits of specified N-nitrosamines should not exceed 100%.

对于每一批，为了确定是否符合总 N-亚硝胺的限度，每种 N-亚硝胺的含量（ppm/ppb）应转换为其各自 AI 限度的百分比。指定 N-亚硝胺的%AI 限度之和不应超过 100%。

Example of control options and specifications for multiple nitrosamines in the same finished product:

同一成品中多种亚硝胺的控制选项和标准示例：

The case of two NAs:

两种 NAs

Two NAs both at or above 10% of their respective AI

两个 NAs 均达到或超过其各自 AI 的 10%

Example:

举例

NDMA and NDEA are both detected at or above 10% of their respective AI) in a finished product with maximum daily dose of 300 mg.

在最大日剂量为 300mg 的成品中，检测到 NDMA 和 NDEA 均达到或超过其各自 AI 的 10%）。

AI limit

AI 限度

• NDEA: 26.5 ng/day / 300 mg/day = 0.088 ppm or 88 ppb = most potent N-nitrosamine （毒性最强 N 亚硝胺）

• NDMA: 96.0 ng/day / 300 mg/day = 0.32 ppm or 320 ppb

Specification possibilities for different control options:

不同控制选项的规格可能性：

Nitrosamine	Option 1	Option 2 - Fixed Example 20:80 ratio[2]	Option 2 - Flexible
NDMA	Not needed	NMT 64 ppb *(320 ppb x 0.2)*	NMT 320 ppb
NDEA	Not needed	NMT 70 ppb *(88 ppb x 0.8)*	NMT 88 ppb
Total Nitrosamines	NMT 88 ppb	Not needed	NMT 100%[1]

亚硝胺	选择 1	选择 2-固定方法 以 20:80 举例 [2]	选择 2-灵活方法
NDMA	不需要	不大于 64ppb （320ppb x 2）	不大于 320ppb
NDEA	不需要	不大于 70ppb （88ppb x 0.8）	不大于 88ppb
总亚硝胺	不大于 88ppb	不需要	不大于 100%[1]

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

NMT 100% = 1:100,000 theoretical excess cancer risk.
NMT 100% =1:100,000 理论超额癌症风险

[2] For option 2 fixed approach, a 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 % AI limits for each specified nitrosamine does not exceed 100%.
[2]对于方案 2 固定方法，20%NDMA 与 80%NDEA 的比例（20：80）仅用作示例。根据存在的相对量，可以在不同的情况下使用不同的比率，前提是每种特定亚硝胺的%AI 限度之和不超过 100%。

Example of presentation of acceptable batch results for each control option:

每个控制选项的可接受批次结果演示示例：

Model data from 1 batch:

1 批演示数据

• NDMA found at 38 ppb

NDMA 38ppb

• NDEA found at 44 ppb

NDEA 44PPB

	Option 1		Option 2 - Fixed Example 20-80 ratio		Option 2 - Flexible	
	Limit	Results	Limit	Results	Limit	Results
NDMA	Not needed	-	NMT 64 ppb	38 ppb	NMT 320 ppb	38 ppb (12% of AI)
NDEA	Not needed	-	NMT 70 ppb	44 ppb	NMT 88 ppb	44 ppb (50% of AI)
Total NA	NMT 88 ppb	82 ppb	Not needed	-	NMT 100%	62%

	选择 1		选择 2-固定方法 20-80 比例举例		选择 2-固定方法	
	限度	结果	限度	结果	限度	结果
NDMA	不需要	-	不大于 64 ppb	38 ppb	不大于 320 ppb	38 ppb (12% of AI)
NDEA	不需要	-	不大于 70 ppb	44 ppb	不大于 88 ppb	44 ppb (50% of AI)
总 NA	不大于 88 ppb	82 ppb	不需要	-	不大于 100%	62%

Control options for Genotoxic APIs

基因毒性 API 的控制选项

Genotoxicity encompasses mutagenicity, clastogenicity and aneugenicity.

基因毒性包括致突变性、致染色体断裂性和遗传毒性

Mutagenic APIs are defined as substances having DNA-reactive properties as described in ICH M7.

如 ICH M7 中所述，致突变 API 被定义为具有 DNA 反应特性的物质

Clastogenic APIs are substances causing structural chromosomal aberrations.

Clastogenic API 是导致染色体结构畸变的物质

Aneugenic APIs are substances causing numerical chromosomal changes.

Aneugenic API 是导致染色体数量变化的物质

The ICH M7(R1) guideline does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9 (Ref. 4). Additionally, there may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. Exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities. Below it is explained in more detail how this is applied to the control of nitrosamine impurities.

ICH M7(R1) 指南不适用于 ICH S9（参考文献 4）范围内定义的用于晚期癌症适应症的原料药和药物产品。此外，在某些情况下，用于其他适应症的药物本身在治疗浓度下具有遗传毒性，并且可能会增加癌症风险。在这些情况下，暴露于致突变杂质不会显着增加原料药的致癌风险。因此，对于非诱变杂质可以控制在可接受的水平。下面更详细地解释了如何将其应用于亚硝胺杂质的控制。

1. Policy for products not within the scope of ICH S9

不在 ICH S9 范围内的产品政策

a. Containing mutagenic or clastogenic APIs:

含有致突变或致畸变的 API

i. Control nitrosamine at or below ICH Q3A/B qualification threshold[1] when genotoxicity of API is considered to produce a significant risk for mutagenicity/clastogenicity at therapeutic exposures;

当 API 的遗传毒性被认为在治疗暴露下产生显着的致突变性/致染色体畸变风险时，将亚硝胺控制在或低于 ICH Q3A/B 资格阈值 [9]

ii. The rules established for the control of nitrosamines as explained in the Article 5(3) referral or elsewhere in the Q&A apply when mutagenicity/clastogenicity of API is considered not to produce a significant risk for mutagenicity/clastogenicity at therapeutic exposures.

