Guideline

- Central Administration for Biological Products, Innovative Products, And Clinical Studies
- Central Administration of Drug Control
- Central Administration for Pharmaceutical Care
- Central Administration of Pharmaceutical Products
- Central Administration of Inspection on Pharmaceutical Institutions
- Central Administration of Pharmaceutical Policies and Market Access

General Administration For _____

Guidelines for Nitrosamine Impurities in Drug substances and pharmaceutical drug Products

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1. Introduction and Background

Nitrosamine impurities have emerged as a significant quality and safety concern in the pharmaceutical industry since their initial detection in 2018. These impurities, classified as probable human carcinogens based on animal studies, present potential cancer risks to patients when present in pharmaceutical products above acceptable levels. The regulatory response to this issue has been global in scope, with health authorities worldwide including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other international regulators working collaboratively to establish comprehensive guidelines for industry. This guidance document synthesizes current regulatory expectations and provides practical recommendations for manufacturers to detect, control, and prevent nitrosamine impurities in active pharmaceutical ingredients (APIs) and finished drug products.

The discovery of nitrosamine contamination first occurred in angiotensin II receptor blockers (ARBs) like valsartan, losartan, and irbesartan, and subsequently extended to other medications including ranitidine, nizatidine, metformin, and various antibiotics. These findings led to widespread recalls and heightened regulatory scrutiny of pharmaceutical manufacturing processes worldwide. The concern stems from the fact that even at low levels, long-term exposure to certain nitrosamine impurities may increase cancer risk in humans. Consequently, regulatory agencies have emphasized that marketing authorization holders bear ultimate responsibility for ensuring the quality and safety of their products, which includes implementing robust controls to prevent nitrosamine formation or contamination.

2. Scope

Guidelines for nitrosamine impurities is applied in all chemically synthesized APIs and drug products containing chemically synthesized APIs or fragments including biological products containing synthesized fragments.

3. Abbreviations

3.1 FDA: Food and Drug Administration

3.2 EMA: European Medicines Agency

3.3 APIs: Active pharmaceutical ingredients

3.4 OMCL: European Official Medicine Control Laboratories

3.5 AI: Acceptable intake

3.6 LOQ: Limit of Quantification

3.7 TD50: Tumour dose 50 – the daily dose causing tumours in 50% of animals in a life time bioassay

4. Definitions

None

5. Main topic

5.1 Types of Nitrosamine Impurities and Their Origins

Nitrosamine impurities in pharmaceuticals fall into two primary categories based on their structural characteristics and origin:

- Small-molecule nitrosamines:

These are relatively low molecular weight compounds that do not share structural similarity with active pharmaceutical ingredients. They are often found across multiple different drug products. Common examples include:

- N-nitrosodimethylamine (NDMA)
- N-nitrosodiethylamine (NDEA)
- N-nitrosomethylphenylamine (NMPA)

- N-nitrosodiisopropylamine (NDIPA)
- N-nitrosoisophenylethylamine (NIPEA)
- N-nitrosodibutylamine (NDBA)
- N-nitroso-N-methyl-4-aminobutyric acid (NMBA)
- And others

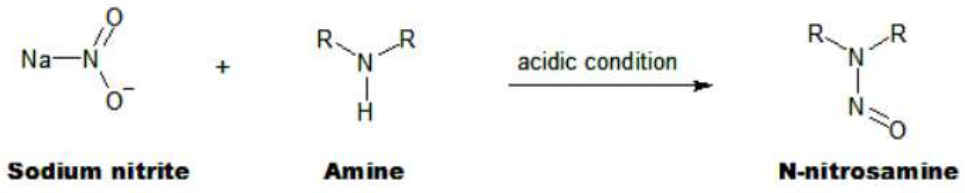
- Nitrosamine Drug Substance-Related Impurities (NDSRIs):

These impurities share structural similarity with the API or are derived from API fragments. They are generally unique to each specific API and form through nitrosation of APIs or API fragments containing (secondary /tertiary) amines when exposed to nitrosating agents in favorable conditions.

5.2 Root Causes and Formation Pathways

The formation of nitrosamine impurities occurs primarily through a chemical reaction between amines (secondary / tertiary) and nitrosating agents typically nitrite salts under acidic conditions.

Figure 1. Representative reaction showing nitrosamine formation



5.3 Risk Assessment Frameworks

5.3.1 Systematic Risk Evaluation

5.3.1.1 Manufacturers should conduct a comprehensive risk assessment for all chemically synthesized APIs and drug products to evaluate the potential for nitrosamine formation or contamination. This assessment should be science-based and systematically documented, considering all potential sources of nitrosamine impurities throughout the manufacturing process and supply chain. The risk is highest when (secondary / tertiary) amines and nitrosating agents are present simultaneously and under favorable conditions (e.g., acidic pH, elevated temperature)

5.3.1.2 Key elements of the risk assessment should include:

- API Manufacturing Process:

- Use of nitrite salts or nitrous acid in processes containing amine precursors.

