

AAM/CHPA/PhRMA Questions for May 4th FDA-Industry Meeting to Discuss Nitrosamine Impurities in Pharmaceuticals

Note: **Bolded** questions are considered a priority for discussion during the May 4th meeting. We welcome FDA's responses to all questions and to consider written responses if there is not sufficient time to address all questions during the May 4th discussion.

Impact & Harmonization

- 1. The magnitude of risk assessments and subsequent confirmatory testing may have an impact on the global supply chain. How will FDA manage potential drug shortages that may result from this exercise?**

FDA's *Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs* (Feb 2021, available at <https://www.fda.gov/media/141720/download>) (Nitrosamine Guidance or guidance) was written to help manufacturers assess the potential for nitrosamine impurities in their products and prevent or mitigate their presence, which will help prevent drug shortages and recalls. The guidance advises manufacturers to prioritize risk assessments based on a series of factors such as maximum daily dose (MDD), therapeutic indication and numbers of patients impacted. FDA can work with manufacturers to mitigate the risk of nitrosamine impurities in active pharmaceutical ingredients (APIs) and drug products while avoiding interruptions by taking into account FDA's determination of the need for the product and impact on drug supply.

As we indicated in the guidance and in correspondence with application holders of drugs at risk for nitrosamine contamination, we are willing to work with facilities that detect excessive nitrosamine contamination to prevent or mitigate a shortage based on FDA's determination of the need for the product to remain available to patients. FDA has in the past permitted manufacturers who found levels higher than the acceptable intake (AI) in certain products and batches to continue to distribute batches to alleviate a shortage, and we will continue to evaluate each product and contamination on a case-by-case basis with a goal of balancing risk to exposure with the benefits from continued use of the drug.

- a. What steps is FDA taking, or planning to take, to collaborate with other regulatory authorities to align on expectations for Step 2 confirmatory testing (e.g., API testing with appropriate justification vs requiring drug product testing) to mitigate the risk of drug shortages that would likely result from divergent regulatory expectations for product control strategies?**

In drafting the guidance, FDA aligned with other regulatory authorities such as European Medicines Agency (EMA), and Health Canada. The 3-step mitigation strategy is consistent with these other authorities. Control strategies are also consistent; if nitrosamine levels are above limits of quantitation (LOQ) and less than AI, manufacturers are expected to implement appropriate controls. If nitrosamine levels are found above AI, manufacturers are expected to promptly address to prevent release of batches, and to report to regulatory authorities whenever

a shortage may be expected.

FDA expects drug product and API manufacturers to assess the risk for nitrosamine impurities. Typically, chemical structure, route of synthesis and raw materials are sources that may place an API at risk. Risk in a drug product may be due to formulation steps, excipients, and storage conditions.

- b. Has FDA had discussions with other regulators about aligning and possibly extending Step 2 deadlines to avoid supply chain disruptions or drug shortages?**

In February 2021, FDA extended the recommended deadlines for steps 1, 2, and 3. The timeline for confirmatory testing and reporting (steps 2 and 3) is now October 1, 2023, one month longer than the original anticipated timeline. FDA believes these timelines provide sufficient opportunity for industry to comply with the recommendations in the guidance.

FDA is willing to re-consider guidance recommendations at any time with appropriate justification, and we are willing to harmonize expectations with our regulatory counterparts while ensuring we are responsive to the needs of U.S. patients.

- 2. The Agency has recommended that documentation of manufacturers' nitrosamine risk assessments be maintained at a firm's manufacturing facilities. Industry understands that this is because FDA plans to review documentation of manufacturers' nitrosamine risk assessments during inspections and/or remote records reviews. How is FDA planning to include review of such documentation into its inspectional protocols and consistently assess the adequacy of nitrosamine risk assessments across manufacturers? In addition, how will FDA's review of documentation of nitrosamine risk assessments factor into FDA's classification of a manufacturing facility?**

FDA staff, including FDA investigators, have been trained and will continue to be trained on the application of the guidance. FDA, including investigators, may evaluate whether a significant risk exists of nitrosamine contamination during the course of inspections and remote regulatory assessments. However, it is ultimately the manufacturer's responsibility to ensure the risk of any potential nitrosamine contamination is properly assessed. We expect some variability among manufacturers' risk assessments and our review and evaluation process will ensure fair consideration. Investigators may reach out to ORA and Center subject matter experts for consult reviews, following our standard procedures.