当 API 的致突变性/致畸变性被认为在治疗暴露时不会产生显着的致突变性/致畸变风险时，适用第 5(3)条推荐或问答中其他地方解释的为控制亚硝胺而制定的规则

b. Containing aneugenic APIs:

包含细胞遗传毒性 API

i. The rules established for the control of nitrosamines as explained in the Article 5(3) referral or elsewhere in the Q&A apply since aneugenicity of API is considered not to produce a significant risk for carcinogenicity at therapeutic exposures

由于 API 的遗传毒性被认为不会在治疗暴露下产生显着的致癌风险，因此适用第 5(3) 条推荐或问答中其他地方解释的为控制亚硝胺而制定的规则

c. Containing non-genotoxic APIs

含有非基因毒性 API

i. The rules established for the control of nitrosamines as explained in the Article 5(3) referral or elsewhere in the Q&A apply

适用第 5(3) 条推荐或问答中其他地方解释的为控制亚硝胺而制定的规则

2. Policy for products within the scope of ICHS9

ICHS9 范围内产品的政策

a. Containing genotoxic or non-genotoxic APIs:

含有基因毒性或非基因毒性的原料药

i. Control nitrosamine at or below ICH Q3A/B qualification threshold.

将亚硝胺控制在或低于 ICH Q3A/B 资格阈值

Higher limits may be set for nitrosamines in certain cases. However, it is expected that the Applicant/MAH will ensure that the presence of nitrosamine impurities in their medicinal products is mitigated as much as possible.

在某些情况下，可能会对亚硝胺设定更高的限度。然而，期望申请人/MAH 将确保尽可能减少其医药产品中亚硝胺杂质的存在。

[1] Wherever it is quoted ”Control nitrosamine at or below ICH Q3A/B qualification threshold”, this implies that control at the qualification threshold is justified from a safety perspective.

凡引述“控制亚硝胺达到或低于 ICH Q3A/B 合格阈值”的地方，这意味着从安全角度来看，控制在合格阈值是合理的。

11. What should I do if a nitrosamine is detected in my medicinal product?

如果医药产品中检测到亚硝胺该怎么办？

If one or several nitrosamine(s) is detected for the first time in my medicinal product:

如果首次在我的医药产品中检测到一种或多种亚硝胺

The MAH/Applicant should forthwith inform the competent authorities, irrespective of the amount detected as described in Q&A 3 for medicinal products subject to the call for review.

MAH/申请人应立即通知主管当局，无论 Q&A 3 中描述的需要审查的药品的检测结果如何。

The levels should be reported in ng and ppm, together with the corresponding calculations used to describe the potential exposure to the detected nitrosamine based on the maximum daily dosage recommended in the SmPC. If SmPCs differ between Member States, the calculations should be provided for each different maximum exposure. Sufficient details should be provided to enable the calculations to be reviewed and verified.

根据 SmPC 中推荐的最大日剂量，连同用于描述检测到的亚硝胺的潜在暴露的相应计算，浓度应以 ng 和 ppm 为单位报告。如果成员国之间的 SmPC 不同，则应针对每个不同的最大暴露提供计算结果。应提供足够的详细信息以使计算能够进行审查和验证。

The calculated exposure(s) should then be compared to the limit defined in Q&A 10:

然后应将计算出的暴露量与 Q&A 10 中定义的限度进行比较

- If the limit is not exceeded for the detected nitrosamine or, in case of presence of multiple nitrosamines, if the total risk remains below a theoretical lifetime excess risk of <1:100,000, the MAH/Applicant shall control the nitrosamine(s) in the FP at or below this limit (see Q&A 10) and should take measures to mitigate the risk of nitrosamine formation or contamination in the medicinal product as much as possible (see Q&A 12).

  如果检测到的亚硝胺未超过限度，或者在存在多种亚硝胺的情况下亚硝胺，如果总风险仍然低于＜1:100,000 的理论生命周期风险，则 MAH/申请人应将 FP 中的亚硝胺控制在或低于此限度（参见问答 10）， 并应采取措施减轻尽可能避免药品中亚硝胺形成或污染的风险（见问答 12）。

- Where the limit defined in Q&A 10 for single or multiple nitrosamines is exceeded, the MAH/Applicant should submit forthwith an (interim) investigation report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment. The competent authorities will then assess the impact on the benefit/risk balance and the consequent need for any action to be taken.

  如果超过 Q&A 10 中针对单一或多种亚硝胺定义的限度，则 MAH/申请人应立即提交一份（临时）调查报告，包括（初步）根本原因、风险控制计划和收益/风险评估。然后，主管当局将评估对利益/风险平衡的影响以及因此需要采取的任何行动。

Please refer to the Assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products for further information.

请参考评估报告 CHMP 关于人用药品中亚硝胺杂质的第 5(3) 条意见，以获取更多信息。

Changes to the marketing authorisation related to measures to prevent or minimise the risk should be introduced without delay and in accordance with the guideline on classification of variation (please refer to Q&A 13).

与预防或最小化风险措施相关的上市许可变更应立即并根据变更分类指南（请参阅问答 13）进行。

If the presence of specific nitrosamine(s) in a medicinal product has already been reported to the authorities by the MAH and is below the limit defined in Q&A 10 or a limit approved by the authorities, there is no need for a further notification to the authorities.

如果 MAH 已经向当局报告了药品中特定亚硝胺的存在，并且低于 Q&A 10 中定义的限度或当局批准的限度，则无需进一步通知 MAH 当局。

Batch records are subject to inspection by competent authorities.

批记录须接受主管当局的检查。

12. Which are the measures to mitigate the risk of presence of nitrosamines?

降低亚硝胺存在风险的措施有哪些？

The presence of N-nitrosamines in the FP shall be mitigated as much as possible and shall be at or below a limit defined in Q&A 10.

