A. Acceptable Intake Limits

FDA recommends the following acceptable intake (AI)[31] limits for the nitrosamine impurities NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA (Table 1). We further recommend that manufacturers use these AIs when determining limits for nitrosamine impurities in APIs and drug products.[32]

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

[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 (ppm = AI (ng)/MDD (mg)).

These limits are applicable only if a drug product contains a single nitrosamine. If more than one of the nitrosamine impurities identified in Table 1 is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the AI for the most potent nitrosamines) based on the maximum daily dose (MDD), the manufacturer should contact the Agency for evaluation. For drug products with an MDD of less than 880 mg/day, a recommended limit for total nitrosamines of 0.03 ppm is not more than 26.5 ng/day and is considered acceptable. For drug products with an MDD above 880 mg/day, the limit for total nitrosamines should be adjusted so as not to exceed the recommended limit of 26.5 ng/day.[33]

If nitrosamines without published AI limits are found in drug products, manufacturers should use the approach outlined in ICH M7(R1) to determine the risk associated with the nitrosamine and contact the Agency about the acceptability of any proposed limit.[34]

Generally, sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb) range are needed to meet the low AIs recommended for nitrosamines. Manufacturers of APIs and drug

[31] The term *acceptable intake (AI)* is used in ICH M7(R1) to indicate the threshold of toxicological concern (TTC) considered for the impurity to be associated with negligible risk of carcinogenicity or other toxic effects. FDA announcements regarding limits for nitrosamines used the term *acceptable daily intake (ADI)*. For the purposes of this guidance, the term *AI* is used rather than *ADI*.
[32] API manufacturers should control nitrosamine impurities to ensure that the drug products in which the APIs are used will meet the recommended AI limits.
[33] Manufacturers should contact CDER-OPQ-Inquiries@fda.hhs.gov 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. Inquiries submitted to this mailbox will be routed to the appropriate FDA office.
[34] See footnote 33 for contact information.

products should use methods with LOQs at or below 0.03 ppm.[35] Manufacturers should establish methods for which the LOQ and limit of detection (LOD) are as low as reasonably practical for products for which the maximum daily dose is high (e.g., greater than 1 g). If more than one nitrosamine listed in Table 1 is detected, then the analytical method should be validated for LOQs below 0.03 ppm to accurately quantify a total nitrosamine level of not more than 26.5 ng/day. For example, if the MDD is 1200 mg, the LOQ should be below 0.02 ppm. FDA's public webpage includes validated analytical test methods recommended for detecting nitrosamine impurities in several different APIs and products.[36, 37]

API and drug product manufacturers should take the following steps to mitigate nitrosamine impurities in their products:

1. Assess the risk of nitrosamine impurities in APIs, marketed products, and products under approved and pending applications. Risk assessments should be conducted in a timely manner based on the prioritization of drugs.[38] Manufacturers do not need to submit risk assessment documents to the Agency, but they should retain these documents so that they are available if requested.

2. Conduct confirmatory testing[39] when there is any risk for the presence of nitrosamine impurities. Due to nitrosamines' physiochemical properties (low molecular weights, some volatility and high toxicity), the analytical methods for nitrosamines need to have specificity, excellent chromatographic separation, and highly sensitive detection capability.

3. Report changes implemented to prevent or reduce nitrosamine impurities in APIs and drug products to FDA. This includes submission of any drug master file (DMF) amendments in accordance with 21 CFR 314.420(c) and changes to approved applications as required under 21 CFR 314.70 and 314.97 and pending applications under 21 CFR 314.60 and 314.96.

[35] The LOQ may be considered the reporting threshold for nitrosamine impurities (i.e., the limit above which an impurity should be reported in the certificate of analysis).
[36] FDA-recommended analytical methods for detecting nitrosamine impurities can be found at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine, at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin, and in the 12/12/2018 update at https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm.
[37] Manufacturers or laboratories are encouraged to make validated test methods publicly available (e.g., by posting on the method developer's website) to facilitate faster testing of other similar products. FDA also accepts requests to post privately developed methods at FDA's website if FDA's review of the method protocol finds it is scientifically sound, and if the method owner provides written authorization for posting by FDA. The manufacturers or laboratories should send their test methods to CDER-OPQ-Inquiries@fda.hhs.gov.
[38] In accordance with quality management principles, manufacturers should consider manufacturing changes and shifts over the product lifecycle that may impact the potential for nitrosamine impurities, including new sources of raw materials or excipients. Risks should be reassessed periodically (see ICH Q9).
[39] Testing using appropriately validated methods may be conducted by the API manufacturer or by a qualified laboratory.