Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2021
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

Revision 1

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Preface

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see Section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2) and (g)(3)). FDA made this determination because of the importance of providing timely information to manufacturers regarding risk assessments, testing, and other appropriate actions they should take to reduce and mitigate nitrosamine impurities in active pharmaceutical ingredients (APIs)[1] and drug products. This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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 https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1530 and complete title of the guidance in the request.

[1] The term *API* used throughout this guidance should be interpreted to mean drug substance, the active ingredient in a drug product. See 21 CFR 210.3(b)(7) (defining *active ingredient*) and 314.3 (defining *drug substance*).

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Contains Nonbinding Recommendations

Control of Nitrosamine Impurities in Human Drugs Guidance for Industry[1]

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. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance recommends steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamine[2] impurities in pharmaceutical products.[3] The guidance also describes conditions that may introduce nitrosamine impurities. The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers (ARBs),[4] ranitidine,[5] nizatidine,[6] and metformin,[7] has made clear the need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product at risk for their presence. This document revises the guidance of the same title issued in September 2020. This revision extends the time period for preparing initial risk assessments to March 31, 2021 (i.e., within 7 months of publication of the original guidance).

[1] This guidance has been prepared by the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2020-D-1530 (available at https:/regulations.gov/docket/FDA-2020-D-1530) (see the instructions for submitting comments in the docket).

[2] The term *nitrosamine* as used in this guidance means *N-nitrosamine*.

[3] New drug application (NDA) and abbreviated new drug application (ANDA) holders or sponsors, drug master file (DMF) holders, and owners of marketed products that are not the subject of approved NDAs or ANDAs (such as compounded products or products marketed under an over-the-counter (OTC) drug monograph) who are not also the manufacturer of the drug products and APIs should work with their contract manufacturers to take the steps recommended in this guidance. This applies to drug products currently available on the U.S. market as well as those with pending applications.

[4] The first nitrosamine detected in ARBs was N-nitrosodimethylamine (NDMA), which is a genotoxic and carcinogenic agent in animals and is classified as probably carcinogenic to humans (Class 2A carcinogen) by the World Health Organization's (WHO's) International Agency for Research on Cancer (IARC). Other nitrosamines, including N-nitrosodiethylamine (NDEA) and N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), have also been detected in various ARB products.

[5] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine

[6] See footnote 5.

[7] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin

The discovery of nitrosamines in some types of drug products led FDA and other international regulators to conduct a detailed analysis of these impurities in affected APIs and drug products.[8,9] Based on the Agency's current understanding, this guidance discusses potential root causes of nitrosamine formation and advises API and drug product manufacturers that they should (1) conduct risk assessments of their approved or marketed products and products with pending applications, and (2) take appropriate actions to reduce or prevent the presence of nitrosamines in APIs and drug products.

Although nitrosamine impurities have been found in only some drug products, and batches of those products have been recalled when there were unacceptable levels[10] of these impurities, nitrosamine impurities might exist in other APIs and drug products due to use of vulnerable processes and materials that may produce nitrosamine impurities. Therefore, the recommendations made in this guidance apply to all chemically synthesized APIs. They also apply to drug products containing chemically synthesized APIs and to drug products at risk due to other factors described in this guidance (see sections II.B and C), and not just to the drug products that have been identified in FDA announcements.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA has been investigating the presence of nitrosamine impurities in certain drug products. Since 2018, several drug products including ARBs, ranitidine, nizatidine, and metformin have been found to contain unacceptable levels of nitrosamines.

In June 2018, FDA was informed of the presence of an impurity identified as N-nitrosodimethylamine (NDMA) in the ARB valsartan.[11] Through investigation, the Agency determined that numerous lots of valsartan and a few other ARB drug products from different manufacturers contained unacceptable levels of nitrosamines. The drug product manufacturers

[8] Other regulators with which FDA has been collaborating include the European Medicines Agency (EMA), European Directorate for the Quality of Medicines and Healthcare (EDQM), Health Canada (HC), Therapeutic Goods Administration (TGA, Australia), Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency (PMDA/MHLW, Japan), Health Sciences Authority, Singapore (HSA, Singapore), and Swissmedic (Switzerland).

