SAHPRA
South African
Health Products
Regulatory Authority

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COMMUNICATION TO STAKEHOLDERS

Issue No.: PEM01-2024/25

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NITROSAMINE COMMUNICATION

INTRODUCTION

This document is intended to provide communication to industry on nitrosamine review for all other new, in-process and registered products including biological medicines and all old medicines. This will be a "living document" and will be updated. It is important that Applicants adhere to the regulatory requirements to avoid delays in the evaluation of applications. This document should be used in conjunction with SAHPRA's notification templates for nitrosamine risk evaluation or confirmatory testing and outcome of risk for nitrosamine investigation, available from SAHPRA's website.

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List of abbreviations and definitions

APIs	Active Pharmaceutical Ingredients
ADI	Approved Daily Intake
AI	Acceptable intake
CEP	Certificate of Suitability
CPQ	Confirmation of WHO API Prequalification
DIPNA	N-nitrosodiisopropylamine
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EIPNA	N-nitrosoethylisopropylamine
EMA	European Medicines Agency
FPPs	Final Pharmaceutical Products
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL limit	Intake limit
LOQ	Limit of Quantification
LTL	Less Than Lifetime
NDMA	N-nitrosodimethylamine
NDEA	N-nitrosodiethylamine
NMBA	N-nitroso-N-methyl-4-aminobutyric acid
NMPA	NMPA - N-nitroso-N-methylaniline
ng	nanogram
PI	Professional Information
ppm	Parts per million
RRA	Recognised Regulatory Authority
SAHPRA	South African Health Products Regulatory Authority
USFDA	United States of America Food and Drug Administration
USP	United States Pharmacopeia

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1. Background

SAHPRA is currently reviewing active pharmaceutical ingredients (APIs) and final pharmaceutical products (FPPs) of specific medicines containing APIs: sartans, metformin, ranitidine and rifapentine which have been reported to show the presence of N-nitrosamine impurities. The investigation of these has recently been expanded to all chemically synthesised medicines including biologicals (excluding complementary medicines). This review was triggered by the detection of an impurity, N-nitrosodimethylamine (NDMA) in the above products which was observed to be above the acceptable intake limit.

NDMA is classified as a probable human carcinogen (a substance capable of causing cancer) based on the results from laboratory tests. The presence of these impurities appears to be generated by the reaction of a secondary amine (which may be present as an impurity or degradant in the solvents and reagents used) and sodium nitrite under acidic conditions where nitrous acid is formed. The impurity may also arise in the manufacturing process through cross contamination or as an impurity from solvents, reagents intermediates and the starting material. The presence of these impurities should therefore be investigated in all other APIs. SAHPRA is therefore expanding the review and investigation of the levels of NDMA and any other N-nitrosamine impurities in all registered (including all old medicines) chemically synthesised medicines including biologicals (excluding complementary medicines) and products in the pre-registration phase.

2. Plan of Action

The plan of action for all products is illustrated below:

2.1. Affected products.

All registered products (including all old medicines) containing chemically synthesised APIs or biological APIs (excluding herbals/complementary medicines).