应尽可能减少 FP 中 N-亚硝胺的存在，并且应等于或低于 Q&A 10 中定义的限度。

MAHs shall design or adapt the manufacturing process of their medicinal products to prevent formation of and contamination with nitrosamines whenever possible.

MAH 应设计或调整其医药产品的制造工艺，以尽可能防止亚硝胺的形成和污染。

MAHs should implement a control strategy regarding W-nitrosamines, which should include current and prospective measures to minimise the risk of generation of/contamination with nitrosamines (e.g. change of manufacturing process, change of raw material quality, introduction of appropriate specifications and development of appropriate methods, and measures on the premise and equipment such as cleaning procedures and environmental monitoring). MAHs should control nitrosamine levels in accordance with the limits defined in Q&A 10 and any future changes that may impact on the risk (e.g. change of supplier, change of manufacturing process and change of packaging).

MAHs 应实施关于 N-亚硝胺的控制策略，其中应包括当前和未来的措施，以尽量减少亚硝胺产生/污染的风险（例如制造工艺的变化、原材料质量的变化、 引入适当的规格和开发适当的方法、场所和设备的措施，例如清洁程序和环境监测）。 MAHs 应根据 Q&A 10 中定义的限制控制亚硝胺水平以及可能影响风险的任何未来变化（例如供应商的变化、制造过程的变化和包装的变化）。

MAHs shall also ensure that active substances and excipients used in their FPs are manufactured in compliance with good manufacturing practices in line with Article 46(f) of Directive 2001/83/EC.

MAH 还应确保其 FP 中使用的活性物质和辅料的生产符合 2001/83/EC 指令第 46(f) 条的良好生产规范。

Please refer to the Assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products for further information.

请参考评估报告 CHMP 关于人用药品中亚硝胺杂质的第 5(3) 条意见，以获取更多信息。

13. Which changes would be required for Marketing Authorisations?

上市授权需要哪些变更？

MAHs should introduce changes to their API and/or FP (e.g. manufacturing process, controls and specification, product formulation, raw materials and packaging), through the timely submission of appropriate variation(s) in accordance with the guideline on classification of variations.

MAH 应根据变更分类指南，通过及时提交适当的变更，对其 API 和/或 FP（例如制造工艺、控制和规格、产品配方、原材料和包装）进行变 更。

When nitrosamine(s) is (are) identified, the corresponding limit(s) as defined in Q&A 10 should be introduced in the specifications of the FP. Please refer to Q&A 15 for information on the test modalities.

当识别出亚硝胺时，应在 FP 的规格中引入 Q&A 10 中定义的相应限度。有关测试方式的信息，请参阅问答 15。

The application for a variation should contain information on amendments to the marketing authorisation - i.e. in module 3 (3.2.S and 3.2.P), the active substance master files (ASMF) or the Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) that is necessary to control nitrosamine impurities in the active substance and/or FP. Variations should be submitted according to the existing variations classification guideline: EUR-Lex - 52013XC0802(04) - EN - EUR-Lex (europa.eu)

变更申请应包含有关上市许可修订的信息即模块 3（3.2.S 和 3.2.P）、活性物质主文件 (ASMF) 或欧洲药典各论的适用性证书 (CEP) 是控制活性物质和/或 FP 中亚硝胺杂质所必需的。应根据现有的变更分类指南提交变更： EUR-Lex - 52013XC0802(04) - EN - EUR Lex (europa.eu)

Depending on the root cause identified and extent of changes to be made, grouping of variations or use of work-sharing procedures might be applicable: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers.

根据确定的根本原因和要进行的更改的程度，可能适用对变化进行分组或使用工作共享程序：

https://www.ema.europa.eu/en/human regulatory/post-authorisation/variations /worksharing-问题-答案

14. What is the approach for new and ongoing marketing authorisation applications (MAA)?

新的和正在进行的上市许可申请 (MAA) 的方法是什么？

Applicants shall design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of W-nitrosamines in their API and FPs (please refer to Q&A 12).

申请人应设计其生产工艺和控制措施，以尽可能防止或尽可能减少其 API 和 FP 中 N-亚硝胺的存在（请参阅问答 12）。

The potential presence of nitrosamines must be evaluated as part of the MAA as follows:

亚硝胺的潜在存在必须进行评估并作为 MAA 的一部分，如下所示

- At the submission stage:

  在提交阶段

  - For the risk evaluation, Applicants are required to follow the principles for step 1 as per Q&A 2. The risk evaluation should be submitted as an attachment to Module 1 with a corresponding reference in Module 3.2 of the marketing authorisation dossier. To supplement the detailed risk evaluation, the template located on the CMDh nitrosamine website (section "For additional specific information related to nationally authorised products (including MRP/DCP)") could also be submitted: https://www.hma.eu/human-medicines/cmdh/advice-from-cmdh/nitrosamine- impurities.html . The template is optional for CAPs. For NAPs, and DCPs, the template is mandatory and the CMDh practical guidance located in the same section of the same website should be followed. 对于风险评估，申请人需要按照问答 2 遵循步骤 1 的原则。风险评估应作为模块 1 的附件提交，并以上市许可注册资料的模块 3.2 作为相应参考。为了补充详细的风险评估，还可以提交位于 CMDh 亚硝胺网站上的模板（“与国家授权产品（包括 MRP/DCP）相关的其他特定信息”部分）：https://www.hma.eu/human-medicines/cmdh/advice-from-cmdh/nitrosamine- impurities.html . 该模板对于 CAP 是可选的。对于 NAP 和 DCP，模板是强制性的，并且应遵循位于 同一网站同一部分的 CMDh 实用指南。
  - If a risk of presence of nitrosamines in the medicinal product is identified, applicants are required to provide the risk assessment outlining the impact on the benefit-risk balance of the product and a risk mitigation strategy. Applicants should also submit confirmatory testing plans or confirmatory testing data as mentioned in step 2 (see Q&A 2).