[9] FDA's validated laboratory methods used in assaying nitrosamine impurities in various drugs as well as the analytical results for various drugs and batches are available at https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current, https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine, and https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin.

[10] See Table 1 in section III.A. of this guidance.

[11] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current

voluntarily recalled the affected batches of these drug products,[12] which led to a drug shortage in some of the affected products.[13] In addition, FDA evaluated processes that use common amines in API synthesis and learned that common synthetic pathways could also introduce other types of nitrosamine impurities besides NDMA.

In September 2019, FDA learned that some common heartburn products (ranitidine, commonly known as Zantac, and nizatidine, commonly known as Axid) contained unacceptable levels of NDMA.[14] FDA recommended that manufacturers voluntarily recall ranitidine and nizatidine products with NDMA levels above what the Agency considers acceptable.[15, 16] Recently, preliminary findings from FDA stability testing raised concerns that NDMA levels in some ranitidine products stored at room temperature can increase with time to unacceptable levels. FDA's preliminary results using accelerated stability testing demonstrated that elevated levels of NDMA were measured in all products after 2 weeks. FDA's testing suggests that NDMA levels increase with storage time. On April 1, 2020, FDA requested that all ranitidine products be withdrawn from the U.S. market.

In December 2019, FDA became aware that some metformin diabetes medicines in other countries were reported to have NDMA. In light of this information, FDA acquired samples of metformin to test for NDMA. By February 2020, the Agency had identified NDMA in some samples but did not find levels exceeding the acceptable intake limit. In May 2020, further FDA testing revealed that certain lots of metformin extended-release formulation contained NDMA above the Agency's recommended acceptable intake limit. Based on that testing, FDA requested that identified applicants voluntarily recall these lots of the extended-release metformin. FDA continues to investigate possible NDMA impurities in metformin and other drug products and will advise companies on appropriate action.

Because the nitrosamine impurity issue extends beyond the U.S. drug supply, FDA and other regulatory authorities have partnered to share information, coordinate inspection efforts, communicate effective analytical methods to detect and identify various nitrosamines, and to develop rapid solutions to ensure the safety and quality of the drug supply.

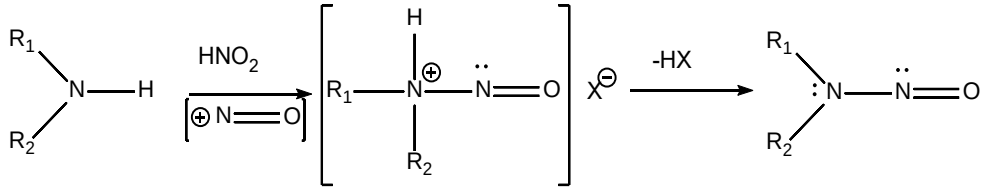
A. Nitrosamine Impurities

The term *nitrosamine* describes a class of compounds having the chemical structure of a nitroso group bonded to an amine ($R^1N(-R^2)-N=O$), as shown in Figure 1. The compounds can form by a

[12] For a list of recalled products, see FDA's Recalls, Market Withdrawals, & Safety Alerts web page at https://www.fda.gov/node/360167.
[13] See FDA's public web page on drug shortages at https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages and FDA's list of recalled ARB products at https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and.
[14] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
[15] https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs
[16] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current

