

Opportunities and Challenges: Perspective from Medical Devices and Combination Product Industry on Recent Regulatory Guidance for Nitrosamines

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What are Nitrosamines?

- Class of compounds: chemical structure of a nitroso group bonded to an amine ($R^1N(-R^2)-N=O$).
- Formed by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions)
- Potent genotoxic compounds; classified as probable or possible human carcinogens by IARC.
- Referred to as “cohort of concern” compounds [ICH M7(R1) 2018]
- Alpha-hydroxylation leading to ion formation and alkylation of DNA

Sources of Nitrosamines

- Food
- Drinking water
- Pesticides
- Rubber
- Medicinal Products
- Cosmetics
- Environment

Scope of Current Regulatory Nitrosamines Guidance

- Active Pharmaceutical ingredients (APIs)
- Human Drug Products/Human Medicines

- No guidance specifically for combination products and medical devices
 - Use the guidance for APIs with some adaptations

Global Regulatory Guidance on Nitrosamines



03 August 2020
EMA/409815/2020

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



29 June 2021
EMA/409815/2020 Rev.4

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



GUIDANCE DOCUMENT

Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

SEPTEMBER 2020

New GC 1469 Nitrosamine Impurities – PF46

New GC 1469 Nitrosamines Impurities is now LIVE!



To protect patients from adverse effects of nitrosamines as impurities, USP has developed a new general chapter to provide information useful for ensuring the appropriate control of nitrosamine impurities in drug substances and drug products. GC 1469 will be official on December 1, 2021



Potential Sources of Nitrosamines in Combination Products and Medical Devices

- Combination products with API (antibiotics, antimicrobials, etc.)
- Animal derived products
- Nitrocellulose (including in lidding foil or blister packs), inks, colorants, elastomers, rubber, etc.
- Nitrosamines form in the presence of secondary, tertiary or quaternary amines and nitrate salts under acidic conditions:
 - Process related (property of material or processing conditions)
 - Supply chain (intermediates)
 - Stability (arise over time)

Analytical Methods for Identification and Quantification of Nitrosamines In APIs

- US FDA: sensitive methods with limits of quantitation (LOQ) in the ppb range are needed to meet the low AIs
 - LOQs ≤ 0.03 ppm
 - If Max Daily Dose is high (e.g., > 1 g), LOQ and LOD as low as reasonably possible
 - FDA's validated laboratory methods used in assaying nitrosamine impurities in various drugs as well as the analytical results for various drugs and batches are available on the FDA website.

Quantification of Nitrosamines In Medical Devices/Combination Products

- For Medical Devices and Combination Products:
 - In many cases there is a dependency on a supplier of raw materials (API, Stopper, etc.) to provide information on nitrosamine content or the presence of precursors (amines or nitrate salts) that may give rise to nitrosamines.
 - Role in controlling nitrosamines and precursors
 - End responsibility still lies with the marketing company to verify and confirm supplier data.
 - There are challenges unique to medical devices and combination products
 - Extractability of the nitrosamines or precursors
 - Adaptation of analytical methods to non-API materials (solubility, effects of extraction)
 - Calculation of release rates

US FDA Risk Assessment Approach for Nitrosamines in APIs

- Acceptable Intake (AI): threshold of toxicological concern (TTC) considered for the impurity to be associated with negligible risk of carcinogenicity or other toxic effects [ICH M7(R1)]
- AI limit is a daily exposure to a compounds that approx. a 1:100,000 cancer risk after 70 yrs. of exposure

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Nitrosamine	AI Limit (ng/day) ^{1,2}
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5



US FDA Guidance: AI limits applicable if a drug product contains a single nitrosamine

¹ The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. Appendix B includes a description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.

² The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label ($\text{ppm} = \text{AI (ng)}/\text{MDD (mg)}$).