    如果确定药品中存在亚硝胺的风险，申请人应需要提供风险评估，概述对利益风险平衡的影

响产品和风险控制策略。申请人还应提交步骤 2 中提到的确认测试计划或确认测试数据（参见问答 2）。

- In case applicants have not submitted a risk evaluation and, if applicable, confirmatory testing plans with their MAA, these should be submitted during the marketing authorisation review procedure.

  如果申请人MAA 未提交风险评估和（如果适用）确认测试计划，则应在上市许可审查程序中提交。

- During the Marketing Authorisation (MA) evaluation procedure:

  在上市许可 (MA) 评估程序中

  - If the risk evaluation was not submitted as part of the MAA, it will be requested during the MA review process. Risk evaluation will have to be adequately documented and, if applicable, supported by confirmatory testing in case a possible risk of presence of nitrosamines has been identified. This information should be submitted as part of the responses to the list of questions.

    如果风险评估未作为 MAA 的一部分提交，则将在 MA 审查过程中提出要求。风险评估必须有充分的文件记录，并且在适用的情况下， 在确定存在亚硝胺的可能风险的情况下，由确认测试支持。此信息应作为对问题列表的答复的一部分提交。

  - If the applicant is not able to provide satisfactory information and justification of a favourable benefit-risk profile of the product at this stage, a request to further assess the risk of presence of nitrosamine will be part of the further list of questions / outstanding issues depending on the stage of the MA procedure.

    如果申请人无法提供此阶段产品有利的利益风险概况方面令人满意的信息和理由，进一步评估亚硝胺存在风险的请求将成为进一步问题/未决问题列表的一部分，具体取决于 MA 程序的阶段。

  - Any outstanding issues related to the quality requirements of the product would have to be addressed before the final opinion on the granting of the MA.

    任何与产品质量要求相关的突出问题必须在授予 MA 的最终意见之前解决。

For new and on-going marketing authorisation applications, the number of batches to be tested as part of any confirmatory testing should be commensurate with the risk in line with ICH M7(R1) guideline. The source of risk has to be well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch. Test results from a minimum of 6 pilot scale batches or 3 production scale batches may be sufficient. Depending on the risk factors for nitrosamine presence, e.g. with risk factors being closer to the FP, more batches may need to be

tested. If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, (or were used historically during development), then testing of additional batches would be necessary to cover these risk factors.

对于新的和正在进行的上市许可申请，作为任何确认测试的一部分，要测试的批次数量应与符合 ICH M7(R1) 指南的风险相称。必须很好地了解风险来源（例如通过加标和清除研究），以便预计各批次的杂质水平保持一致。至少 6 个中试规模批次或 3 个生产规模批 次的测试结果可能就足够了。根据亚硝胺存在的风险因素，例如风险因素更接近 FP，可能需要测试更多批次。如果使用多个制造商、制造工艺 和/或有风险原材料的来源（或在开发过程中曾使用过），则需要测试额外的批次以涵盖这些风险因素。

If a product is available in multiple strengths of the same dosage form with the same risk factors applicable to each, then testing could be rationalised by testing only the worst-case scenario strength. The worst-case approach should be justified by the MAH on a case-by-case basis.

如果一种产品有多种规格的相同剂型，且每种规格都适用相同的风险因素，则可以仅测试最坏情况下的规格。MAH 应根据具体情况对最坏情况的方法进行论证。

During development of an analytical method, a reference standard of the relevant nitrosamine impurity is generally needed. If, despite extensive efforts, it becomes apparent that the relevant nitrosamine impurity cannot be synthesised, then this could be an indication that the nitrosamine either does not exist or that there is no risk of it being formed. In such cases, it may not be necessary to conduct confirmatory testing. This should be justified thoroughly on a case-by-case basis according to appropriate scientific principles. The justification could include relevant literature, information on structural/stereo-electronic features and reactivity of the parent amine, stability of the nitrosamine and experimental data to illustrate the efforts made to synthesise and to analyse the impurity. The justification should be included in the submitted risk assessment.

在分析方法的开发过程中，通常需要相关亚硝胺杂质的标准品。如果尽管付出了广泛的努力，但很明显无法合成相关的亚硝胺杂质，那么这 可能表明亚硝胺不存在或没有形成亚硝胺的风险。在这种情况下，可能没有必要进行确认测试。这应该根据适当的科学原则在个案的基础上 进行彻底的论证。理由可以包括相关文献、关于母体胺的结构/立体电子特征和反应性的信息、亚硝胺的稳定性和实验数据，以说明为合成和分 析杂质所做的努力。理由应包含在提交的风险评估中。

15. When should a test for nitrosamines be included in the MA dossier?

何时应在 MA 注册资料中说明亚硝胺测试?

When a nitrosamine is identified after Step 2 confirmatory testing, a limit will usually need to be included in the specifications of the finished product and the product must comply if tested. If the root cause has been identified in the finished product manufacturing process or storage, or nitrosamines have been detected in the finished product, but the actual source of contamination remains unclear, routine testing of the finished product is required by default.