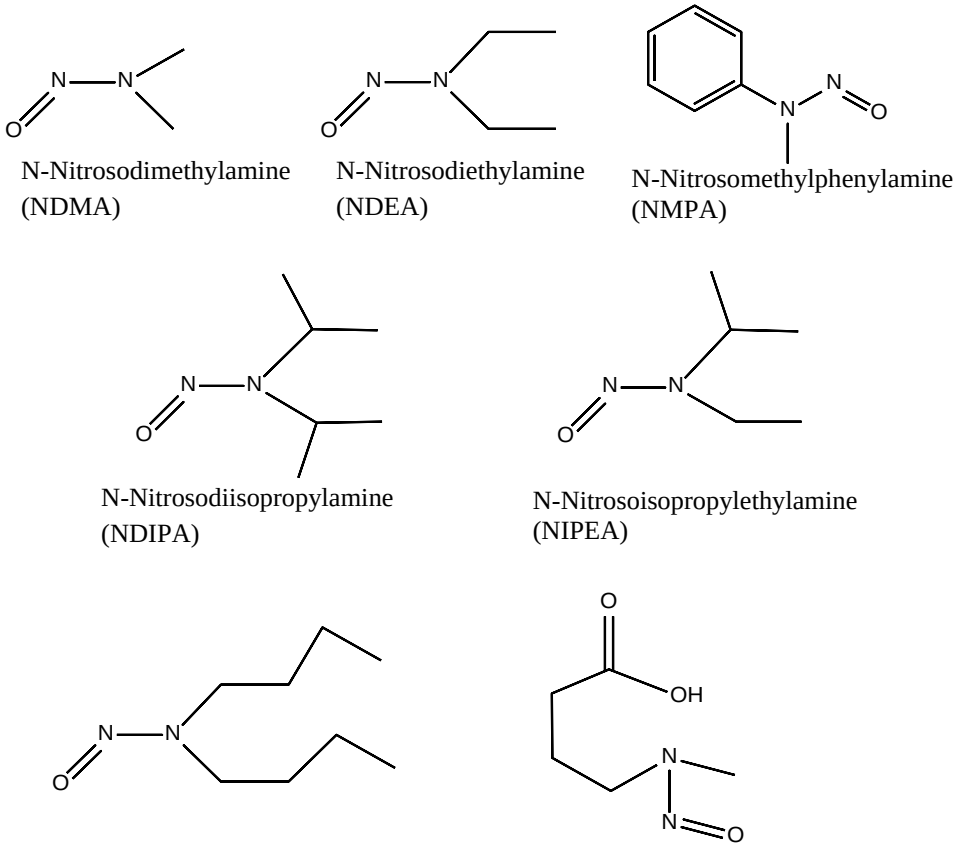
nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions).

Figure 1. Representative Reaction to Form Nitrosamines



FDA has identified seven nitrosamine impurities that theoretically could be present in drug products: NDMA, N-nitrosodiethylamine (NDEA), N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitrosoisopropylethyl amine (NIPEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), and N-nitrosomethylphenylamine (NMPA) (Figure 2). Five of them (NDMA, NDEA, NMBA, NIPEA, and NMPA) have actually been detected in drug substances or drug products.

Figure 2. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products



Nitrosamine compounds are potent genotoxic agents in several animal species and some are classified as probable or possible[17] human carcinogens by the International Agency for Research on Cancer (IARC).[18] They are referred to as "cohort of concern" compounds in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018).[19] The guidance recommends control of any known mutagenic carcinogen, such as nitroso-compounds, at or below a level such that there would be a negligible human cancer risk associated with the exposure to potentially mutagenic impurities. Following the discovery of nitrosamine contaminants in ARBs, FDA published interim acceptable limits for these impurities.[20] FDA recommended that manufacturers take action to quantify nitrosamine levels in their drugs and to reduce or remove these impurities when above the interim limit; FDA has used the interim limits to guide immediate decision-making for additional evaluation and product recalls[21] while balancing the risks of potential long-term carcinogen exposure with disruption to clinical management of patients.

B. General Root Causes for the Presence of Nitrosamine Impurities in APIs

Recent information gathered by FDA suggests several general root causes of the presence of nitrosamine impurities in APIs:

1. General Conditions That Lead to Nitrosamine Formation

Formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines[22] and nitrite salts[23] under acidic reaction conditions. Under these conditions, nitrite salts may form nitrous acid, which can react with an amine to form a nitrosamine (see Figure 1). There is a greater risk of nitrosamine formation if nitrous acid is used to quench residual azide (a reagent commonly used in tetrazole ring formation or introduction of azide functional group into a molecule) in the presence of precursor amines.

Nitrites used as reagents in one step can carry over into subsequent steps, despite purification operations, and react with amines to generate nitrosamine impurities. Therefore, whenever nitrite salts are present, carryover into subsequent steps cannot be ruled out. In general, processes that use nitrites in the presence of secondary, tertiary, or quaternary amines are at risk of generating nitrosamine impurities.