Any potential deficiencies related to risk assessments would be evaluated according to Current Good Manufacturing Practice (CGMP) requirements. Failure to comply with CGMPs can render a drug product adulterated. Under section 501 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug that is not manufactured, processed, packed, or held in conformity with CGMP to ensure that the drug meets certain quality and purity standards is considered adulterated. FDA may exercise regulatory discretion when warranted to prevent or mitigate a shortage of a drug.

FDA would be interested in information suggesting that manufacturers are performing inappropriate risk assessments, and we would be interested in knowing if manufacturers are being treated differently by different regulators regarding the suitability of risk assessments.

Risk assessments should be retained at the manufacturing site and maintained by the site's quality management system. The risk assessment should be part of an overall quality risk management approach throughout the drug lifecycle. FDA may request specific information to support an application such as root cause analysis, and supportive data for the risk reduction strategy and related testing that demonstrates the effectiveness of the proposed overall control strategy in the application.

- a. **Is FDA planning to review nitrosamine risk assessments and related documentation only in the context of routine surveillance activities (i.e., routine surveillance inspections, 704(a)(4) records requests issued in advance or in lieu of routine surveillance inspections)?**

All types of inspections may cover risk assessments. FDA may also remotely request records and other information related to any change in required processing or control strategy from drug manufacturers, including testing (per section 704(a)(4) of the FD&C Act).

- b. **In a supply chain that uses contract manufacturing sites, the facility may not actually hold the entire risk assessment for the licensed product. What are FDA's documentation expectations of the manufacturing facility vs the marketing authorization holder?**

Risk assessments should be held onsite at the manufacturing facility and be specific to the manufacturer's operations and associated potential risk of nitrosamine contamination. For example, if there are multiple manufacturing facilities associated with the final drug product, e.g., one site granulates and another site compresses tablets, the final drug product batch releasing facility should have adequate assurance that the drug product they release for distribution conforms to CGMP. In this example, the granulator would be receiving the active and inactive ingredients for granulation and would be responsible for conforming to CGMP for the ingredients they receive and use, and may fulfill this responsibility by requesting information or assurances from each original ingredient manufacturer that the material is free of objectionable impurities, including nitrosamines. The tableting facility that compresses and then packages and releases the final product for distribution would be responsible for assuring the incoming quality of the granulation but could rely on the granulator's risk assessment/quality testing as an element of their supplier qualification and nitrosamine impurity risk assessment. The tableting facility would be responsible for assessing the risk associated with their own operations and any additional materials used in those steps. The final drug product site would also be accountable for assessing any drug product stability-related risk to nitrosamine formation.

We also recommend that application holders who are not manufacturing maintain appropriate oversight of the quality and safety of the drugs they sponsor for marketing. This oversight would be in addition to that required of those producing the API and the drug product and any drug product in-process materials.

3. Does FDA consider that biologics, pure fermentation products, and semi-synthetic products are out of scope of risk assessments for nitrosamine impurities?

In general, these products are out of scope. However, biologics with synthesized fragments, i.e., those containing a synthetically conjugated API component, for example an antibody conjugate, should be assessed because the synthetic component could be at risk for nitrosamines. This is consistent with the guidance's recommendation to assess APIs that are manufactured via chemical synthesis.

a. How does FDA factor in the very limited exposure from some OTC medicines like dentrifice (rinse and spit) and antimicrobial washes (rinsed off)? Could these categories be excluded from the risk assessments described in FDA's September 2020 guidance on nitrosamines?

The recommendations from the Nitrosamine Guidance apply to OTC medicines, as well as prescription medicines. Manufacturers should consider the potential causes of nitrosamine formation as well as any other pathways observed and evaluate the risk for contamination or formation in their APIs and drug products. Prioritization for assessment of APIs and drug products should be based on multiple factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated (see Nitrosamine Guidance, Section III).