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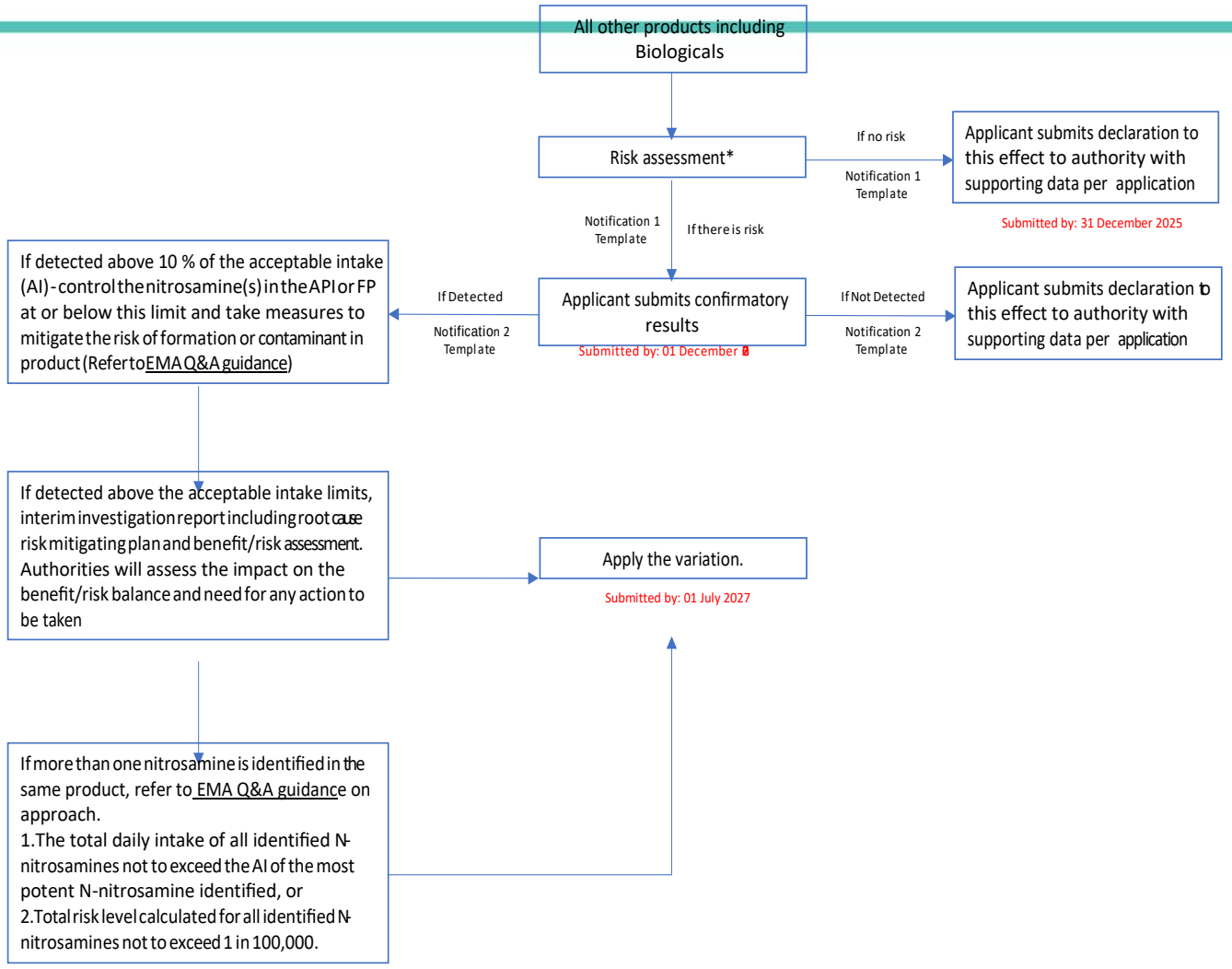

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A risk assessment should be conducted by API manufacturers in collaboration with respective FPP manufacturers as described above. The timelines have also been stipulated, Applicants are expected to provide feedback before or on the set timelines to the following email address nitrosamines@sahpra.org.za.

- The templates to be used for the risk assessment outcome are located on the SAHPRA website.

  https://www.sahpra.org.za/document/notification-template-1-for-nitrosamine-risk-evaluation/

  https://www.sahpra.org.za/document/notification-template-2-for-nitrosamine-confirmatory-testing/

- Should the impurities be detected, confirmatory results should be submitted on the excel spreadsheet located on the SAHPRA website.

  https://www.sahpra.org.za/document/outcome-of-risk-for-nitrosamine-investigation/

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. HCRs'/Applicants' compliance with the above-mentioned obligations is subject to regular controls by SAHPRA including during inspections.

Applicants that cannot comply with the respective timelines can submit risk assessments using the code:

- Type IA, B.I.z.n: Provision of nitrosamine risk assessment report as requested in Nitrosamine

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Communication.

Variation codes for changes relating to nitrosamines that requires updating of the specifications should be submitted as follows:

- Type IB, B.I.b.1.h: Addition of specification parameter with its corresponding test method as a result of a safety or quality issue - for nitrosamine impurities affecting the API specification.
- Type IB, B.II.d.1.g: Addition of specification parameter with its corresponding test method as a result of a safety or quality issue - for nitrosamine impurities affecting the finished product specification.

2.2. New applications

A risk assessment report will be required for these applications to confirm the potential of formation of the N-nitrosamine impurities. Manufacturers are advised to follow the EMA 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/16 and related annexes as well as the USFDA Control of Nitrosamine Impurities in Human Drugs guidance documents as guides to conduct the risk assessment.

Supporting data required includes batch analysis data on batches tested and data submitted to RRAs for reviews and sameness declaration. For products where reliance is used, provide a confirmation that the recognized regulatory authority (RRA) has assessed the presence of nitrosamine impurities in the API and have therefore approved its safety.

The risk assessment reports will not be requested where the certificate of suitability (CEP) and confirmation of WHO API Prequalification (CPQ) since EDQM and WHO are currently conducting investigations on these.

The risk assessment report submitted should be located in 3.2.S.3.2 for the API and 3.2.P.5.5 for the FPP.

2.3. Applications in the pre-registration phase.

The method of synthesis will be evaluated to determine if there is potential of formation of N-nitrosamine impurities. If there is potential of formation, a risk assessment report will be requested in

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accordance with the available guidance documents as highlighted above.

