June 2021
CMDh/412/2019, Rev.12

# CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines

With regard to the Art. 5(3) referral, MAHs are requested to evaluate the risk of the presence of nitrosamine impurities in human medicinal products containing chemically synthesized APIs or biological APIs ("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"). This evaluation should be performed in 3 sequential steps:

Risk evaluation: all activities in step 1.

Risk assessment: all activities in step 2.

Step 3 – Changes to the marketing authorization

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

This practical guidance is prepared in line with the "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" in order to give additional guidance and explain the necessary steps for fulfilling the requested risk evaluation specifically for nationally authorized products. Q/As are enclosed for each of the three steps. Further details on how to proceed with the confirmatory testing and necessary changes of the marketing authorization will later be added to this living document. Furthermore, questions from MAHs/API and FP manufacturers might also be included in this document at a later stage if regarded necessary.

## 1. Step 1 – Risk evaluation

MAH should perform a risk evaluation for their medicinal products containing chemically synthesized APIs or biological APIs. The risk evaluations should be prioritized according to the published "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" and the outcome templates should be submitted per product as soon as available. MAHs are obliged to submit the conclusions of the risk evaluations for all of their products, until 31.03.2021 for chemically synthesised APIs and until 01.07.2021 for biological APIs as outlined below.

### *1.1. How should I submit the outcome of the risk evaluation to the competent authorities?*

Two templates have been prepared (https://www.hma.eu/620.html) for the outcomes "no risk identified" and "risk identified". The relevant template for each medicinal product has to be sent to all national competent authorities where the respective product is authorized as soon as the individual risk evaluation is finalized:

- By attaching it to an email (for contact points see Annex below);
- The heading should include "Outcome of risk evaluation nitrosamines - Step 1", "no risk" or "potential risk" and in case of MRP/DCP the EU procedure number; Guidance given by authorities on national websites also has to be regarded and national portals have to be used where applicable (see Annex below).

The risk evaluation documents do not have to be submitted to the authorities at this moment, but should be available upon request.

The Excel sheet (https://www.hma.eu/620.html) does not have to be submitted with each notification email but might be submitted at the end of the risk evaluation for all products of a MAH or on request of the member states. Note that member states may require the submission of the excel sheet with the relevant notification as part of national guidance.

### *1.2. Can we combine several MAs in one template of the risk evaluation step 1 outcome?*

Yes, you can combine several products on one template (when the outcome is identical) but you should consider national requirements as mentioned in the practical guidance. These national requirements may not be overruled by the general possibility as given by CMDh.

In case several MRP/DCP products are included in one template, the email header should just read "Outcome of risk assessment nitrosamines – Step 1" and "no risk" or "potential risk" without mentioning any MRP/DCP number. In the template itself it is mandatory to mention the marketing authorisation number AND the MPR/DCP number for each product included. Furthermore, MAHs are still required to indicate the expected testing timeline on the related "Step 1 risk identified response template" excel file.

### *1.3. Is the risk evaluation also required for products that are currently not marketed or is it sufficient to give a commitment that the risk evaluation will be performed before placing the product on the market?*

The risk evaluation has to be performed for ALL products covered by the ""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", independent from their marketing status.

### *1.4. Are radiopharmaceuticals excluded from the risk evaluation?*

No, the risk evaluation has to be performed also for radiopharmaceuticals.

## *1.5. Are herbal medicinal products, traditional herbal medicinal products and homeopathic medicinal products, excluded from the call for review?*

The outcome of the Art. 5(3), i.e. the principles for risk assessment, limits, root causes etc. apply to all medicinal products authorised and new marketing authorisation applications in the EU. However, the call for review does currently not include herbal medicinal products, traditional herbal medicinal products and homeopathic medicinal products, but they might be considered at a later point in time, depending on the experience gained.

