FDA Nitrosamine Updates and Issues Observed

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Disclaimer

This presentation reflects the views of the speaker which do not necessarily reflect FDA, HHS or other government opinion / policy

Objectives

- **Recommended AI limits**
- **Implementation Timeline & Progress Updates**
- **Emerging Issues**
- **Common Issues Observed**

Why the Nitrosamine Webpage Matters

This webpage is the central regulatory communication tool

- Updated frequently as new scientific data become available, such as, new AI limits, emerging issues.
- Immediately implementable
- Reflects latest science (AI limits, emerging issues)

FDA recommendations:

- Check before and during development
- Review before submission
- Reassess when changes occur

Recommended AI Limits – The Three Tables

Webpage contains three tables for the recommended AI limits.

- **Table 1 – Theoretical AI limits, calculated based on predicted carcinogenic potency categorization (CPCA)**
- **Table 2 – Compound-specific or Surrogate-Based AI limits**
- **Table 3 – Interim AI limits for marketed medical necessity products (serves as temporary regulatory discretion to prevent drug shortage)**

Key Points:

- ✓ **Inclusion in a table ≠ confirmation in your product.**
- ✓ **AI limits are safety thresholds, not observed levels.**
- ✓ **Require risk assessment report / Progress Update**

Critical Clarifications on AI Limits

Table 1 (CPCA)

- Hypothetical, based on molecular structure
- **Not** all-inclusive list
- Can be moved to Table 2 when sufficient toxicology data are available

Table 2

- Use Table 2 AI limits when nitrosamines are moved from Table 1.

Table 3 (Interim Limits)

- Temporary measures to prevent drug shortage
- Include estimated duration

✗ **NOT** permanent solution

✗ **NOT** appropriate as specification limits

✗ **CANNOT** be used to justify specification limits

✗ **DO NOT** replace long-term control / mitigation strategies

Implementation Timeline Update

For approved and currently marketed products with identified nitrosamine risk:

- ***Original Deadline*: Completion of confirmatory testing and submission of changes by August 1, 2025.**
- ***June 23, 2025 Update* – If not feasible, submit Progress Update by August 1, 2025.**

What Must Be Included in the Progress Update

- Determination of whether NDSRIs can form under targeted forced degradation
- NDSRI(s) detected(identify which ones)
- Nitrosamine test method with validation
- Product batch(es) analyzed, and date analyzed relative to date of manufacture
- Confirmatory test results for NDSRI(s) in the drug product (in ng/day or ppm)
- Root cause (if known)
- Description of mitigation attempts, if mitigation is necessary
- Estimated timeframe for completion of mitigation.

Note: If you cannot provide all above requested information, provide justification for the omissions.

How to Submit Progress Update

Application Products (NDA/ANDA)	• ***Title***: "NDSRI Update“ • **Location**: Annual Report, section 1.13.14. Log of Outstanding Regulatory Business • If AR already submitted – revise section 1.13.14 • Does **NOT** change next AR due date
Products with Interim AI	• Should also submit progress update • FDA may revise interim duration based on progress reports
Non-Application Products (OTC, 503B)	• Retain progress report at facility and make available upon FDA request

Emerging Issues: What's New

FDA communicate new information:

- Alert industry to newly identified nitrosamine issues
- Explain root causes and formation mechanisms
- Provide mitigation recommendations

Recent updates:

- Leachable NDBA and other small-molecule nitrosamines in infusion bags
- Newly identified NDSRIs in Ritonavir drug products

FDA recommendations:

- Monitor the webpage regularly for emerging issues
- Assess applicability to your products
- Implement recommended mitigation strategies promptly, when applicable

Common Issues Observed in Application

Inadequate Control Strategies

- Solely rely on release testing without addressing formation mechanisms.
- Lack justification for effectiveness and sustainability across product lifecycle

Expectation: Prevent formation — not just detect it.