If the above-requested information on the investigation of N-Nitrosamine impurities is not available at the time of request, a commitment to conduct these investigations within a specified time from the date of receipt will be requested.

When the information becomes available, the required documentation must be submitted as a new sequence and a notification of upload should be sent to the following email addresses: nitrosamines@sahpra.org.za and newmedicines@sahpra.org.za.

2.4. Applications that are finalised and not yet registered.

The N-nitrosamine investigations will not be assessed in the pre-registration phase for these applications. The request for nitrosamine investigation will only be required post registration. The submission deadlines will be amended accordingly and communicated to the Applicant upon registration to allow for sufficient time to conduct the risk assessment.

2.5. Acceptable limits

In the case where nitrosamines are detected and confirmatory testing is required, the acceptable daily intake limits for a single known nitrosamine to use in calculating the acceptance limits are included in the table below:

Table 1: Acceptable daily intake limits when a single known nitrosamine is identified[1]:

Name of Nitrosamine impurity*	**acceptable daily intake (ng/day)**
N-nitrosodimethylamine (NDMA)	96.0
N-nitrosodiethylamine (NDEA)	26.5
N-nitrosoethylisopropylamine (EIPNA)	26.5
N-nitrosodiisopropylamine (DIPNA)	26.5
N-nitroso-N-methyl-4-aminobutyric acid (NMBA)	96.0
1-Methyl-4-nitrosopiperazine (MeNP)	26.5

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N-Nitroso-di-n-butylamine (NDBA)	26.5
N-Nitroso-N-methylaniline (NMPA)	34.3
N-nitrosomorpholine (NMOR)	127
N-nitroso-varenicline (NNV)	37.0
N-nitrosodipropylamine (NDPA)	26.5

*Adopted from EMA, these limits are applicable only if the final product contains a single N-nitrosamine.

The acceptable limit is calculated as:

Acceptable Intake (ppm) = Allowable daily intake (ng/day)/ Maximum Daily Dose (mg/day) of a given product as reflected in the PI.

The acceptable limit should not be exceeded. Ensure that the above process is followed to notify the authority of the risk and confirmatory testing.

https://www.ema.europa.eu/en/documents/other/appendix-2-carcinogenic-potency-categorisation-approach-n-nitrosamines_en.pdf.

The number of batches to be tested should be commensurate with the risk. Applicants or holder of the certificate of registration (HCR) 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.

2.6. The ICH M7 (R1) less than lifetime approach

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 SAHPRA as a temporary measure until further measures can be implemented to reduce the contaminant at or below the limits defined

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above. In the case where the acceptable limit is exceeded for FPPs with a limited treatment period or intermittent treatment (e.g. once a week), higher daily exposures may be used as an adjusted acceptable limit. The approach described in the ICH M7 guideline as the Less Than Lifetime (LTL) approach can be used to calculate adjusted acceptable limits for impurities present in medicinal products given for LTL and these are described in the followingtable:

Table 2: Calculation of the acceptable intake limit based on LTL approach.

Duration	1 day - 1 month	1 month – 1 year	1 year - 10 years	10 years - lifetime
Daily intake	80 x intake limits (IL)	13.3 x IL	6.7 x IL	IL

The risk approach is applicable to all routes of administration and no corrections to interim limits are generally warranted unless data justify route-specific differences that should be evaluated case by case. The LTL approach may be acceptable on a case-by-case basis where it is difficult to develop a sensitive method for the API. If nitrosamine impurities are detected, levels should be reported in ppm, along with the relevant calculations used to describe the potential exposure to the detected nitrosamine based on the maximum daily dosage and duration of treatment described in the Professional Information (PI). If thePI varies between the different regions, then the calculations for each different maximum exposure should be provided. These exposures should then be compared to the acceptable lifetime or less than lifetime approaches set out in the table above.

Sufficient detail should be provided to enable the calculations to be reviewed and verified. Note that SAHPRA also accepts limits approved by authorities which it aligns itself with. Confirmationof approval by the RRA should be provided.

2.7. Analytical procedures for nitrosamines

Manufacturers can select appropriate validated analytical methods to use for the analysis of nitrosamines. The USP and EDQM have also developed analytical methods for nitrosamines. The analytical method selected should be shown to be suitable for the product under review. Please note that SAHPRA accepts validated in-house methods as well as those proposed by the above-mentioned authorities.

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3. Reference Links

1. https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf
2. https://www.fda.gov/media/141720/download
3. https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities#:~:text=Nitrosamines%2C%20or%20more%20correctly%20N,impurities%20are%20probable%20human%20carcinogens.
4. https://www.ema.europa.eu/en/documents/other/appendix-2-carcinogenic-potency-categorisation-approach-n-nitrosamines_en.pdf.

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