4. There are a significant number of products that are regulated as drugs in the U.S. (oral care, sunscreens, dandruff shampoos, antiperspirants, etc.) but are considered cosmetics in other regions. When FDA's nitrosamines guidance was published in September 2020, it was the first time that a regulator announced its expectations for many OTC products to be included in nitrosamine risk assessments. As such, the FDA guidance significantly expanded the number of products within scope of the nitrosamine risk assessments, particularly for the OTC industry.

The guidance covers both prescription and non-prescription drugs. FDA public announcements regarding nitrosamine contamination included reminders to industry of its obligation to assure the quality of any drug in distribution. The contamination events to date and the known failure modes indicate that excessive nitrosamine impurities are a concern with drugs, even those that are not subject to the application approval process.

a. Currently, the Agency expects confirmatory testing of drug products and submission of required changes in any drug application be concluded within 3 years of publication of the original guidance (i.e., September 2023). In view of the volume of products added from OTC manufacturers' portfolios, would the Agency consider extending the deadline for confirmatory testing?

FDA has determined that an extension of the timeline beyond the extension already afforded industry in the February 2021 revised guidance is not warranted at this time. FDA is willing to consider additional proposals submitted to the public docket established for the guidance to extend or alter any recommendation in the guidance.

5. What are FDA's thoughts on extending the risk assessment deadline to September 1, 2021, as requested by Industry in our document titled, *An Overview of Nitrosamine Impurity-related Regulatory and Scientific Challenges Facing the Pharmaceutical Industry*, submitted to the Agency on March 8, 2021?

As noted earlier, FDA extended the risk assessment to March 31, 2021. We have not planned for additional extensions at the current time. We encourage you to submit the document titled, *An Overview of Nitrosamine Impurity-related Regulatory and Scientific Challenges Facing the Pharmaceutical Industry*, to the public docket established for the guidance.

6. Many excipient suppliers are using the IPEC *Questionnaire for Excipient Nitrosamine Risk Evaluation* to conduct nitrosamine risk assessments. Does FDA accept prepared questionnaires, such as the one developed by IPEC, as a valid risk assessment tool?

Drug product manufacturers need to verify that the excipients used in their process and in conjunction with other ingredients, including the active ingredient and any processing aids, do not lead to the formation of objectionable nitrosamine levels. FDA has not evaluated external tools, like IPEC's questionnaire, for evaluating the risk of nitrosamine impurities. We recommend that the firm compares any prepared questionnaire or other risk assessment tool with the recommendations in the nitrosamine guidance and other relevant guidance and regulations to ensure it covers all appropriate requirements and recommendations.

7. What are FDA's recommendations for manufacturers, or plans for thought leader engagement, to ensure public confidence and continued medical adherence while working through Step 2 confirmation testing?

FDA recommends that manufacturers review and follow the nitrosamine guidance to ensure quality products are available to the U.S. public. FDA will continue to engage consumers, health care professionals, and industry about this issue by posting updates to our website and messaging through other media channels.

FDA is receptive to suggestions from industry and others regarding gaps in public messaging to fully educate patients and health care professionals about nitrosamine testing and the importance of medical adherence.

8. What are FDA's thoughts on developing a Q&A guidance to clarify aspects of the September 2020 guidance on nitrosamines?

We do not have plans for a Q&A document at this time. Because the guidance is intended to comprehensively address investigation of nitrosamine risks and application of mitigation strategies, it is unclear how a Q&A document would bring clarity.

9. Given the potentially substantial economic impact of the guidance, has FDA conducted, or have plans to conduct, an economic impact assessment?

FDA ensures that drug products are free from unacceptable levels of impurities based on the FD&C Act, FDA regulations on CGMPs, and recommendations in guidance documents. The Nitrosamine Guidance provides industry with recommendations on how to test and prevent unacceptable levels of nitrosamines in drug substances and drug products. In publishing the guidance, FDA complied with all applicable statutory and regulatory requirements.