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

The potential presence of nitrosamines will be evaluated as part of the marketing authorisation application as follows:

- **At the submission stage:**
  - Applicants are required to submit as part of their MAA a **risk evaluation –**including the relevant documentation **-** as per principles outlined in step 1 of the "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".
  - If at this stage the risk of presence of nitrosamines in the medicinal product is already identified, the applicants are required to provide the **risk assessment** outlining the impact on the benefit-risk balance of the product and a risk mitigating strategy. Applicants should also submit confirmatory testing plans or confirmatory testing data as mentioned in the step 2 of the "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".
  - In case applicants have not submitted a sufficient risk evaluation, risk assessment if applicable, including confirmatory testing results or testing plans with their MAA, these should be submitted during the marketing authorisation review procedure.
- **During the MA evaluation procedure:**
  - If the **risk evaluation** was not submitted as part of the MAA, it will be requested during the MA review process as a major objection (for all products other than the exceptions listed in ICH M7). Where a risk of the presence of nitrosamine has been identified in the risk evaluation, a **risk assessment** will have to be provided, adequately documented and supported by confirmatory testing. This information should be submitted as part of the Day 106 responses to the list of questions.
  - If the applicant is not able to provide satisfactory information and justification of a favourable benefit-risk profile of the product until Day 106, the procedure will remain in clock stop until the necessary data is provided.
  - Any outstanding issues would have to be addressed before Day 210;
  - If concerns on quality of the products are still not sufficiently addressed at Day 210, considerations on the impact of the risk evaluation/ assessment on the presence of nitrosamines in the product will be made and final decision on granting the MA will be made by the RMS in liaison with CMS.

For information on batch testing please do also regard in this respect the "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".

### *1.7. How to deal with pending or newly submitted MRPs or RUPs or line extensions?*

No risk evaluation is generally necessary when submitting an application for RUP, MRP or a line extension. Instead, the MAH has to submit the outcome of the risk evaluation to all member states in which the MA is already approved within the deadline as mentioned in the "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".

However, in some cases depending on the product a risk evaluation can be requested by the RMS or CMS during the procedure, i.e. in cases where changes are introduced possibly impacting the currently identified root causes for presence of nitrosamines as defined in EMA/CHMP/428592/2019.

### *1.8. Where should I place the outcome of the risk evaluation and risk assessment in the dossier of a new marketing authorisation application?*

The risk evaluation in a new marketing authorisation application should be submitted as an attachment to Module 1, preferably under "additional data", corresponding reference can be made in Module 3, section 3.2.P.5.6 Justification of specification. The risk assessment should be included in Module 3.2.

### *1.9. When in the step 1 template a potential risk for nitrosamines is identified as not all relevant data were available and later on it is clarified that there is actually no risk, may I submit updated templates, i.e. replace the "risk identified" template by a "no risk identified" template?*

No, the submission of the risk evaluation template as outcome of step 1 can take place only once. If the template is completed with a potential risk identified than the confirmatory testing has to be started immediately. This has to be confirmed anyway, including the relevant performance dates, in the template submitted as step 1 outcome. It should therefore be avoided to submit premature risk evaluation outcomes mentioning a potential risk because of missing data.

### *1.10. How to deal with variations?*

No risk evaluation is generally necessary when submitting an application for a variation. Instead, the MAH has to submit the outcome of the risk evaluation to all member states in which the MA is already approved within the deadline as mentioned in the "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".

However, in some cases questions on nitrosamines may be raised if a potential risk is identified in the assessment. Otherwise, no reference to the ongoing Art. 5(3) procedure should be included in the AR.

### *1.11. What should I do when I detect a nitrosamine risk after the evaluation in the MAA or after the call for review is finalised?*

If after finalisation of a MAA or the call for review a new potential risk for nitrosamines is identified the MAH should immediately start testing activities in the finished product and in case nitrosamine is

detected he should immediately inform CAs accordingly via the steps described in section 3 of this guidance document by submitting the relevant variation.

MAHs together with API and finished product manufacturers are expected to maintain the quality of the product throughout its lifecycle and therefore to review the outcome of the risk evaluation and testing as and when new information on potential root causes for nitrosamine formation or contamination becomes available.

