U.S. FOOD & DRUG ADMINISTRATION

Contains Nonbinding Recommendations

September 24, 2026: Application of Less-Than-Lifetime Adjustment to Nitrosamine Impurities

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

I. BACKGROUND

As explained in FDA's guidances for industry *Control of Nitrosamine Impurities in Human Drugs* (Sept. 2024) (Nitrosamine Guidance) and *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023) (RAIL Guidance),[1] as FDA becomes aware of new and emerging information on nitrosamine impurities, we may communicate that information on the nitrosamine guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits. In this guidance document, we communicate that, based upon new and emerging science, a less-than-lifetime (LTL) adjustment to a recommended lifetime acceptable intake (AI) limit may be appropriate for nitrosamine impurities.

In the Nitrosamine Guidance and the RAIL Guidance, FDA recommends that manufacturers of active pharmaceutical ingredients and drug products take appropriate measures to prevent unacceptable levels of nitrosamine impurities in their drug products. Because nitrosamine compounds have the potential to be potent genotoxic agents in several animal species and some are classified as probable or possible human carcinogens,[2] nitrosamine compounds are included in a group of high potency mutagenic carcinogens referred to as "cohort of concern" compounds in the International Council for Harmonisation (ICH) guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023) (ICH M7(R2)). ICH M7(R2) recommends that any known or potential mutagenic carcinogens, such as nitroso-compounds, be controlled at or below a level associated with negligible human cancer risk due to exposure to these impurities.[3]

An AI limit is a level that approximates an increased cancer risk of one additional case in 100,000 people (1:100,000) based on a conservative assumption of daily exposure to the impurity over a lifetime (70 years). This risk level represents a small theoretical increase in risk when compared to

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[2] See the International Agency for Research on Cancer (IARC) Monographs on the Identification of Carcinogenic Hazards to Humans web page at https://monographs.iarc.who.int/list-of-classifications.
[3] See ICH M7(R2), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

human overall lifetime incidence of developing any type of cancer, which is greater than 1 in 3. If a potential risk for a nitrosamine impurity has been identified, and appropriate testing has confirmed the nitrosamine level, then an appropriate control strategy leveraging process understanding and analytical controls should be developed to ensure that the nitrosamine impurity is at or below the applicable AI limit.[4]

ICH M7(R2) provides for the adjustment of AI limits for mutagenic impurities for drug products with LTL treatment durations. The LTL adjustment in ICH M7(R2) is based on the principle that cancer risk increases as a function of lifetime cumulative dose. Accordingly, where the treatment duration is LTL, a higher daily intake of a mutagenic impurity may be considered without increasing the theoretical 1:100,000 excess cancer risk.

To date, the Center for Drug Evaluation and Research (CDER) has not recommended the LTL adjustment described in ICH M7(R2) for nitrosamine impurities in drug products due to several data gaps.[5] CDER's position was due to insufficient scientific evidence to establish that the cancer risk from nitrosamines is a function of lifetime cumulative dose. Other concerns that informed this position included the potential for LTL exposures to exceed cellular DNA repair capacity, and the potential for polypharmacy to result in higher nitrosamine exposure. CDER acknowledges that industry may have been relying on CDER's prior recommendation but recognizes the singular importance of updating its policies as science evolves and CDER becomes aware of new and emerging information on nitrosamine impurities.

II. APPLICATION OF LTL ADJUSTMENT TO NITROSAMINE IMPURITIES

Based upon new and emerging science on nitrosamine impurities, an LTL adjustment, as described in ICH M7(R2), may be appropriate for nitrosamine impurities.

A. Basis for Application of LTL Adjustment

CDER is aware of two recent publications that provide sufficient evidence to address previous concerns regarding application of the LTL adjustment in ICH M7(R2) to nitrosamine impurities, where appropriate.[6] The scientific evaluations and data analyses from these recent

[4] An AI limit can be converted into a parts per million (ppm) control limit for a manufacturer or applicant. The conversion varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug labeling (ppm = AI (nanograms (ng))/MDD (milligrams)). Nitrosamine Guidance at 13.

[5] See Docket No. FDA-2020-D-1530-0021.