当在第 2 步确认测试后发现亚硝胺时，通常需要在成品标准中规定一个限度，并且产品测试结果必须符合要求。如果在成品生产过程或贮存过程中查明原因，或成品检出亚硝胺，但实际污染源不明，默认要求对成品进行常规检测。

The control point (finished product, API or an intermediate) for nitrosamines should be selected in such a way that it will give assurance of presence of the impurity below the acceptable limit based on acceptable intake (AI) in the finished product. Testing is usually expected to be carried out in the finished product, however if the source of a nitrosamine impurity is identified in the active substance manufacturing process, control options 1 to 3 as stated in ICH M7(R1) guideline could be used to demonstrate that the nitrosamine will not be present above the acceptable limit based on AI in the finished product. Testing of raw materials (e.g. excipients) should also be considered if these are potential sources of nitrosamine impurities. Exceptions from routine testing may be possible, if the root cause of contamination is demonstrated to be well-understood:

亚硝胺的控制点（成品、API 或中间体）的选择方式应确保杂质的存在低于成品中基于可接受摄入量 (AI) 的可接受限度。通常期望在成品中进行测试，但是如果在活性物质生产过程中确定了亚硝胺杂质的来源，则可以使用 ICH M7(R1) 指南中规定的控制选项 1 至 3 来证明成品中亚硝胺的含量不会超过基于 AI 的可接受限度。如果原材料（如赋形剂）是亚硝胺杂质的潜在来源，也应考虑对其进行检测。如果根证明污染的原因是众所周知的，可以不对产品进行常规测试：

- Only if the amount of nitrosamine present is consistently below 10% of the acceptable limit based on AI in the API or in the finished product, then a test for the nitrosamine could be omitted from the specification.
  只有当亚硝胺的存在量始终低于 API 或成品中基于 AI 的可接受限度的 10% 时，才可以从标准中不规定对亚硝胺的测试
- Only if levels of a single nitrosamine are consistently below 30% of the acceptable limit based on AI in the API or the finished product, skip-testing according to the ICH Q6A definition could be

acceptable.

仅当单一亚硝胺的水平始终低于可接受限度的 30%（基于 API 或成品中的 AI，根据 ICH Q6A 定义的定期测试是可以接受的。

16. What are the responsibilities of MAHs for APIs with CEPs or ASMFs?

对于具有 CEP 或 ASMF 的 API，MAH 的职责是什么？

MAHs/Applicants, manufacturing authorisation holders and API manufacturers should work together and take precautionary measures to mitigate the risk of presence of nitrosamines during the manufacture and storage of all medicinal products containing chemically synthesised APIs.

MAHs/申请人、生产授权持有人和 API 生产商应共同努力，采取预防措施，降低所有含有化学合成 API 的医药产品在生产和储存过程中存在亚硝胺的风险。

MAHs/Applicants must ensure that appropriate and robust risk evaluations are carried out by the relevant manufacturing authorisation holders and API manufacturers (including ASMF or CEP holders) in accordance with Article 46 of Directive 2001/83/EC.

MAH/申请人必须确保相关制造授权持有人和 API 制造商（包括 ASMF 或 CEP 持有人）根据指令 2001/83/EC 第 46 条进行适当和稳健的风险评估。

17. How does the lessons learnt exercise from presence of nitrosamines in sartans relate to the Article 5(3) Referral Outcome?

从沙坦类中亚硝胺的存在中吸取的教训与第 5(3) 条推荐结果有何关系？

The lessons learnt exercise was conducted by experts from the EU Regulatory Network to determine which lessons can be learnt from the handling of the cases of sartans with nitrosamine impurities. The objective is to make recommendations on how to reduce the risk of such impurities in medicines and to ensure that regulators are better prepared to manage cases of unexpected impurities in the future. Although the exercise focussed on lessons learnt from the assessment conducted for the sartans with a tetrazole ring, the recommendations apply to all human medicines.

经验教训练习由欧盟监管网络的专家进行，以确定可以从处理含有亚硝胺杂质的沙坦类案件中吸取哪些经验教训。目的是就如何降低药物中此类杂质 的风险提出建议，并确保监管机构在未来更好地管理意外杂质的情况。

The recommendations set forward include new or additional guidance on areas such as the control of

impurities (including cohort of concern compounds), Good Manufacturing Practice, the roles and responsibilities of manufacturers and MAHs/Applicants but also proposals for improvement of communication with patients and healthcare professionals and cooperation with international partners. The full recommendations are available on EMA's website. The European medicines regulatory network will develop an implementation plan and then work with the parties that will implement each action.

提出的建议包括新的或额外的指导，如杂质控制（包括关注化合物群组）、良好生产规范、制造商和MAHs/申请人的角色和责任，以及改善与患者和医疗保健专业人员沟通以及与国际合作伙伴合作的建议。完整的建议可以在 EMA 的网站上找到。欧洲药品监管网络将制定一项实施计划，然后与实施每项行动的各方合作。

It should be noted that the lessons learnt exercise outcome has been taken into account in the Article 5(3) procedure. The implementation of recommendations of the lessons learnt exercise will strengthen the regulatory framework and complement the outcome of this Article 5(3) procedure which provides the scientific opinion on the presence of nitrosamine impurities in human medicines.

应当指出，在第 5（3）条程序中考虑了以往经验教训。吸取经验教训将加强监管框架，并补充第 5（3）条程序的结果，该程序提供了关于人类药物中亚硝胺杂质存在的科学意见。

18. What about regulatory requirements in other regions?

其他地区的监管要求如何？

Regulatory authorities in the EU have been cooperating with international partners in the United States, Canada, Japan, Singapore, Switzerland, Australia and other countries to mitigate presence of nitrosamines in medicinal products and to align requirements. For questions about regulatory requirements outside the EU, please contact the relevant authorities.

欧盟监管机构一直在与美国、加拿大、日本、新加坡、瑞士、澳大利亚和其他国家的国际合作伙伴合作，以减少药品中亚硝胺的存在，并调整要求。有关欧盟以外的监管要求的问题，请联系相关机构。

19. What is the approach for line extensions and variations applications not linked to changes required as part of article 5(3) recommendation?

对于与第 5 条第（3）款建议所要求的变更无关的生产线延长和变更申请，采用什么方法？

No risk evaluation is generally necessary when submitting line extension or variation application. The risk evaluation is only required to be submitted for products in scope of the call for review as reported

in Q&A 3.

提交生产线延长或变更申请时，通常不需要进行风险评估。只有在问答 3 中报告的要求审查范围内的产品才需要提交风险评估。

Nevertheless, in some exceptional cases questions on the presence of nitrosamines in the product may be raised if a potential risk is identified during the assessment.