# 2. Step 2 – confirmatory testing of the finished product for approved products

## *2.1. When and how should I perform confirmatory testing for nitrosamines?*

For the purpose of confirmatory testing as part of step 2 of the call for review to MAHs, testing should always be carried out on the FP. For details on the confirmatory testing to be conducted by MAHs and manufactures see Q/A No 3 and 8 of the "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".

## *2.2. How should I submit the outcome of the confirmatory testing to the competent authorities?*

Two templates have been prepared (https://www.hma.eu/620.html) for the outcomes "no nitrosamine detected" and "nitrosamine detected". The relevant template for each medicinal product has to be sent to all national competent authorities where the respective product is authorised as soon as the individual risk assessment is finalised:

- By attaching it to an email (for contact points see Annex below)
  - to the concerned national competent authorities in case of purely national MAs,
  - to the RMS in case of MRP/DCP products (copying the CMS's) or
  - to the EMA in case of CAPs
- The heading should include "Outcome of confirmatory testing nitrosamines - Step 2". For MRP/DCP products the EU procedure number should be added as well. Please also regard guidance given by national competent authorities in this respect.
- When nitrosamines have been detected the template "Step 2 – Nitrosamine detected response template" has to be submitted independent from the amount detected.
- Only in case no nitrosamines have been detected the template "Step 2- no nitrosamine detected response template" has to be submitted.
- In case nitrosamines have been detected and are exceeding the acceptable intake limit (AI) or exceeding the lifetime excess cancer risk of 1:100,000, or in case of newly identified nitrosamines which were not included in CHMP article 5 (3) opinion regardless of the results, the following supportive documentation is required at the time of reporting: testing results expressed in ng and ppm, interim investigation report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment as well as proposed CAPAs. The "Step 2 Nitrosamine detected above AI or new nitrosamine detected response template" should also be filled out in these cases. The RMS will

then evaluate the results for MRP/DCP products and inform the CMSs about the outcome of their evaluation, so that the CMSs are aware that the MAH has performed and finalised Step 2. Necessary measures will then be decided on by the authorities.

- In all other cases related documentation should be made available upon request.
- Several products can be combined on one step 2 outcome response template 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 template when the supporting documentation is completely identical for all products concerned; if not the response has to be submitted separately. In case nitrosamines have been detected and are exceeding the acceptable intake limit (AI) or exceeding the lifetime excess cancer risk of 1:100,000, or in case of newly identified nitrosamines which were not included in CHMP article 5 (3) opinion regardless of the results, the requested "Step 2 Nitrosamine detected above AI or new nitrosamine detected response template" has to be added as well including all products mentioned in the template.

Furthermore, please also take into account guidance from national competent authorities given below for submission details (see Annex) as well as regarding the notification of product defects and recalls. The national requirements may not be overruled by the general possibility for a combined template as given by CMDh.

### *2.3. Is the risk assessment also required for products that are currently not marketed or is it sufficient to give a commitment that the risk assessment will be performed before placing the product on the market?*

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. However, it is recognized that step 2 may not be possible for medicines that are not marketed since there may be no finished product batches available for confirmatory testing. Only in these cases where no batches of finished products are available, it would be acceptable to submit a written confirmation that step 2 confirmatory testing will be conducted before 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, even if this is after the step 2 and 3 deadlines.

## 3. Step 3 Changes to the marketing authorization

### *3.1. When should any necessary variations be submitted?*

For product containing **chemically** synthesised APIs, confirmatory testing activities at Step 2 and submission of any changes required to Marketing Authorisations (Step 3), are expected to be finalized at the latest by **26th September 2022.**

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

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 finalized in advance of these deadlines.

Worksharing is highly recommended in all cases where the same variation applies to several national or MRP/DCP products.

When the variation(s) under Step 3 have been submitted, please send a notification to the email addresses (as given below- 'the nitrosamines mailboxes'),

- to the concerned national competent authorities in case of purely national MA's and
- to the RMS in case of MRP/DCP products (copying the CMS's)

including "Submission of variation- nitrosamines - Step 3" in the heading. The notification should outline the details of the authorised product(s) and date of submission of the relevant variation. The Member State's reference number for the variation case should be provided or in the case of the MRP/DCP products, the EU procedure number should be stated.

