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.

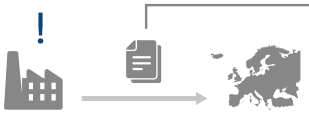
STEP 3 CHANGES TO THE MARKETING AUTHORISATION

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.

Overview of the call for review to MAH

STEP 1 Risk evaluation (API/FP)

STEP 2 Testing if risk (FP)



Known or new nitrosamine (scenario d) identified- process depends on the amount detected

scenarios at end of STEP 2

Scenario a

Nitrosamine(s) content:
AI exceeded: further assessment from Rapporteurs/RMS

Scenario b

Nitrosamine(s) content:
AI not exceeded and >10%:
(includes the case where 10%AI <nitrosamine level < 30%AI):
assessment during STEP 3

Scenario c

Nitrosamine not detected or ≤10% AI: file case and no further action

STEP 3 Submission of changes to MA (variation/referral)

Source: 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 (EMA/425645/2020)

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Pharma Nitrosamines Labs Global Service

OUR CUTTING-EDGE TECHNOLOGY

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)
    15. 1-Nitroso-4-methyl piperazine (MeNP)

- **Targeted methods for almost 20 specific nitrosamines (on demand /R&D level)** - ***not exhaustive list***
  - Glycazide impurity B
  - 1-nitroso-4-(2-hydroxyethyl)-piperazine (Opipramol, Aripiprazol)
  - N-methyl-N-nitrosophenylethylamine (NMPEA)
  - Methyl-N-Nitroso-Indoline (Indapamide)
  - N-nitroso-desalkylquetiapine (NDAQ) (Quetiapine)
  - N-Nitroso-Azathioprine
  - N-Nitroso-Atenolol
  - N-Nitroso-Benazepril
  - N-Nitroso-Impurity A Benzydamine
  - N-Nitroso-Betahistin
  - N-Nitroso-Biotin
  - N-Nitroso-CAF (Calcium Folinate)
  - N-Nitroso-Ciprofloxacin
  - N-Nitroso-Clonidine
  - N-Nitroso-Diclofenac
  - N-nitroso-Diphenhydramine
  - N-Nitroso-Dorzolamide
  - N-Nitroso-Duloxetine
  - N-Nitroso-Enalapril
  - N-Nitroso-Fluoxetine
  - N-Nitroso-Folic Acid
  - N-Nitroso-Furosemide
  - N-Nitroso-Flumazenil
  - N-Nitroso-Guanidine (Triamterene)
  - 4-Nitroso-Hydrochlorothiazide
  - N-Nitroso-Lisinopril
  - N-Nitroso-Metoprolol
  - N-Nitroso-Naphazoline
  - N-Nitroso-Nebivolol
  - N-Nitroso-Nortriptyline (Amitriptyline, Nortryptyline)
  - N-Nitroso-Paroxetine
  - N-Nitroso-Perindopril
  - N-Nitroso-Phenylephrine
  - N-Nitroso-Piroxicam
  - N-Nitroso-Pramipexole
  - N-Nitroso-Proline
  - N-Nitroso-Propranolol
  - N-Nitroso-Pseudoephedrine
  - N-Nitroso-Quinapril
  - N-Nitroso-Ramipril
  - N-Nitroso-Rasagiline
  - N-Nitroso-Ropivacaine
  - N-Nitroso-Salbutamol
  - N-Nitroso-Sertraline
  - N-Nitroso-Sotalol
  - N-Nitroso-Tadalafil
  - N-Nitroso-Tamsulosin
  - N-Nitroso-Tetryzoline
  - N-Nitroso-Zolmitriptan
  - Methyl N-methyl-N-nitrosoanthranilate

- **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:
  - WHO NAP TEST (based on EMA Assessment Report) - acidic acqueos nitrosating conditions TBN NAP TEST - aprotic solvent nitrosating conditions
  - NAP TEST Combined Approach

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

Analytical techniques

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

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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.

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Better Food. Better Health. Better World.

Mérieux NutriSciences
Via Fratta 25, 31023 Resana (TV), Italy
Ph. +39 0423 7177
E-mail: gxp.italy@mxns.com
www.merieuxnutrisciences.com/eu

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