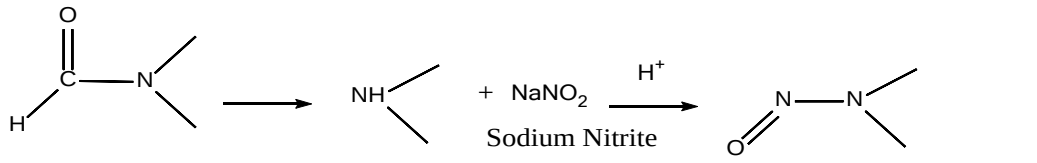
[17] NDBA is classified as possibly carcinogenic (2B) by IARC.
[18] https://monographs.iarc.fr/list-of-classifications
[19] The Agency updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[20] See the 2/28/2019 announcement at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan.
[21] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
[22] Secondary and tertiary amines may be present as impurities or degradants of quaternary ammonium salts.
[23] Secondary, tertiary, and quaternary amines and nitrite also can be called nitrosamine precursors.

2. Sources of Secondary, Tertiary, and Quaternary Amines That Can Form Nitrosamines

Amines may be present in a manufacturing process for a variety of reasons. The API (or API degradants), intermediates, or starting materials may contain secondary or tertiary amine functional groups. Tertiary and quaternary amines may also be added intentionally as reagents or catalysts. All of these types of amines can react with nitrous acid or other nitrosating agents to form nitrosamines.[24, 25, 26]

Amide solvents, which are susceptible to degradation under certain reaction conditions, are another source of secondary amines. For example, under high reaction temperatures for an extended reaction period, N,N-dimethylformamide can degrade into dimethylamine, which can react with nitrous acid to form NDMA (see Figure 3). N-methylpyrrolidone, N,N-dimethylacetamide, and N,N-diethylacetamide also have similar degradation pathways to form secondary amines that can react with nitrous acid to form nitrosamine impurities. Secondary amines could also be present as impurities in amide solvents. For example, dimethylamine, which can react with nitrous acid to form NDMA, may exist as an impurity in N,N-dimethylformamide.

Figure 3. Formation of NDMA From N,N-Dimethylformamide



Tertiary and quaternary amines used as reagents in the synthesis of APIs may contain other amine impurities. Tertiary amines, such as triethylamine, have been shown to contain low levels of other secondary amines (such as dipropylamine and isopropylethylamine). Secondary and tertiary amines may be present as impurities or degradants formed by dealkylation of quaternary amines. For example, a common phase-transfer catalyst, tetrabutylammonium bromide, may contain tributyl- and dibutylamine impurities. The amine impurity level that may lead to nitrosamine contamination of the API is process dependent and should be determined by each API manufacturer.

This list of the aforementioned sources is not exhaustive, as amine reagents can be used to mediate a wide range of synthetic transformations. Manufacturers should evaluate other reagents containing amine functional groups for potential risk of nitrosamine formation.

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[24] Smith, PAS and RN Loeppky, 1967, Nitrosative cleavage of tertiary amines, J Am Chem Soc, 89(5): 1147–1157

[25] Fiddler, W, JW Pensabene, RC Doerr, and AE Wasserman, 1972, Formation of N-nitrosodimethylamine from naturally occurring quaternary ammonium compounds and tertiary amines, Nature, 236: 307

[26] Gillatt, PN, RJ Hart, CL Walters, and PI Reed, 1984, Susceptibilities of drugs to nitrosation under standardized chemical conditions, Food Chem Toxicol, 22(4): 269–274

3. Contamination in Vendor-Sourced Raw Materials

Nitrosamine impurities can be introduced when vendor-sourced materials, including starting materials and raw materials, are contaminated. The Agency has observed the following contaminations due to this root cause:

- Nitrosamine contamination has occurred when fresh solvents (*ortho*-xylene, toluene, and methylene chloride) were contaminated during shipment from vendors (e.g., during transfer between storage vessels).