然而，在一些特殊情况下，如果在评估过程中发现潜在风险，可能会对产品中是否存在亚硝胺提出质疑。

20. What are the regulatory steps taken by authorities following the identification of an N-nitrosamine exceeding the AI?

药监当局在发现一种 N-亚硝胺超 AI 后采取哪些管制措施？

The regulatory process dealing with the outcomes of the call for review is outlined in European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines.

根据关于人类药物中亚硝胺杂质监管流程见 European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines.。

Chapter 3.2 provides a description on how regulators will approach the outcome from the call for review in accordance with the different scenarios reported by MAHs.

第 3.2 章描述了监管机构将如何根据 MAHs 报告的不同情景如何处理审查请求结果。

In case of identification of one or more N-nitrosamine exceeding the AI in the finished product, or in case that the sum of all detected N-nitrosamines exceeds the 1 in a 100,000 lifetime risk (scenario A), the following steps are taken in order to protect public health and ensure availability of critical medicines:

如果在成品中发现一种或多种 N-亚硝胺超过 AI，或者如果所有检测到的 N-亚硝胺总和超过 100,000 分之一的终生风险（情景 a），将采取以下步骤，以保护公众健康并确保关键药物的供应：

- A lead authority is identified as responsible for reviewing the information available and for providing the (preliminary) assessment of the case. The lead authority is selected as outlined in chapter 5.1.

  指定一个牵头机构负责审查现有资料并对事件进行（初步）评估。牵头机构的选择如第 5.1 章所述。

- The Rapid Alert Network (RAN) and the availability Single Point Of Contacts (SPOCs) are informed in order to determine the criticality of the product (in accordance with Criteria for classification of critical medicinal products for human and veterinary use).

  向快速警报网络(RAN)和可用的单点联络点(SPOCs)提供信息，以确定产品的关键程度（根据人用和兽用关键医药产品分类标准）。

- The feedback from RAN and availability SPOCs is taken into account by the lead authority when providing the preliminary recommendations on any interim or eventual required market actions and on the acceptability of corrective and preventive actions proposed by the MAH.
  牵头机构在就任何临时或最终要求的市场行动，以及 MAH 提出的纠正和预防行动的可接受性提供初步建议时，会考虑 RAN 和可用的 SPOCs 的反馈。
- The Incident Review Network (IRN) is consulted in order to facilitate the exchange of information and to evaluate whether additional measures are needed or whether a different regulatory pathway is warranted.
  咨询事故审查网络（IRN）是为了促进信息交流，并评估是否需要额外的措施，或是否需要不同的监管途径。
- If market actions are recommended, each National Competent Authority (NCA) will follow up in accordance with their national procedures and depending on the criticality of the product for their markets. The LTL concept or the use of interim limits may be considered by the lead authority and NCAs on a temporary basis for market action purposes in case of a critical product. Please refer to chapter 3.2.1.1.
  如果建议采取市场行动，每个国家主管当局将根据其国家程序，并根据产品对其市场的关键程度采取后续行动。如果是关键产品，为了市场行动的目的，牵头机构和国家竞争机构可以临时考虑 LTL 概念或临时限度的使用。请参考第 3.2.1.1 章。

21. What is the approach to control the presence of nitrosamines until a substance specific AI is established?

在确定特定物质 AI 之前，如何控制亚硝胺的存在？

Considering the new approaches for setting nitrosamines limits using the carcinogenic potency categorisation approach (CPCA) and the enhanced AMES test (EAT) protocol (see Q&A 10 above), the approach for a universal temporary AI (t-AI) while a formal AI is established is no longer considered necessary, as such the contents of this question has been deleted in July 2023.
考虑到使用致癌效力分类方法（CPCA）和增强型 AMES 试验（EAT）方案（见上文问答 10）设定亚硝胺限度的新方法，在建立正式 AI 的同时，通用临时 AI（t-AI）的方法不再被认为是必要的，因此该问题的内容已于 2023 年 7 月被删除。

22. What is the approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation?

在 CAPA 实施期间，控制 N-亚硝胺超过 AI 的方法是什么？

In accordance with the regulatory steps taken by authorities following the identification of an N-

nitrosamine exceeding the AI and outlined in Q&A20, the less-than lifetime (LTL) concept or the use of interim limits may be considered by the lead authority and NCAs on a temporary basis in order to inform market actions and at the same time ensure availability of medicines. MAHs are expected to establish and implement corrective and preventive actions (CAPAs) in authorised medicines without any delays in order to ensure patients safety and product quality. Nevertheless, it is recognised that implementation of CAPAs may require some time before the MAH is able to mitigate the presence of the identified N-nitrosamine below the established AI. Therefore, in order to avoid unnecessary risk of supply disruptions, a harmonised approach promoting the establishment of interim limits in a streamlined way is agreed. The approach is applicable to all authorised products that have:

根据 Q&A 20 中概述的当局在确定 N-亚硝胺超过 AI 后采取的监管步骤，牵头机构和 NCAs 可临时考虑使用寿命不足（LTL）概念或临时限度，以便为市场行动提供信息，同时确保药品的可获得性。MAH 应立即在授权药物中建立和实施纠正和预防措施（CAPAs），以确保患者安全和产品质量。然而，人们认识到，在 MAH 能够将已鉴定的 N-亚硝胺的存在降低到既定的 AI 以下之前，实施 CAPAs 可能需要一些时间。因此，为了避免不必要的供应中断风险，商定了一种协调的方法，以简化的方式促进临时限度的建立。该方法适用于具备以下条件的所有授权产品：

- CAPA implementation timeline of up to 3 years from the establishment and publication of the AI (nevertheless MAHs are expected to expedite CAPAs implementation).