-The use of sodium nitrite (or other nitrites) in the same equipment as amines without adequate cleaning in between could be a cross-contamination risk.

- Presence of amine functional groups in APIs, degradants, intermediates, or raw materials.

- Secondary / Tertiary amines added as reagents or catalysts.

- Degradation of amide solvents (e.g., N,N-dimethylformamide) into secondary amines.

- Amine impurities in reagents or solvents.

- Use of nitrous acid to quench residual azide in the presence of precursor amines.

- Inadequate process optimization and control (temperature, pH, reagent addition sequence).

- Drug Product Formulation and Storage:

- Reaction between APIs with amine functional groups and nitrite impurities in excipients

- Use of potable water containing nitrite impurities in manufacturing.

- Assessment of process conditions that could facilitate nitrosamine formation (presence of nitrites, acidic conditions, etc.).

- Leachates from container closure systems and secondary packaging components. (e.g. rubber stoppers in vials could be a potential source of nitrosating agents.)

- Usage of multipurpose manufacturing equipment as a source of nitrite or nitrosamine cross contamination.

- Supply Chain Considerations:

- Vendor-sourced raw materials containing nitrosamine precursors

- Impurities in fresh solvents

- Cross-contamination at manufacturing sites

- Recovered materials (solvents, reagents, catalysts) containing residual amines or nitrosamine formation during recovery processes (e.g. the use of recovered solvents, especially from third-party recyclers, poses a significant and well-documented risk if not rigorously controlled).

- Inadequate cleaning between different materials or customers.

- Drug product manufacturing control:

- Nitrites are common nitrosating impurities that have been reported in many excipients so it should be taken into consideration during risk analysis.

- controlling of nitrites in processing water.

- controlling of the manufacturing process conditions e.g pH, Temperature and drying conditions.

- Evaluation of the packaging material.

- Storage conditions:

Evaluation of potential nitrosamine formation during storage over the product's shelf life.

5.3.2 Confirmatory Testing Strategies

When a risk assessment identifies potential nitrosamine formation or contamination, manufacturers should perform confirmatory testing using appropriately validated analytical methods, Key considerations for testing include:

- Method validation: Analytical methods should demonstrate specificity (avoid matrix effect), excellent chromatographic separation, and highly sensitive detection capability (Cover the expected LOQ, 10 % of the Acceptable limit).
- Testing scope: Confirmatory testing should be performed on at least three representative batches of drug product or API
- Stability testing: if risk is identified, testing of stability samples to evaluate potential nitrosamine formation over the product's shelf life or aged reference samples is required to be sure that the nitrosamine impurities level not exceed the acceptable limit.
- Method development: Consider published methods from regulatory agencies including FDA and European Official Medicine Control Laboratories (OMCL)

5.4 Acceptable Intake Limits and Safety Assessment

5.4.1 Establishing Acceptable Intake Limits

Regulatory agencies recommend several approaches for determining AI limits:

- Compound-specific carcinogenicity data:

When robust substance-specific animal carcinogenicity data exists, the TD50 (tumorigenic dose that induces tumors in 50% of test animals) should be calculated and used to derive a substance-specific limit for lifetime exposure as recommended in ICH M7(R2) guideline.

- Predicted Carcinogenic Potency Categorization Approach (CPCA):

For NDSRIs lacking compound-specific data, AI limits can be assigned based on predicted carcinogenic potency categorization which categorizes nitrosamines into five potency categories based on their structural features:

Table: Carcinogenic Potency Categories and Corresponding AI Limits

Category	Acceptable Intake (AI)
1	26.5 ng/day FDA or 18 ng/day EMA
2	100 ng/day
3	400 ng/day
4	1500 ng/day
5	1500 ng/day

- Read-across analysis:

Using robust carcinogenicity data from a structurally similar surrogate compound when substance-specific data is unavailable.

- Default approach:

If the AI limit cannot be determined using the above approaches, AI limit may be recommended according to the FDA/EMA AI limit for the most potent nitrosamines.

5.4.2 Specification Setting

5.4.2.1 If testing confirms the presence of a nitrosamine impurity above 10% of the acceptable intake limit, manufacturers should:

- Establish specifications: Implement a specification limit for the nitrosamine impurity to ensure it remains at or below the recommended AI limit
- Routine testing: Implement testing of each batch on release and stability samples for nitrosamine impurities for at-risk APIs or drug product with an impurity detected above 10% of the acceptable intake limit.
- Control strategy: Develop an appropriate control strategy considering batch-to-batch variations.

