Nitrosamine Impurities
Current Gaps and Industry Challenges

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Use of Clinically Relevant MDDs for Establishing Nitrosamine Specification Limits

- Nitrosamine impurity specifications are determined using two key parameters.
  - AI (Acceptable Intake) of Nitrosamine daily exposure limit.
  - MDD (Maximum Daily Dose) of drug product administered per day.
- Conversion of AI limit into parts per million will vary by product and is calculated based on a drug's MDD (ppm= AI (ng/day)/MDD(mg/day)).
- MDD values are typically derived from the approved product labeling.
- These labeled values represents the maximum recommended dose used for safety and efficacy evaluation.
- In real world use, the labeled MDD may not always reflect the actual administered dose.
- Patients often receive lower doses depending on indication, age or tolerance and dosage regimens can vary significantly across patient populations and dosage strengths.

Use of Clinically Relevant MDDs for Establishing Nitrosamine Specification Limits

- Case Study:
  - ✓NDSRI AI limit: CPCA Category-1; 26.5 ng/day
  - ✓Approved Labeled MDD = 2000 mg/day
  - ✓Dosage Form: Tablets
  - ✓Drug Product Strengths: 10 mg, 25 mg, 50 mg, 100 mg and 200 mg
  - ✓As per labeled MDD NDSRI specification across all strengths is 0.01325 ppm
- To reach labeled MDD of 2000 mg/day

Tablet Strength	Required Units
200 mg	10 units/day
100 mg	20 units/day
50 mg	40 units/day
25 mg	80 units/day
10 mg	200 units/day

Use of Clinically Relevant MDDs for Establishing Nitrosamine Specification Limits

<u>Industry Recommendations:</u>

- Uniform specification limits based on labeled MDDs are not scientifically meaningful.
- Real world dosing is significantly lower than labeled MDDs.
- Clinical relevance based MDD framework supports flexibility and promotes science-based and patient-relevant compliance rather than rigid uniformity.
- The Agency allow clinically relevant MDDs instead of strictly relying on labeled MDDs wherever justified.
- This approach enables strength-specific specification limits that align with real-world clinical exposure, ensuring harmonization with toxicological assessments and maintaining the total daily nitrosamine intake within the established AI limits across all strengths.

Recommended Interim AI Limits for Certain Nitrosamine Impurities

- The Agency evaluates, on a case-by-case basis, distributed drug products nitrosamine impurity levels exceeding the FDA-recommended AI limit and may allow interim limits for such impurities for a temporary period.

Table 3: Recommended Interim AI Limits* for Certain Nitrosamine Impurities** for Approved or Currently Marketed Products

(Updated: 7/29/2025)

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Nitrosamine Name	Source	Recommended Interim AI Limit (ng/day)	Recommended Interim Control Limit (ppm)	Estimated Duration***
1-methyl-4-nitrosopiperazine (MNP)	Rifampin (injection and capsules)	3,000 ng/day	5 ppm	8/1/2026
N-nitroso-ciprofloxacin	Ciprofloxacin (tablets)	12,000 ng/day	8 ppm	8/1/2026
N-nitroso-desmethyl-amitriptyline	Amitriptyline (tablets)	450 ng/day	1.5 ppm	8/1/2026
N-nitroso-dorzolamide	Dorzolamide (single ingredient product only)	500 ng/day	139 ppm	8/1/2026
N-nitroso-fluoxetine	Fluoxetine (tablets and capsules)	7,200 ng/day	90 ppm	8/1/2026
N-nitroso-nortriptyline	Nortriptyline (capsules)	600 ng/day	4 ppm	8/1/2026
N-nitroso-protriptyline	Protriptyline (tablets)	3,000 ng/day	50 ppm	8/1/2026
N-nitroso-sertraline	Sertraline	600 ng/day	3 ppm	8/1/2026

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Recommended Interim AI Limits for Certain Nitrosamine Impurities

- Need for a harmonized approach to streamline interim limit establishment during the ongoing mitigation phase.
- FDA guidance currently lacks defined criteria for interim limit establishment and CAPA timelines.
- EMA’s interim limit strategy follows the ICH M7 LTL approach, applying conservative adjustment factors of 6.7× and 13.3× the AI.

Treatment duration	Up to 12 months	>12 months
Interim limit	13.3 x AI*	6.7xAI*

- The EMA guidance defines a CAPA period of up to three (3) years from the establishment and publication of the Interim AI limit.
- Industry encourages FDA to adopt EMA-like principles to enable clear targets for mitigation and remediation prioritization.

Safety Testing methods for Nitrosamine Impurities

- FDA permits alternative approaches-such as compound-specific or surrogate read-across, to scientifically justify higher AI limits.
- Regulatory recommendations are not fully aligned across agencies.

Recommendation	FDA	Other Agencies (EMA/HC)
To Support AI limit up to 1500 ng/day	A Negative result in an GLP Compliant EAT (OECD471). A Negative Result in an GLP Compliant In Vitro mammalian cell mutation assay along with in vitro metabolism data (including human hepatocyte or microsome)	A negative result in an GLP-compliant EAT(OECD471).
To Support higher than 1500 ng/day	A negative result in an in vivo mutagenicity data may be requested to support AI limits above 1500 ng/day and may not be supportive of an AI limit equal to the ICH Q3A(R2) and ICH Q3B(R2) limits.	A negative result in a relevant well-conducted in vivo transgenic rodent (TGR) mutagenicity study (OECD 488) can allow control of the N-nitrosamine as a non-mutagenic impurity (NMI), i.e. according to ICH Q3A(R2) and ICH Q3B(R2) limits.
To Support a surrogate-based AI	Surrogate should structurally be similar with robust carcinogenicity data FDA caps surrogate AI values maximum at 1,300 ng/day (based on N-nitroso-piperidine, NPIP).	Surrogate should structurally be similar with robust carcinogenicity data EMA/Health Canada allow AI limits up to 78,000 ng/day (based on N-nitroso-diphenylamine, NDPh)

Safety Testing methods for Nitrosamine Impurities

- FDA acknowledges that its recommendations may not be fully aligned with other regulatory authorities.
- FDA has not provided specific recommendations for the second in vitro mammalian cell mutation assay and in vitro metabolism data to support AI of 1500 ng/day.
- Unclear regulatory recommendation from FDA on the type and design of in vivo mutagenicity studies required to justify AI limits >1,500 ng/day.
- With respect to read-across analysis using a surrogate approach, a well-defined, stepwise scientific framework is required for the selection and justification of a suitable surrogate compound.
- There is a need for regulatory agencies to publish and expand the list of recommended surrogate compounds that can be used for read-across analysis.

Safety Testing methods for Nitrosamine Impurities

<u>Industry Recommendations:</u>

- Regulatory recommendations on safety testing should be harmonized across agencies to ensure consistent scientific interpretation and global alignment.
- The industry acknowledges and appreciates the forthcoming addendum to ICH M7 on the risk assessment and control of nitrosamine impurities; however, until its implementation, regulatory agencies are encouraged to maintain alignment and consistency in their recommendations.
- FDA should consider allowing manufacturers to propose an AI limits higher than 1,500 ng/day in cases where other regulatory agencies have classified similar nitrosamines as non-mutagenic impurities (NMIs), supported by robust in vivo data.
- Allow application of LTL adjustment factors aligned with therapeutic indication and treatment duration.

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