Nitrosamines Analysis

on pharmaceutical products

Mérieux NutriSciences

THE DETERMINATION OF NITROSAMINE IMPURITIES ON PHARMACEUTICAL PRODUCTS IS AVAILABLE AT MÉRIEUX NUTRISCIENCES GMP FACILITY

WHAT ARE NITROSAMINES?

Nitrosamines, or more correctly N-nitrosoamines, refer to any molecule containing the nitroso functional group. These molecules are of concern because **nitrosamine impurities are probable human carcinogens**, signifying that long-term exposure above certain levels may increase the risk of cancer development.

THE RISK EVALUATION PROCESS

On September 26th, 2019 the CMDh (Heads of Medicines Agencies) published the notice "**Information on nitrosamines for marketing authorisation holders**" asking to all Marketing Authorization Holders (MAHs) of human medicinal products containing chemically synthesised active pharmaceutical ingredients to **evaluate the risk of the presence of nitrosamine impurities in their products**.
On September 2020, **FDA published the Guidance for Industry Control of Nitrosamine Impurities in Human Drugs** applicable to all chemical synthesized APIs and relative drug products recommending the following deadlines: March 2021 for Risk Assessment, and September 2023 for confirmatory testing and changes in drug applications.

STEP 1 RISK EVALUATION

MAHs should perform risk evaluation of their medicinal products containing chemically synthesised APIs.

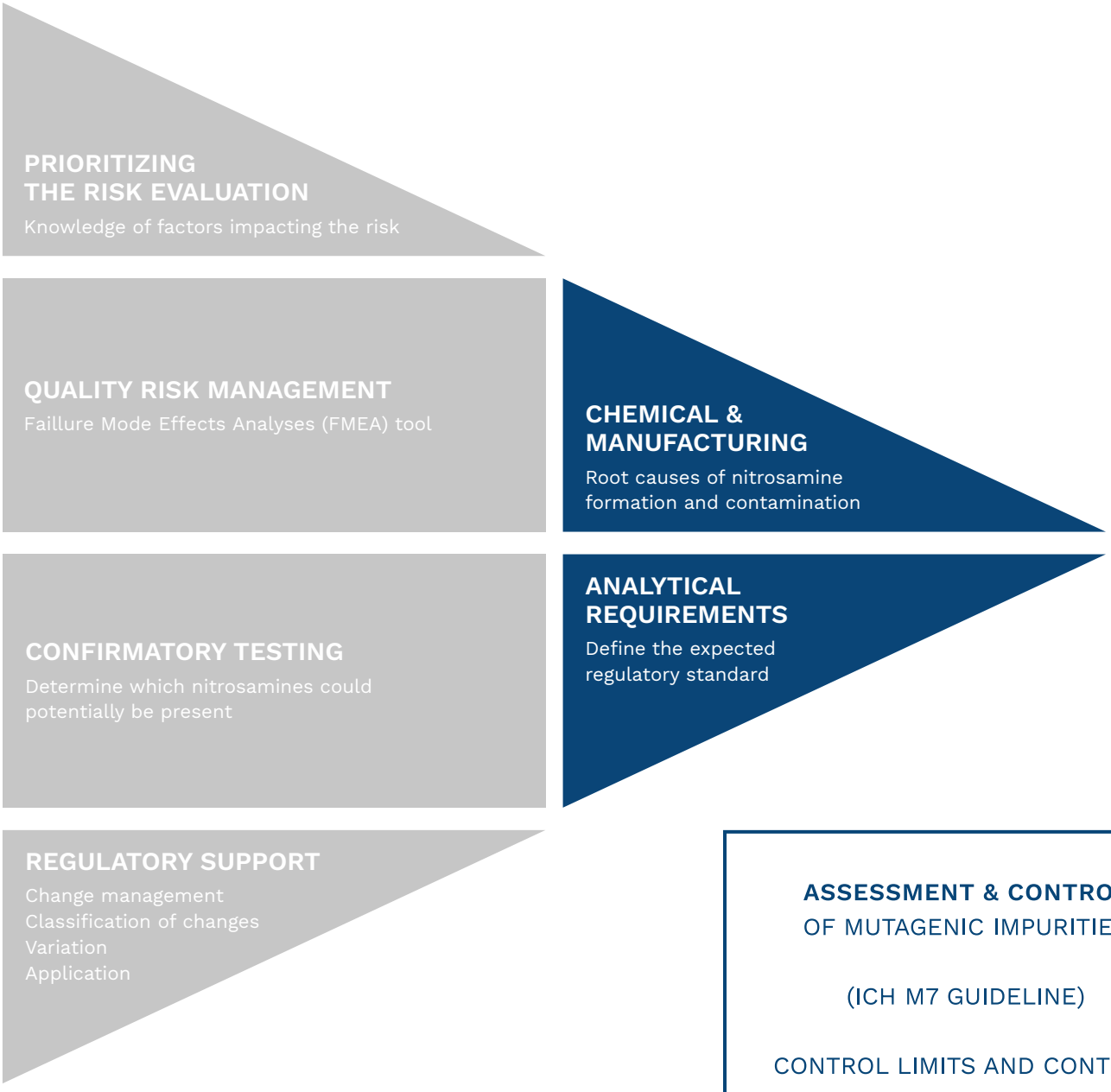
STEP 2 CONFIRMATORY TESTING

Confirmatory tests should be carried out using validated and sensitive methods. MAHs should inform the competent authorities immediately if tests confirm the presence of a nitrosamine impurity irrespective of the amount detected.

STEP 3 CHANGES TO THE MARKETING AUTHORISATION

MAHs should apply for a variation in a timely manner to introduce any required changes, such as amendment of the manufacturing process or changes to product specifications.