## Annex: Member States' email addresses and links to published guidance

| MS | Email address | Published guidance to be considered |
|---|---|---|
| **AT** | nat@basg.gv.at | https://www.basg.gv.at/en/companies/medicinal-products/quality-of-medicines#c20671 |
| **BE** | N/A | Step 1 – risk assessment:<br>• No risk identified: https://www.famhp.be/en/nitrosamines_risk_evaluation_outcome_confirmation_of_no_risk_identified<br>• Risk of nitrosamine presence identified: https://www.famhp.be/en/nitrosamines_risk_evaluation_outcome_risk_of_nitrosamine_presence_identified<br>Step 2 – confirmatory tests:<br>• No nitrosamine detected: https://www.famhp.be/en/nitrosamines_step_2_confirmation_of_no_nitrosamine_detected<br>• Nitrosamine detected: https://www.famhp.be/en/nitrosamines_step_2_nitrosamine_detected |
| **BG** | nitrosamines@bda.bg | |
| **CY** | nitrosamines@phs.moh.gov.cy | |
| **CZ** | nitrosaminy@sukl.cz | http://www.sukl.eu/pozadavek-na-drzitele-rozhodnuti-o-registraci-ke-zhodnoceni?lang=2 |
| **DE – BfArM** | nitrosamines@bfarm.de | https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/EN/RV_STP/m-r/nitrosamin_2019-09-26.html |
| **DE-PEI** | esubmission@pei.de | https://www.pei.de/EN/newsroom/notifications/notifications-node.html |
| **DK** | nitrosamines@dkma.dk | |
| **EE** | nitrosamines@ravimiamet.ee | |
| **EL** | nitrosamines@eof.gr | https://www.eof.gr/web/guest/home?p_p_id=62_INSTANCE_0eNL&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-2&p_p_col_count=11&_62_INSTANCE_0eNL_struts_action=%2Fjournal_articles%2Fview&_62_INSTANCE_0eNL_groupId=12225&_62_INSTANCE_0eNL_articleId=4699553&_62_INSTANCE_0eNL_version=1.0 |
| **ES** | | https://sinaem.agemed.es/registroComunAEMPS/Login.aspx |
| **FI** | nitrosamines@fimea.fi | |
| **FR** | nitrosamines@ansm.sante.fr | https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Procedure-pour-la-transmission-a-l-ANSM-des-resultats-de-l-evaluation-du-risque-de-presence-d-impuretes-nitrosamines-dans-les-medicaments-chimiques-Point-d-information |
| **HR** | nitrosamines@halmed.hr | |
| **HU** | nitrozamin@ogyei.gov.hu | https://ogyei.gov.hu |
| **IE** | nitrosamines@hpra.ie | https://www.hpra.ie/homepage/medicines/regulatory-information/medicines-authorisation/nitrosamine-impurities |
| **IS** | nitrosamines@ima.is | |

| MS | Email address | Published guidance to be considered |
|---|---|---|
| **IT** | nitrosamine@aifa.gov.it | |
| **LT** | nitrosamines@vvkt.lt | |
| **LU** | nitrosamines@ms.etat.lu<br>maa.hum@ms.etat.lu | |
| **LV** | nitrosamines@zva.gov.lv | |
| **MT** | nitrosamines.medicinesauthority@gov.mt | |
| **NL** | nitrosamines@cbg-meb.nl | No national requirements |
| **NO** | nitrosamines@noma.no | https://legemiddelverket.no/nyheter/reporting-of-nitrosamines-risk-evaluering-outcome |
| **PL** | nitrozoaminy@urpl.gov.pl | |
| **PT** | | |
| **RO** | nitrozamine@anm.ro | https://www.anm.ro/medicamente-de-uz-uman/informatii-despre-nitrozamine-pentru-dapp/ |
| **SE** | RIC@mpa.se | |
| **SI** | nitrosamines@jazmp.si | |
| **SK** | nitrosamines@sukl.sk | |
| **UK** | | https://www.gov.uk/guidance/medicines-marketing-authorisation-holders-submission-of-nitrosamine-risk-evaluation |