- Sodium nitrite is a known impurity in some starting materials (such as sodium azide) and may be present and react with amines under acidic conditions to form nitrosamines. Nitrate-containing raw materials, such as potassium nitrate, may contain nitrite impurities. The amount of nitrite impurity that can be tolerated is process dependent and should be determined by each API manufacturer.

- Secondary or tertiary amines have been reported as impurities in some raw materials (see details in section II.B.2 in this guidance) and in fresh solvents such as toluene.

- Starting materials or outsourced intermediates may be at risk through cross-contamination if they are manufactured at sites where nitrosamine impurities are produced in other processes.

Awareness of the supply chain of raw materials is an important factor in preventing contamination. For example, API producers may not be aware of nitrosamine contamination in raw or starting materials they have sourced from vendors; a producer whose manufacturing process is not normally susceptible to nitrosamine formation may not realize that vendor-sourced material may have had impurities introduced during production or transport.

4. Recovered Solvents, Catalysts, and Reagents as Sources of Contamination

Recovered materials such as solvents, reagents, and catalysts may pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine). If the recovery process involves a quenching step (i.e., nitrous acid used to decompose residual azide), nitrosamines could form during solvent recovery. These nitrosamines may be entrained if they have boiling points or solubility properties[27] similar to the recovered materials, depending on how recovery and subsequent purification takes place (e.g., aqueous washes or distillation). This further increases the risk of contamination in material recovery. For these reasons, some drug products using APIs manufactured by certain "low" risk processes[28] were found to be contaminated. The Agency has observed the following contaminations due to this root cause:

[27] NDMA and NDEA have boiling points of 151–153°C and 175–177°C, respectively (https://pubchem.ncbi.nlm.nih.gov). Both are miscible with water and soluble in organic solvents.
[28] "Low" risk processes are those deemed not normally susceptible to nitrosamine formation.

- A manufacturing site may produce the same API by more than one synthetic process that uses common solvents. If any of those synthetic processes produces nitrosamines or contains precursor amines, the solvents sent for recovery are at risk. The use of recovered solvents that are comingled from different processes or across manufacturing lines without control and monitoring can introduce nitrosamine impurities. If a recovered solvent is contaminated in this way and then used to manufacture an API, the API will be contaminated even if the synthetic route is not normally susceptible to nitrosamine formation.

- Recovery of raw materials (e.g., solvents, reagents, and catalysts) is often outsourced to third-party contractors. Process outsourcing can pose a risk if the third-party recovery facility does not receive enough specific information on the contents of the materials they are processing and relies solely on routine recovery processes.

- Raw materials can be contaminated if adequate cleaning of equipment between customers, or between different materials, is not carried out or is not validated as capable of removing each impurity of concern. It was reported that *ortho*-xylene and toluene were contaminated during recovery due to inadequate cleaning and to use of shared storage equipment between different customers. Inadequate and unvalidated cleaning procedures can also lead to cross-contamination if precautions to avoid nitrosamine contamination are not in place before materials from different customers are combined for recovery. For example, the catalyst tri-N-butyltin chloride (used as a source of tri-N-butyltin azide) was contaminated at a third-party contractor facility due to the combination of this catalyst from different customers.

5. Quenching Process as a Source of Nitrosamine Contamination

There is a risk of nitrosamine formation when a quenching step is performed directly in the main reaction mixture (i.e., when nitrous acid is added to the reaction mixture to decompose residual azide). This allows nitrous acid to come into direct contact with residual amines in the raw materials used in the manufacturing process. The nitrosamine impurities could be carried to the subsequent steps if there are not adequate removal or purification operations in place, or if the operations are not optimized for removing specific impurities of concern. This can contaminate the entire downstream process once they are introduced. Even if the quenching process is conducted outside of the main reaction mixture (see section II.B.4 in this guidance), there is a risk if contaminated recovered materials are introduced into the main process.

6. Lack of Process Optimization and Control

Another potential source of formation of nitrosamine impurities is lack of optimization of the manufacturing process for APIs when reaction conditions such as temperature, pH, or the sequence of adding reagents, intermediates, or solvents are inappropriate or poorly controlled. FDA has seen instances in which reaction conditions varied widely between batches and even between different processing equipment in the same facility for the same API.