[6] See Felter SP, Mudd AM, Ponting DJ, Thomas R, Vespa A, McGovern TJ, Zeller A, Froetschl R, Haas B, Yang Y, Lynch A, White A, Schmitz M, Puglisi R, and Bercu JP, 2025, Evaluating the Lifetime Cumulative Dose as a Basis for Carcinogenic Potency of Nitrosamines — A Key Tenet Underpinning Less-Than-Lifetime Approaches for Establishing Acceptable Intake Limits, Regul Toxicol Pharmacol, 162:105903, doi: 10.1016/j.yrtph.2025.105903, PMID: 40645516, and Felter SP, Bercu JP, Jolly RA, McGovern TJ, Yang Y, Trejo-Martin A, Froetschl R, Haas B, Brant K, Vespa A, Ponting DJ, Lynch A, Mudd AM, White A, Zeller A, and Puglisi R, 2026, Applicability of the ICH M7 Guidelines for Assessing Less-Than-Lifetime Exposure to Nitrosamine Impurities in Drug Products, Regul Toxicol Pharmacol,

publications address the data gaps previously identified by CDER relating to the applicability of the ICH M7(R2) approach to LTL adjustment to nitrosamine impurities.

These data, developed in part through the Nitrosamines Research Program of the Health and Environmental Sciences Institute (HESI), support the scientific conclusion that the cancer risk from nitrosamine impurities is consistent with a cumulative dose response relationship and that the concerns previously identified regarding DNA repair capacity and polypharmacy do not preclude an LTL adjustment when appropriate safeguards are in place.

B. Application of LTL Adjustment to Recommended AI Limits

In general, application of the following LTL adjustment factors[7] to recommended AI limits[8] for nitrosamine impurities in drug products intended for an LTL duration of treatment may now be scientifically supported. The application of these LTL adjustment factors, as described in Table 1 below, may be applied to drug products.

Table 1. LTL Adjustment Factors for Individual Nitrosamine Impurities

Duration of Treatment	Adjustment Factor
≤ 1 month	80 × Recommended Lifetime AI Limit
> 1 month – 12 months	13.3 × Recommended Lifetime AI Limit
> 1 year – 10 years	6.67 × Recommended Lifetime AI Limit
> 10 years to lifetime	Recommended Lifetime AI Limit (no adjustment)

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[7] The adjustment factors are adapted from ICH M7(R2) to account for the lifetime cumulative dose when compressed into each relevant duration of treatment category in Table 1 of this guidance.

[8] LTL adjustment is not recommended for interim AI limits, including those listed in Table 3 of the nitrosamine guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits.

C. Applicability of LTL Adjustment Factors

CDER recognizes that application of LTL adjustment factors requires accurate characterization of the intended treatment duration as reflected in approved labeling.[9] Manufacturers and applicants should ensure that the duration of treatment used to determine the applicable adjustment factor is consistent with the labeled indication and dosing regimen. Manufacturers and applicants should refer to ICH M7(R2), Table 4, for examples of clinical use scenarios with different treatment durations.[10]

If a drug product label includes dosing instructions for both short-term and long-term use, CDER generally intends to consider long-term use in calculating the LTL-adjusted AI limit. For intermittent dosing or treatment of recurrent symptoms, the LTL-adjusted AI limit should be based on the total number of dosing days and then related to the relevant duration category in Table 1 above.[11]

For drug products with multiple nitrosamines, applicants should propose a control strategy for total exposure to nitrosamine impurities that does not exceed a cancer risk estimate of 1 in 100,000 when using the LTL adjustment factors in Table 1. Applicants should refer to the Nitrosamine Guidance for recommendations on control strategies to limit the total nitrosamine impurities in a drug product.[12]

In certain circumstances, FDA may request that manufacturers or applicants provide additional information and a scientifically justified rationale to pursue an LTL-adjusted AI limit.

III. SUBMISSION RECOMMENDATIONS

CDER recommends that manufacturers and applicants seeking an LTL-adjusted AI limit for a drug product refer to the recommendations in ICH M7(R2) regarding LTL adjustment and the adjustment factors identified in this guidance in Table 1, LTL Adjustment Factors for Individual Nitrosamine Impurities. CDER recommends that manufacturers and applicants seeking advice on the application of an LTL adjustment use the applicable regulatory pathway to contact the Agency.[13]

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[9] Alternatively, for over-the-counter monograph drug products, the adjustment factor should be consistent with labeling that complies with relevant requirements.

[10] See ICH M7(R2), Note 7 Table 4. After the duration of treatment is determined, manufacturers and applicants should apply the corresponding adjustment factor in Table 1 of this guidance to the recommended lifetime AI limit to calculate the LTL-adjusted AI limit.

[11] For example, the LTL-adjusted AI limit for N-Nitrosodiethylamine (NDEA) in a drug administered for less than 30 days in a lifetime would be 2,120 nanograms (ng)/day (26.5 ng/day x 80). In a drug administered once per week for 2 years (i.e., 104 dosing days in a lifetime), the LTL-adjusted AI limit for NDEA would be 352.5 ng/day (26.5 ng/day x 13.3).

[12] See Nitrosamine Guidance, Appendix C.