Safety

10. **What are FDA’s expectations for establishing acceptable intakes (AIs) for potential cohort of concern (CoC) nitrosamines with insufficient safety data?**

We refer you to ICH M7 and to Appendix B in FDA’s Nitrosamine Guidance for “FDA Determination of the Acceptable Intake.” For nitrosamines with insufficient safety data, computational toxicology assessments may be used to identify structurally similar, surrogate compounds with the n-nitroso alert, for determining the AI. Closely related compounds with robust carcinogenicity data should be considered in determination of AI. The rationale for your choice of surrogate and acceptability of the AI will be a review issue. When an appropriate surrogate is not identified, FDA has referred to the established AIs for N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) and identified an appropriate AI for the nitrosamine of interest.

- a. **Does FDA support a read across safety evaluation to set comparative limits for structurally complex nitrosamines (e.g., API-related nitrosamines and nitrosamines without safety data)?**

We refer you to ICH M7 and FDA’s nitrosamine guidance for information on calculating an AI for a nitrosamine. Read-across evaluations could be considered for safety evaluation of structurally complex nitrosamines or nitrosamines without safety data. A read-across approach involves the identification and selection of data-rich compounds that are similar in structure and reactivity to a data-poor compound of interest. Test data from the similar compounds are then used to “read-across” to generate an estimate, either quantitatively or qualitatively, of the missing values for the data-poor compound.

- b. **When using read across to derive an AI for a nitrosamine with insufficient carcinogenicity data, what specific scientific considerations does FDA believe are most important?**

There are several considerations for using read-across approach to derive an AI for structurally complex nitrosamines or nitrosamines without safety data. FDA considers the nitrosamine structural alert environment to be an important factor when selecting appropriate reference compounds for a read-across analysis. This includes consideration of the degree of substitution, steric bulk, electronic influences, potential for metabolic activation, stability/reactivity of the resulting metabolites, and overall molecular weight.

FDA currently uses a combination of methods to identify the most structurally relevant nitrosamine reference compound(s) for a data-poor nitrosamine.

As discussed at a recent [FDA workshop](#), this is an area requiring further development.

11. What is FDA’s scientific rationale for the stated AI limits for nitrosamine compounds (single and multiple) in the FDA Guidance [Control of Nitrosamine Impurities in Human Drugs](#)?

We refer you to ICH M7 and to Appendix B in FDA’s Nitrosamine Guidance for “FDA Determination of the Acceptable Intake.” As noted in the FDA Nitrosamine Guidance, if multiple nitrosamine impurities are present in the active pharmaceutical ingredient or drug product, the total nitrosamine level should be limited to 26.5 ng/day based on the maximum daily dose. When total nitrosamine level exceeds 26.5 ng/day, contact FDA via CDER-OPQ-Inquiries@fda.hhs.gov.

a. What are FDA’s views on studies that may be needed, and on the type and extent of data needed, for a manufacturer to qualify a scientifically justified AI for a nitrosamine compound?

We refer to you to ICH M7 and to Appendix B of FDA’s Nitrosamine Guidance for “FDA Determination of the Acceptable Intake.” A compound-specific AI can be calculated based on rodent carcinogenicity potency data such as TD50 values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2) identified in the public literature. The quality of carcinogenicity studies in the published literature can be quite variable. Studies of lesser quality are defined in ICH M7 as those where one or more of the following scenarios were encountered:

- < 50 animals per dose per sex;
- < 3 dose levels;
- Lack of concurrent controls;
- Intermittent dosing (< 5 days per week);
- Dosing for less than lifetime.

Use of less robust data can sometimes be considered acceptable when no more complete data exist, given the highly conservative nature of the risk assessment in which TD50 was linearly extrapolated to a 1:100,000 excess cancer risk.

12. What are the conditions under which FDA considers less-than-lifetime calculations to be unacceptable for establishing AIs?