The multiple root causes of nitrosamine contamination listed above can occur within the same API process. Therefore, multiple strategies may be necessary to identify all potential sources of

contamination. Typical routine tests (e.g., HPLC) for API purity, identity, and known impurities are unlikely to detect the presence of nitrosamine impurities. Further, each failure mode could result in different nitrosamines in different amounts across batches from the same process and the same API producer, with contamination detected in some batches but not all.

C. Nitrosamine Impurities in Drug Products From Sources Other Than API Contamination

Nitrites are common nitrosating impurities that have been reported in many excipients at ppm levels. Nitrite impurities are found in a range of commonly used excipients, which may lead to nitrosamine impurities forming in drug products during the drug product manufacturing process and shelf-life storage period. The supplier qualification program[29] should take into account that nitrite impurities vary across excipient lots and may vary by supplier. Drug product manufacturers should also be aware that nitrite and nitrosamine impurities may be present in potable water.

Some drug products may undergo degradation pathways that form nitrosamine impurities; this could potentially occur during drug product storage.

III. RECOMMENDATIONS

Because nitrosamines are probable or possible human carcinogens, FDA recommends that manufacturers consider the potential causes of nitrosamine formation described in this guidance as well as any other pathways observed and evaluate the risk for nitrosamine contamination or formation in their APIs and drug products. Manufacturers should prioritize evaluation of APIs and drug products based on factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated.[30] As new information becomes available and FDA's understanding of nitrosamines in drugs evolves, the Agency may recommend that certain drug products become higher priorities for risk assessment.

Manufacturers should refer to the ICH guidance for industry *Q9 Quality Risk Management* (June 2006) for details related to quality risk identification, analysis, and management. Manufacturers of APIs and drug products should take appropriate measures to prevent unacceptable levels of nitrosamine impurities in their products.

[29] In accordance with the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009), the manufacturer's pharmaceutical quality system extends to control of the quality of purchased materials. The supplier qualification program is a manufacturer's system (e.g., audits, material evaluations, qualification) for selecting material suppliers who can provide materials using a defined and approved supply chain.

[30] For example, a drug product with a maximum daily dose (MDD) of 2000 mg with the same detected level of the same type of nitrosamine would pose a greater risk than a drug product with a maximum daily dose of 200 mg. A drug product intended for only short-term use (e.g., a 7-day course of an antibiotic) poses less risk than a drug product intended for chronic use.

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.

B. Recommendations to API Manufacturers

While nitrosamines are not expected to form during the manufacture of the vast majority of APIs, all manufacturers of chemically synthesized APIs should take appropriate actions to mitigate the risk of nitrosamine contamination for APIs where there is a potential for nitrosamine impurities.

API manufacturers should review their API manufacturing processes and perform risk assessments to identify the potential for nitrosamine impurities. If a risk of nitrosamine impurities is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods. If the risk assessment determines that there is no potential for nitrosamine impurities, there is no need to take further action. If a nitrosamine impurity is detected, API manufacturers should investigate the root cause. They should implement changes in the manufacturing process to reduce or prevent nitrosamine impurities.[40]

1. Mitigating the Presence of Nitrosamine Impurities in APIs

FDA recommends that API manufacturers take the following actions:

- API manufacturers should optimize the design of the manufacturing process for APIs during route of synthesis (ROS) development to minimize or prevent the formation of nitrosamine impurities. API manufacturers should refer to the recommendations in ICH M7(R1) and the ICH guidances for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) and *Q11 Development and Manufacture of Drug Substances* (November 2012) in this respect. The following factors should be considered during process development:
    - Avoiding reaction conditions that may produce nitrosamines whenever possible; when not possible, demonstrating that the process is adequately controlled and is capable of consistently reducing nitrosamine impurities through appropriate and robust fate and purge studies.
    - Using bases other than secondary, tertiary, or quaternary amines (when possible) if ROS conditions may form nitrosamines.
    - Using caution when the ROS involves the use of amide solvents (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, and N-methylpyrrolidone).
    - Replacing nitrites with other quenching agents for azide decomposition processes.
    - Optimizing and consistently controlling the sequences of reactions, processes, and reaction conditions (such as pH, temperature, and reaction time).
    - Designing a manufacturing process that facilitates the purge of nitrosamine impurities in the subsequent processing steps.