5.4.2.2 Skip-testing according to the ICH Q6A can be considered, if the root cause for nitrosamine formation is identified and controlled, the manufacturer can prove that the amount of nitrosamine present is consistently below 30% of the acceptable limit based on AI in the API or in the finished product. If upon testing, the level of the nitrosamine impurities fails to meet the acceptance criteria established for the periodic test, the drug producer should immediately commence full testing.

5.4.2.3 Batch rejection: Do not release any API or drug product batch containing levels of nitrosamine impurities above the recommended AI limit for distribution .

The batch rejection rule applies at two key stages:

- At Release: Before a batch is released to the market, it must be tested (if it falls under a routine testing control strategy). If the test result shows a nitrosamine level at or above the AI, the batch must not be released. It is considered non-compliant and unsafe.

- During Shelf Life (Stability): The control strategy must ensure the impurity does not exceed the AI throughout the product's shelf life. If stability testing on a marketed batch shows that the nitrosamine level has risen to or above the AI before the expiry date, this typically triggers a batch recall. The product is no longer considered safe for its entire intended use period.

5.4.2.4 To avoid potential disruption of drug supply, EDA can consider interim limit for a temporary period based on case by case basis under certain circumstances and that limit will be illustrated in the updated EDA High risk APIs List on EDA website.

5.5 Mitigation and Control Strategies for manufacturers

5.5.1 Process Optimization and Design

Manufacturers should implement preventive measures to avoid nitrosamine formation through careful process design and optimization:

- Route of synthesis evaluation: During process development, evaluate alternative synthetic routes that avoid conditions conducive to nitrosamine formation
- Reagent selection: Avoid or replace amine bases, amide solvents, and nitrites whenever possible.
- Process conditions: Optimize reaction conditions (temperature, pH, reagent addition sequence) to minimize nitrosamine formation
- Quenching modifications: Remove quenching steps from the primary reaction mixture or replace nitrites with alternative quenching agents
- Purification steps: Incorporate purification steps capable of removing nitrosamine impurities when prevention is not fully achievable

5.5.2 Supply Chain Management

Robust supplier qualification and material controls are essential for preventing nitrosamine contamination.

- Material specifications: it is recommended to establish appropriate specifications for raw materials regarding nitrite and amine content
- Chain of custody: Request documented records of the name of the raw material manufacturer and its supplier and the roles of actual manufacturers
- Recovered materials: Use recovered materials only in the same step or earlier steps of the same process from which they were collected to avoid cross-contamination unless otherwise justified.
- Water quality: Analyze water used in manufacturing for nitrites and nitrosamines and use purified water when necessary

5.5.3 Packaging and Storage Controls

Packaging selection and storage conditions can significantly impact nitrosamine formation:

- Packaging evaluation: Assess container closure systems for potential to leach nitrosamines or nitrosating agents into the drug product
- Alternative materials: Select packaging materials that do not contain nitrosamine precursors
- Storage conditions: Establish appropriate storage conditions that minimize nitrosamine formation over time
- Stability studies: Conduct comprehensive stability studies that include nitrosamine testing to verify control throughout the shelf life.

5.6 Scope of implementation:

EDA Recommended Timeline for Implementing Risk Assessments, Confirmatory Testing depending on the regulatory status of the drug product and the type of nitrosamine impurity at issue.

5.6.1 For drug substances:

All APIs listed in the updated **High Risk APIs List** that can form nitrosamine impurities should submit a detailed nitrosamine risk assessment through the specific link on the EDA website based on importation approval issued by central administration of pharmaceutical policies and market access.

5.6.2 For finished drug products

5.6.2.1 Finished drug products submitted for registration or renewal evaluation containing any of APIs listed in the **High Risk APIs List** that can form nitrosamine impurities, Comprehensive nitrosamine risk assessment should be included in the dossier from 1-1-2026.

5.6.3 The Egyptian drug Authority confirms the need that manufacturers and applicants consider the potential causes of nitrosamine formation and evaluate the risk for nitrosamine formation for all chemically synthesized APIs and drug products. Manufacturers and applicants do not need to submit risk assessment documents to the Authority for APIs not listed in the updated **High Risk APIs List** that can form nitrosamine impurities, but they should retain these documents so that they are available if requested.

6. References:

6.1 ICH M7(R2) Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.

6.2 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 22 February 2021.

6.3 FDA, Control of Nitrosamine Impurities in Human Drugs Guidance for Industry, September 2024, Revision 2.

6.4 Swissmedic nitrosamine impurities in medicinal products: updated requirements for risk assessments, data submission and parallel import products, 30.06.2025.

6.5 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.