Inadequate Justification for AI Limit Exceeding Recommended

FDA **DOES NOT** accept:

- Less-than-lifetime exposure arguments
- Reliance solely on other agencies' AI limits. FDA requires independent justification
- Use of interim limits to justify permanent specifications

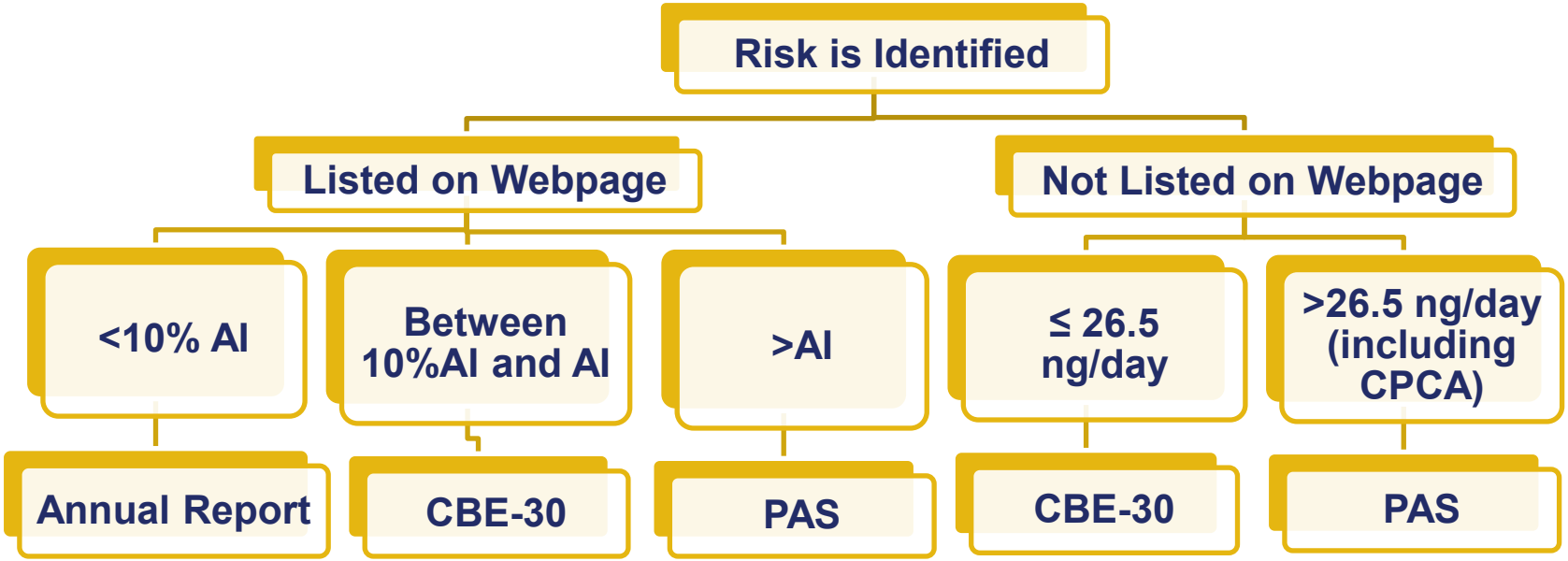
Common Issues Observed in Application

Incorrect Filing Categories

Filing Categories – Quick Reference

- Using interim limit in Table 3 to prevent drug shortage – No supplement. However, progress update should be submitted with batch data. Contact DSS.
- No Risk – No submission. However, for NDSRIs listed on webpage, progress update should be submitted with justification and supporting documents / data.
- Formulation / Process changes to mitigate risk – PAS
- Other see next page

Filing Categories – Specification Change Based on Confirmatory Data



Key Points:

- **A specification change alone may be CBE-30. Multiple Changes to mitigate risk could be PAS.**

Take-Aways

- The webpage is a dynamic regulatory communication platform
  - Updated frequently and immediately implementable
- Apply the correct and most current AI limit
- Interim AI limits are not permanent and do not replace long-term control strategies
- Submit required changes or detailed progress update
- Implement effective, preventive and sustainable mitigation
- Emerging issues require attention
- Submit changes under correct filling category

Resources

FDA Nitrosamine Webpage:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits

Guidance Documents:

- Control of Nitrosamine Impurities in Human Drugs (Sept 2024, Rev. 2)
- Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) (August 2023)

FDA Contacts:

- Drug Shortages: drugshortages@fda.hhs.gov
- General Questions: CDER-OPQ-inquiries@fda.hhs.gov

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