从 AI 建立和发布之日起，CAPA 的实施时间表长达 3 年（尽管如此，MAH 预计将加快 CAPA 的实施）。

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

治疗周期	最长 12 个月	大于 12 个月
临时标准	13.3 x AI*	6.7 x AI*

*In any case the limit should not exceed 1.5 µg/day unless the established AI (Table 1, Q&A10) is > 1.5 µg/day or the nitrosamine concerns a category 5 according to CPCA or the nitrosamine is shown to be negative in an enhanced Ames test (EAT).

在任何情况下，限度都不应超过 1.5 g/天，除非确定的 AI（表 1，Q&a 10）>1.5 g/天，或者亚硝胺根据 CPCA 属于第 5 类，或者亚硝胺在强化 Ames 试验(EAT)中显示为阴性。

The approach is not applicable to the below instances where other approaches may be considered on a case-by-case basis in consultation with the appropriate regulatory authority:

该方法不适用于以下情况，在这些情况下，可与适当的监管机构协商，在个案基础上考虑其他方法：

- CAPA implementation exceeding 3 years from the establishment and publication of the AI;

自 AI 建立和发布之日起超过 3 年的 CAPA 实施；

- New/ongoing regulatory applications.

新的/正在进行的监管申请

The above interim limits are based on the LTL approach outlined in the ICH M7 guideline, using the two most conservative adjustment factors (6.7 and 13.3 x AI). The application of these adjustment factors would not be expected to exceed a theoretical excess cancer risk of 1 in 100,000 during the period of CAPA implementation.

上述临时限度是基于 ICH M7 指南中概述的 LTL 方法，使用了两个最保守的调整系数（6.7 和 13.3 x AI）。在 CAPA 实施期间，这些调整因素的应用预计不会超过 100,000 分之一的理论超额癌症风险。

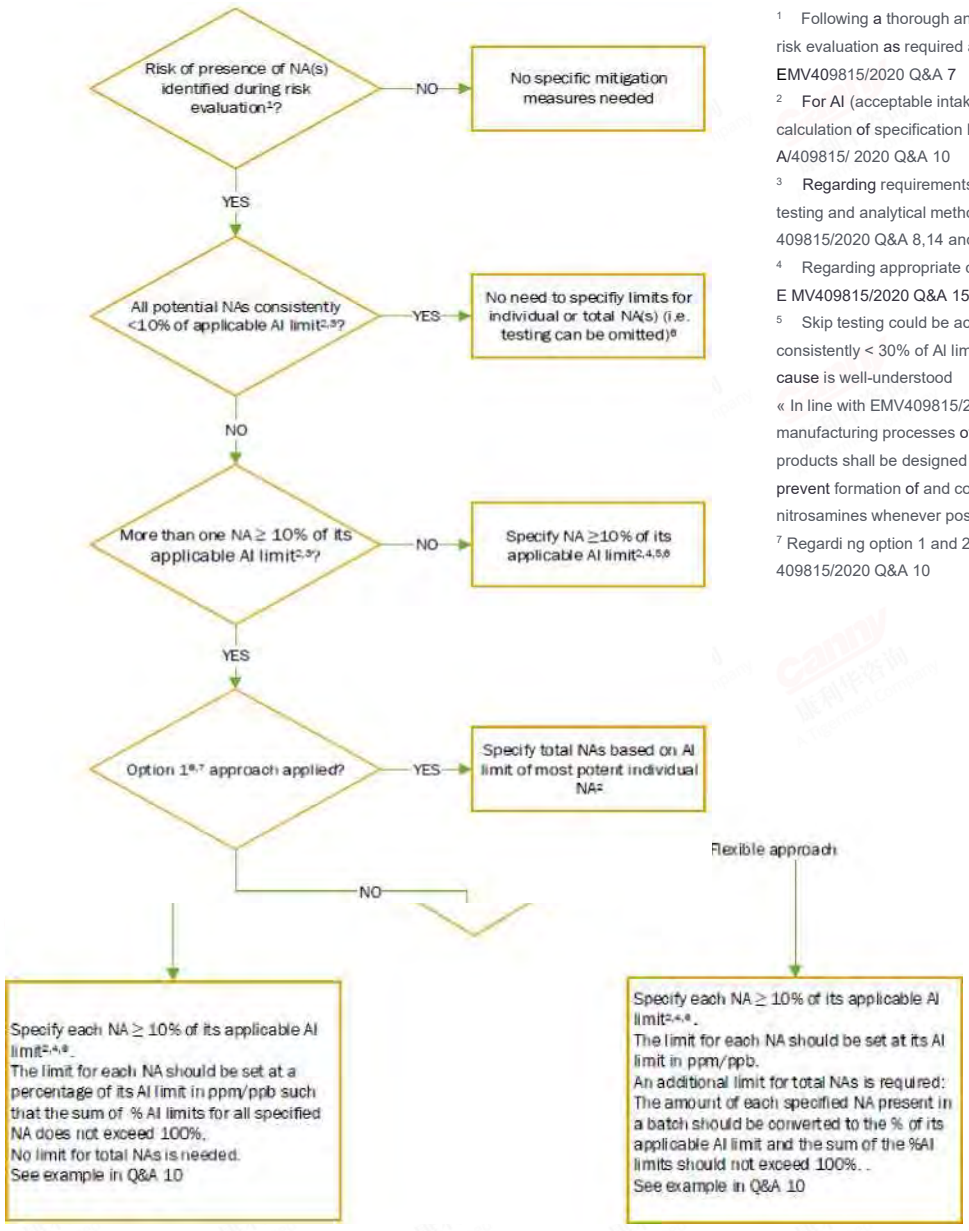
The approach is intended to be evaluated by the lead authority during the assessment of the case and is expected to be communicated by the lead authority to the concerned MAH as part of assessment conclusions. In terms of retrospective application, where more restrictive interim limits were previously agreed for some products as part of case assessment, upon request from the MAH, the lead authority can re-assess interim limits taking into consideration this approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation.