According to EMA requirements, confirmatory testing should be concluded at the latest by 26 September 2022 for chemical medicines and 1 July 2023 for biological medicines whereas submission of Variations to the Marketing Authorization is expected within 1 October 2023



ASSESSMENT & CONTROL
OF MUTAGENIC IMPURITIES

(ICH M7 GUIDELINE)

CONTROL LIMITS AND CONTROL
STRATEGY TOXICOLOGY ASSESSMENT

Mérieux NutriSciences

Thanks to the long-standing experience, Mérieux NutriSciences has been **developing various strategies and approaches for the determination of nitrosamines residues in different matrices** through sophisticated mass spectrometry combined with a pool of experts.

OUR CAPABILITIES: THE GMP FACILITY OF MÉRIEUX NUTRISCIENCES IS EQUIPPED WITH ALL THE ANALYTICAL TECHNIQUES USED BY THE OFFICIAL MEDICINES CONTROL LABORATORIES (OMCLS).

- **Dedicated Team & Lab** for analytical testing of NAC by: LC-HRMS or GC-HRMS with Orbitrap and/or TOF Technology; LC-MS/MS or GC-MS/MS (Triple Quadrupole Technology).
- **Target method development & validation** of high sensitive methods.
- **Targeted screening by HRMS and/or MS/HRMS** (for detection of NI without available reference standards).
- **Confirmatory testing**: method development and validation, and GMP quantitative tests with validated methods on medium and high risk nitrosamine impurities (NI) on representative drug products (DPs).
  - **Multiresidual analysis (standard set)**
    1. N-Nitrosodimethylamine (NDMA)
    2. N-Nitrosodiethylamine (NDEA)
    3. N-Nitrosomethylethylamine (NMEA)
    4. N-nitrosoethylisopropylamine (NEIPA)
    5. N-methyl-4-aminobutyric acid (NMBA)
    6. N-nitrosodiphenylamine (NDPHA)
    7. N-nitrosodi-n-propylamine (NDPA)
    8. N-nitroso-diisopropylamine (NDIPA)
    9. N-nitroso-di-n-butylamine (NDBA)
    10. N-nitrosomethylaniline (NMA)
    11. N-nitroso-di-ethanolamine (NDELA)
    12. N-nitroso-piperidine (NPIP)
    13. N-nitroso-pyrrolidine (NPYR)
    14. N-nitroso-morpholine (NMOR)

- **Targeted methods for almost 20 specific nitrosamines (on demand /R&D level)** - ***not exhaustive list***
  - N-nitrosomethylpiperazine (MeNP)
  - mono-N-nitrosopiperazine (MNPZ)
  - N,N'-dinitrosopiperazine (DNPZ)
  - 1-Nitroso-4-phenylpiperazine
  - 4-(N-methyl-N-nitrosoamino)-1-(3-pyridil)-1-butanone (NNK)
  - 4-(N-methyl-N-nitrosoamino)-1-(3-pyridil)-1-butanol (NNO)
  - 4-amino-1-nitroso-1H-imidazole-5-carbonitrile
  - Ethyl-4-(methyl-N-nitroso-amine)benzoate
  - N-Nitroso Ambroxol
  - N-Nitroso Benazepril
  - N-Nitroso Betahistin
  - N-Nitroso Clonidine
  - N-Nitroso Diclofenac
  - N-Nitroso Diphenhydramine
  - N-Nitroso Dorzolamide
  - N-Nitroso Duloxetine
  - N-Nitroso Enalapril
  - N-Nitroso Fluoxetine
  - N-Nitroso Furosemide
  - 4-Nitroso Hydrochlorothiazide (4-Nitroso HCT)
  - N-Nitroso Ketamine
  - 2-(4-nitrosopiperazin-1-yl)ethan-1-ol (Aripiprazole nitrosamine related impurity)
  - N-Nitroso Naphazoline
  - N-Nitroso Nevibolol
  - N-Nitroso Phenylephrine
  - N-Nitroso Pramipexole
  - N-Nitroso Propranolol
  - N-Nitroso Pseudoephedrine
  - N-Nitroso Quinapril
  - N-Nitroso Rasagiline
  - N-Nitroso Tamsulosin
  - N-Nitroso Zolmitriptan
  - Torasemide Nitrosamines related impurities
  - Vinblastine Nitrosamines related impurities
  - Azathioprine Nitrosamines related impurities
  - N-Nitroso desmethyl tripelennamine
  - Methyl-N-Nitroso-Indoline (NMI, Indapamid Impurity A)
- **Nitrosation assay procedure - NAP test**. Residual qualitative test / trace analysis to identify a specific nitrosamine through the following analytical techniques: LC MS and/or MS/MS and/or HRMS and/or MS/HRMS and/or TOF and/or MS/TOF:
  - NAP TEST based on EMA Assessment Report
  - NAP TEST based on Mérieux NutriSciences Internal Procedure
  - (verified/effective on most of amynes compounds)

Our equipment

- LC-MS/HRMS - LC-MS/HRMS (Orbitrap and/or TOF Technology)
- GC-MS/MS - GC-MS/HRMS - GC/MS

- **GMP QC** tests for analytical batch release
- **Rush** service

Mérieux NutriSciences

A STRONG PRESENCE IN EUROPE AND WORLDWIDE

MÉRIEUX NUTRISCIENCES OFFERS ITS SCIENTIFIC EXCELLENCE IN PHARMACEUTICAL, FOOD, CHEMICAL, BIOCIDE AND COSMETIC PRODUCTS TESTING AND CONSULTING TO ENSURE SUPPORT, OPTIMAL REACTIVITY AND FLEXIBILITY TO ITS CUSTOMERS ALL OVER THE WORLD.

Mérieux NutriSciences

Better Food. Better Health. Better World.

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