[13] Applicants can discuss a proposed LTL-adjusted AI limit with FDA via (1) contact with the review division for new

CDER evaluates the adequacy of each applicant's proposed approach on a case-by-case basis during the application review process. Each submission should include a scientific justification for the proposed LTL-adjusted AI limit using the LTL adjustment factor calculation, along with the proposed indicated population. Applicants should include the title "LTL Request" in the subject line of any communication with CDER regarding a proposed LTL-adjusted AI limit.

A. Applications Pending With the Agency

Applicants with pending applications should inform CDER if they intend to propose an LTL-adjusted AI limit and amend the application as appropriate. CDER intends to work with applicants to resolve issues during the review cycle. For pending new drug applications, applicants should contact the review division or request a Type C Meeting. For pending abbreviated new drug applications (ANDAs), applicants should submit controlled correspondence if appropriate[14] or contact the project manager specified for the ANDA.

FDA intends to review applications consistent with the performance goals and procedures in the respective commitment letters that accompany the current Prescription Drug User Fee Act and the Generic Drug User Fee Amendments.

B. Approved or Marketed Drug Products

As described in the Nitrosamine Guidance and the RAIL Guidance, if a risk of nitrosamine drug substance-related impurities in a drug product is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods. If a nitrosamine impurity is detected, manufacturers should investigate the root cause and implement changes in the manufacturing process or drug product formulation to eliminate, mitigate, or reduce nitrosamine impurities consistent with the recommendations in the Nitrosamine Guidance.[15] Manufacturers must implement any changes in accordance with appropriate requirements.[16] Generally, CDER considers a proposal for an AI limit higher than the FDA-recommended limit, or higher than an AI limit FDA has previously found to be justified, to be a major change requiring a prior approval supplement.[17] A proposal for an LTL-adjusted AI limit for an approved drug product should be submitted directly to the application.

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drug applications (NDAs), supplements, and amendments, (2) Type C meeting requests for NDAs, supplements and amendments, (3) pre-abbreviated new drug applications (ANDA) meetings, and (4) controlled correspondence.

[14] For circumstances when controlled correspondence may be appropriate, see the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (March 2024).

[15] Nitrosamine Guidance at 14.

[16] See, e.g., requirements related to manufacturing changes in section 506A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356a). See also 21 CFR 314.70, 21 CFR 314.97, and 21 CFR 601.12.

[17] See 21 CFR 314.70(b); see also 21 CFR 314.97(a) and 21 CFR 601.12(b).

The Nitrosamine Guidance provides that a specification is not needed if nitrosamine levels are consistently not more than 10 percent of the recommended AI limit provided the root cause is well understood and manufacturing process controls are established and validated.[18] The Nitrosamine Guidance also provides that if testing results show that nitrosamine levels are not more than 10 percent, for approved drug products, confirmatory test results can be included in the annual report. Adoption of a nitrosamine control strategy based on an LTL-adjusted AI limit, however, would typically constitute a change that requires assessment of whether LTL adjustment is warranted and acceptable, and would, therefore, necessitate submission of a supplement. [19]

Manufacturers of over-the-counter monograph drugs and other marketed products that are not the subject of approved applications should contact FDA at CDER-OPQ-inquiries@fda.hhs.gov if considering adopting an AI limit that exceeds the AI limit recommended by FDA.

IV. CONCLUSION

Based upon the evolving science, application of an LTL-adjustment factor to an AI limit for nitrosamine impurities in drug products intended for an LTL duration of treatment may be scientifically supported. Where appropriate, manufacturers and applicants may propose an AI limit calculated using the corresponding adjustment factor in Table 1, LTL Adjustment Factors for Individual Nitrosamine Impurities, and CDER will evaluate each proposal.

The Nitrosamine Guidance and the RAIL Guidance, including the information on the associated nitrosamine guidance web page, represent the current thinking of FDA. They do not establish any rights for any person and are not binding on FDA or the public. Additionally, as with all guidance documents, manufacturers and applicants can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

The public may comment on the information in this guidance update by submitting a comment to the public docket established for the Nitrosamine Guidance and the RAIL Guidance (See Docket No. FDA-2020-D-1530). Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to www.regulations.gov. Follow the instructions for submitting comments. All comments should be identified with the Docket No. FDA-2020-D-1530 and complete title of the relevant guidance or guidances. For additional information, refer to the Federal Register notices for the guidances for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (88 FR 52183; published August 7, 2023) and the *Control of Nitrosamine Impurities in Human Drugs* (89 FR 72408; published September 5, 2024), available at www.regulations.gov (search Docket No. FDA-2020-D-1530).

[18] Nitrosamine Guidance at 21-22.
[19] See 21 CFR 314.70(b); see also 21 CFR 314.97(a) and 21 CFR 601.12(b).