该方法旨在由牵头机构在案例评估期间进行评估，并有望由牵头机构作为评估结论的一部分传达给相关的 MAH。就回顾性申请而言，如果之前作为案例评估的一部分，对某些产品商定了更严格的临时限度，应 MAH 的要求，牵头机构可以同时考虑到这种方法，重新评估临时限度，以控制 CAPA 实施期间超过 AI 的 N-亚硝胺的存在。

MAHs are expected to ensure that the implementation of adequate controls for the detected nitrosamines is done as a matter of priority. During the use of the interim limit, monitoring measures may be evaluated by the lead authority as required. However, it is not the expectation that MAHs include these interim limits in specifications via variation.

MAHs 被期望对检测到的亚硝胺实施充分的控制确保作为优先事项。在使用临时限度期间，牵头机构可根据需要对监测措施进行评估。但是，并不期望 MAH 通过变更将这些临时限度包含在标准中。

Annex 1: Decision tree with control options for products containing multiple W-nitrosamines:



NA= Nitrosamine

[1] Following a thorough and comprehensive risk evaluation as required according to EMV409815/2020 Q&A 7

[2] For AI (acceptable intakes) and calculation of specification limits see EM A/409815/ 2020 Q&A 10

[3] Regarding requirements of confirmatory testing and analytical methods see EMA/ 409815/2020 Q&A 8,14 and 9

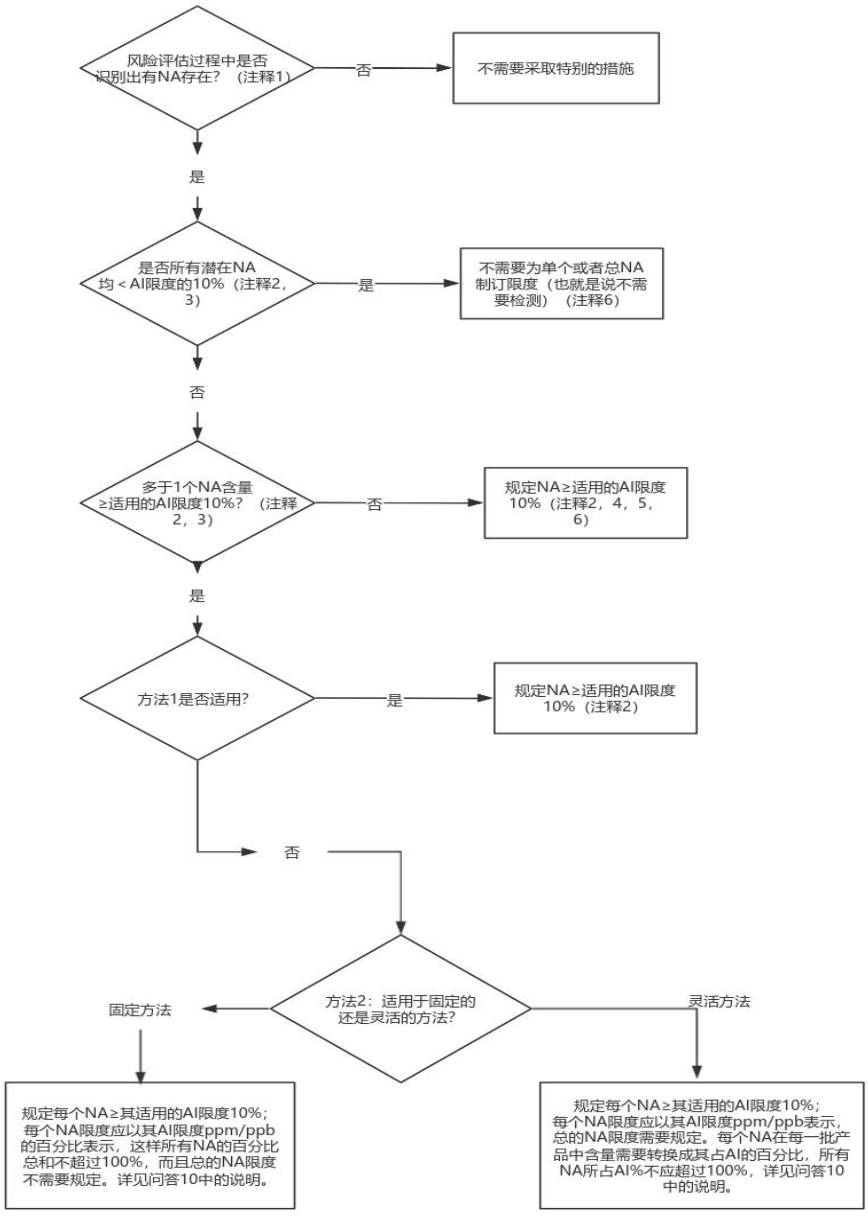
[4] Regarding appropriate control point see E MV409815/2020 Q&A 15

[5] Skip testing could be acceptable, if NAis consistently < 30% of AI limit and the root cause is well-understood

« In line with EMV409815/2020 Q&A 12 manufacturing processes of medicinal products shall be designed or adapted to prevent formation of and contamination with nitrosamines whenever possible.

[7] Regardi ng option 1 and 2 see EMV 409815/2020 Q&A 10

附件 1：含有多种 N-亚硝胺的产品的控制方法决策树：



NA=亚硝胺

1.根据要求进行全面彻底的风险评估 EMV409815/2020 问答 7

2.AI（可接受摄入量）和规格限度的计算见 EM A/409815/2020 Q&A 10

3.关于确认测试和分析方法的要求，见 EMA/409815/2020 问答 8、14 和 9

4.关于适当的控制点，见 EMA/409815/2020 问答 15

5.如果 NA 始终小于 AI 限度的 30%，并且根本原因已被充分理解，则跳过测试是可以接受的

6.根据 EMA/409815/2020 Q&A 12，药品生产工艺的设计或调整应尽可能防止亚硝胺的形成和污染

7 关于方法 1 和 2，见 EMA/ 409815/2020 Q&A 10