FDA has determined that less than lifetime (LTL) adjustments are not appropriate for nitrosamine impurities. ICH M7 describes an acceptable increase in cancer risk as 1:100,000. In calculating the AI, FDA considers the extent and quality of the data available. An LTL adjustment considers the number of dosing days in determining allowable exposures while maintaining a comparable risk level. Nitrosamines belong to a group of

highly potent mutagenic carcinogens called the cohort of concern (CoC). Multiple nitrosamines have been shown to induce tumors in multiple species at relatively low doses and after very short durations of dosing, including single doses. There is also uncertainty as to how the LTL limit would be derived given uncertainty in how the cancer risk of CoC carcinogens changes with shorter duration of exposure. For these reasons, FDA does not apply LTL scaling factors to the AI for nitrosamines. FDA will permit exposures above lifetime AI on a case-by-case basis to maintain patient access to medically necessary drugs. FDA physicians and scientists make these case-by-case decisions based on the severity of disease, the potential impact of a drug shortage for the medication, and discussions with a manufacturer as to their ability to reduce or eliminate these impurities.

13. A suitably predictive bacterial mutagenicity test can be used to de-risk a structurally complex nitrosamine. What are FDA's expectations for the design of such tests?

We refer you to ICH M7 for guidance on mutagenicity evaluation and risk assessment of nitrosamine impurities. A standard bacterial reverse mutation assay may be informative to identify mutagenic potential of nitrosamine compounds. However, information in literature suggests that the Ames test conducted with rat S9 may not always be sensitive to qualify the mutagenicity of N-nitroso compounds. The insensitivity of the Ames test in assessing N-nitrosamine compounds is due to species-specific differences in metabolic activation of potential mutagens. Therefore, when this initial standard assay indicates a lack of mutagenic potential, applicants should further demonstrate that the test conditions were suitable to provide a reliable assessment with appropriate metabolism and exposure. Follow-up testing using a modified in vitro assay or in vivo assessment could be conducted to address these issues. For specific questions on study design of in vitro or in vivo studies with nitrosamine impurities in your drug, contact FDA.

a. What aspects of the Ames assay procedure require optimization to routinely/confidently apply the assay to de-risk Nitrosamine impurities?

Information in the literature suggests that the Ames test conducted with rat S9 may not always be sensitive to qualify the mutagenicity of N-nitroso compounds. The insensitivity of the Ames test in assessing N-nitrosamine compounds is due to species-specific differences in metabolic activation of potential mutagens. FDA genotoxicity experts are currently conducting research in this area. We note industry is also a key partner in developing and optimizing risk assessment strategies for N-nitroso impurities in drugs.

Rao TK (1984) Structural Basis for Mutagenic Activity of N-Nitrosamines in the Salmonella Histidine Reversion Assay. In: Rao T.K., Lijinsky W, Epler J.L. (eds) Genotoxicology of N-Nitroso Compounds. Topics in Chemical Mutagenesis, vol 1. Springer, Boston, MA.

Andrews AW, Lijinsky W (1984) N-Nitrosamine Mutagenicity Using the Salmonella/Mammalian-Microsome Mutagenicity Assay. In: Rao TK, Lijinsky W, Epler JL (eds) Genotoxicology of N-Nitroso Compounds. Topics in Chemical Mutagenesis,

vol 1. Springer, Boston, MA.

Prival MJ and Mitchell V. Influence of microsomal and cytosolic fractions from rat, mouse, and hamster liver on the mutagenicity of dimethylnitrosamine in the Salmonella plate incorporation assay. Cancer research, 1981, 41(11),4361-7.

- 14.** Does FDA accept ICH S9 approaches for management of potential nitrosamine impurities in therapeutics for advanced cancer therapies?

Yes, the ICH S9 approach, where set limits for genotoxic impurities are not considered appropriate for pharmaceuticals intended to treat patients with advanced cancer, is acceptable.

- a.** In cases where a drug substance is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk, does FDA agree that exposure to a mutagenic nitrosamine impurity would not significantly add to the cancer risk of the drug substance, and that nitrosamine impurities could be controlled at acceptable levels for non-mutagenic impurities, in line with ICH M7?

Given the observed potency of nitrosamines, they may still significantly add to the overall cancer risk while adding no direct benefit to the patient. As previously discussed, nitrosamine impurities in drug substances and products indicated for advanced cancer may be controlled at levels for non-mutagenic impurities. However, an AI should be determined for nitrosamine impurities in drug substances and products developed for other indications. As noted in ICH M7, when the alerting structure associated with the impurity is unrelated to the drug substance, the impurity should be controlled at or below acceptable limits. Flexibility in setting drug substance and product specifications may be applied in some scenarios depending on the indication, availability of other treatments and potential impacts on drug shortage.