US FDA Risk Assessment Approach for Nitrosamines in APIs

- Nitrosamines with published AI limits:
 - Use value from Table 1
- Nitrosamines without published AI limits:
 - Use ICH M7(R1) approach to determine the risk associated with the nitrosamine and contact the Agency about the acceptability of any proposed limit
 - Use of compound specific AI

US FDA Determination of AI limit for Nitrosamines in APIs

- For compound specific AI:
 - Rodent carcinogenicity potency data such as TD_{50} values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2)
 - Available in CPDB or use a surrogate
 - For Class 1 impurities (known mutagenic carcinogens) with no established threshold mechanism: Linear extrapolation from a TD_{50} value (1 in 100,000 accepted lifetime risk level) = $TD_{50} / 50,000$
 - $AI \times 50 \text{ kg [assumed body weight]} = \text{mg/day}$
 - $AI \rightarrow \text{ppm}$
 - $AI \text{ in ppm} = AI \text{ (ng)} / \text{Drug's Maximum Daily Dose (MDD) in mg}$

US FDA Determination of AI limit for Nitrosamines without Sufficient Data

- Computational toxicology assessments to identify structurally similar, surrogate compounds with the n-nitroso alert.
- Consider closely related compounds with robust carcinogenicity data
- No appropriate surrogate → refer to established AIs for NDMA and NDEA
- Considerations for using read across for structurally complex nitrosamines:
 - nitrosamine structural alert environment (degree of substitution, steric bulk, electronic influences, potential for metabolic activation, stability/reactivity of the resulting metabolites, and overall molecular weight)

US FDA Risk Assessment Approach for Multiple Nitrosamines in APIs

- Greater than 1 nitrosamine impurity:
 - Drugs with maximum daily dose (MDD) < 880 mg/day → recommended limit for total nitrosamines of 0.03 ppm (26.5 ng/day).
 - MDD > 880 mg/day → total nitrosamines not to exceed 26.5 ng/day (contact the agency if multiple nitrosamine impurities are detected in an API or drug product in which the total nitrosamine level exceeds 26.5 ng/day based on MDD)

EMA: Determination of AI limit for Nitrosamines in APIs

N-Nitrosamine (CAS number)	ng/day***
NDMA* (62-75-9)	96.0
NDEA*(55-18-5)	26.5
EIPNA**(16339-04-1)	26.5
DIPNA**(601-77-4)	26.5
NMBA**(61445-55-4)	96.0
MeNP**(16339-07-4)	26.5
NDBA**(924-16-3)	26.5

These limits are applicable only if a finished product contains a single N-nitrosamine.

* Limit calculated on the basis of harmonic mean TD50 derived from carcinogenic potency database (CPDB)

**Limit derived using SAR/read-across approach

***The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective above limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC .

> 1 nitrosamine impurity identified in finished product:

- total risk level of the sum of all detected N-nitrosamines does not exceed 1 in 100,000 life-time risk.
OR
- sum of all detected N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified



EMA: Determination of AI limit for Nitrosamines in APIs

- When robust carcinogenicity data is available
 - Follow ICH M7(R1) principles for “cohort of concern” substances and consider lifetime daily exposure
 - TD_{50} as POD to calculate AI
 - $AI \times 50 \text{ kg}$ [assumed body weight] = mg/day
- When robust TD_{50} values are not available:
 - Default class specific TTC of 18 ng/day
 - Justify a higher limit based on SAR described in ICH M7(R1) → TD_{50} of structurally closest related nitrosamine
- ‘Less than lifetime’ (LTL) approach should not be applied but can be considered after consultation with competent authorities as a temporary measure



Summary of Risk Assessment Tools (Medical Device/Combination Products)

- FDA and EMEA AIs (96, 26.5, and 18 ng/day)
- Calculation of compound specific AIs if not available
- Computational toxicology to identify surrogate compounds
 - Consider data from a related compound with robust data
- Use of Less than Lifetime values generally not accepted
- Calculation of release rates or extractable amount of nitrosamine
 - Contributes to risk assessment strategy

Challenges:

- Scope and applicability of the regulatory guidance:
 - does it apply to devices and combination products?
- Identification and quantification of nitrosamines in non-API matrices
 - Less control of 3rd party suppliers of API or components
 - Route of synthesis/ manufacturing changes may not be supported by supplier
- Lack of validated methods in non-API matrices
- Risk assessment approaches for nitrosamines
 - less than lifetime exposure approach

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Thank you!

Questions?

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