- 15.** What is FDA's preferred approach for establishing acceptable intakes when multiple nitrosamine impurities might be present?

We refer you to FDA's Nitrosamine Guidance on how to address scenarios with multiple nitrosamines.

Control Strategies

- 16.** Can FDA confirm that the control strategy for a nitrosamine can utilize the same principles outlined in ICH M7 for mutagenic impurities, and the same associated four control strategy options?

- a.** Does FDA agree that Option 3 should be an appropriate control strategy, per ICH M7. If not, does FDA have a perspective on specific alternatives?

If levels in the API are above LOQ and less than AI, FDA recommends a control in the

specification of the API. However, adequate justification for an Option 3 approach (e.g., an upstream or in-process control coupled with fate and purge studies that demonstrate the level consistently remains well below the AI may be possible

- b. If a nitrosamine is known to be present in a manufacturing process, is an ICH M7 Option 4 control strategy an acceptable mitigation? Or is a control strategy that includes an analytical test automatically required?**

If a nitrosamine is above LOQ in the API then an Option 4 control strategy may not be appropriate. Option 4 requires complete understanding of process parameters, including fate and purge studies, as well confidence that there is negligible risk that the impurity will be present above AI. ICH M7 suggests that this approach may be used for inherently unstable impurities, which does not describe nitrosamines. For application products, Option 4 will be considered on a case-by-case basis if proposed in an application or Drug Master File (DMF). However, ICH M7 principles, with appropriate supporting data and justification, including option 3 and 4, are applicable.

Given existing uncertainties regarding nitrosamine impurities and their presence in drugs, for APIs with an impurity detected above the LOQ or at-risk APIs, testing of each batch on release should be conducted. Alternate approaches (e.g., upstream test of an intermediate) should be supported by sufficient process understanding and evidence of adequate statistical control and, for application products, should be submitted to FDA in a supplement prior to implementation.

Any drug product batch found to contain levels of nitrosamine impurities at or above the recommended AI should not be released by the drug product manufacturer for distribution. Manufacturers should contact the Agency if a recall is initiated. Under section 501 of the FD&C Act, a drug that is not manufactured, processed, packed, or held in conformity with CGMP to ensure that the drug meets certain quality and purity standards is considered adulterated. FDA may exercise regulatory discretion when warranted to prevent or mitigate a shortage of a drug.

- 17. Calculated purge factors in API synthesis are an important tool for assessing the presence and/or formation of nitrosamines. However, FDA's guidance suggests testing all lots of API using at-risk materials in the route of synthesis. What is FDA's position on the use of calculated purge factors to discharge the risk of nitrosamine presence?**

As noted in the response to question #16 above, calculated purge studies that demonstrate the absence of nitrosamines, if suitably justified by the use of experimental data along with process understanding, may be appropriate in controlling nitrosamines.

- 18. Does FDA consider a nitrosamine level above the limit of quantitation (LOQ) but below the AI an acceptable risk level without the need to perform routine testing?**

As stated in the guidance, if nitrosamine levels are above LOQ but below AI, a control

should be implemented. This would be typically a specification; thus, testing would be required. However, there may be instances where alternative approaches are allowable.

19. Does FDA agree that confirmatory testing lots can be selected to be representative of the product to be evaluated, with number of lots tested justified dependent upon the product supply risk?

By confirmatory testing, we assume that you are referring to step 2 as described in the Nitrosamine Guidance. The number of batches of API or drug product tested should be determined by the manufacturer. The drug product batches should be representative of the manufacturing process for the marketed drug product.

Companies should consider that there may be significant batch to batch variability. For this reason, the number of batches should consider the number and volume of samples from each lot representing each supplier or vendor, including confidence in the source that may be a source of nitrosamine impurities or precursors. Wherever possible, potential sources of nitrosamine in the manufacturer's supply chain should be eliminated (e.g., qualification of raw materials throughout the product lifecycle).

20. How does FDA factor in the duration of use of a medicine in establishing an appropriate control strategy?

Duration of use is not factored into the control strategy for nitrosamine impurities.