[40] See section V in this guidance for reporting changes to approved applications and DMFs.

- API manufacturers should consider removing quenching steps (when there is a risk of nitrosamine formation, e.g., using nitrous acid to decompose residual azide) from the main reaction mixture to reduce the risk of nitrosamine formation. The API, or an intermediate formed through a reaction using an azide salt, can be separated from the mother liquor into the organic phase. The aqueous waste phase separated from the organic phase should then be quenched with nitrous acid without contacting the API, its intermediate, or solvents intended for recovery.

- API manufacturers should audit their supply chains and monitor them for any at-risk raw materials, starting materials, and intermediates.[41] API manufacturers should maintain records including the name of the raw material manufacturer and its supplier,[42] roles of the actual manufacturers of such materials, and any repackers and distributors who handle the materials before API manufacture. When appropriate, API manufacturers should establish controls and consider additional specifications for at-risk materials to prevent nitrosamine contamination.

- To avoid cross-contamination when recovered materials such as solvents, reagents, and catalysts are used in the manufacturing process, recovered material should be used only in the same step or in an earlier step (if there is sufficient purification) of the same process from which it was collected. The recovered materials should meet appropriate standards before reuse. If the recovery of materials is outsourced to third-party contractors, the API manufacturer should audit the contractors' validation of cleaning procedures. API manufacturers should follow recommendations in ICH Q7 for ensuring that cross-contamination with nitrosamine or nitrosamine precursors can be prevented. API manufacturers should also verify with their suppliers whether the purchased materials used in their processes are recovered.

- API manufacturers should be aware that potable water used in API manufacture may contain low levels of nitrite and even nitrosamines from environmental contamination.[43] The existence of nitrites in processing water may lead to nitrosamine contamination in API manufacture. Therefore, to avoid unacceptable levels of nitrosamine impurities in APIs, API manufacturers should analyze nitrite and nitrosamine levels in water and use water that has been purified to remove unacceptable impurities.

  If a nitrosamine is introduced to the API through exogenous sources[44] that can be avoided, manufacturers should eliminate the source of contamination.

- API batches may be reprocessed or reworked to control the level of nitrosamine impurities as provided in ICH Q7 for amending and controlling such operations. If a batch is found to

[41] For a description of "at-risk materials," see section II.B in this guidance.
[42] ICH Q7
[43] See the latest version of the WHO's *Guidelines for Drinking-Water Quality* at https://www.who.int/water_sanitation_health/water-quality/guidelines/en/.
[44] Exogenous sources, for the purposes of this guidance, refer to materials such as solvents and raw materials used in synthesis or processing that may introduce contamination.

contain nitrosamine and is reprocessed or reworked in any way, these operations should be conducted under oversight of the quality unit.

2. *Control of Nitrosamine Impurities in APIs*

If a nitrosamine impurity is detected above the LOQ, the API manufacturer should develop a strategy to ensure that the nitrosamine level remains within the AI limit. Manufacturers should develop an appropriate control strategy, which should include specification limits, to ensure that the nitrosamine level reliably remains well below the AI limit in the API. 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 should be submitted to FDA in a supplement prior to implementation.[45]

Any API batch found to contain levels of nitrosamine impurities above the recommended AI should not be released by the API manufacturer for distribution unless, with prior FDA agreement, the API is needed to prevent or mitigate a shortage of a drug.

C. Recommendations to Drug Product Manufacturers

Drug product manufacturers should conduct risk assessments to determine the potential for nitrosamine impurities in drug products. A risk assessment should involve collaboration with the API manufacturer to aid in the identification of the API ROS or other process conditions of the API's manufacture that put the drug product at risk for nitrosamine impurities. The risk assessment should also include evaluation of any pathway (including degradation) that may introduce nitrosamines during drug product manufacture or storage. If the risk assessment determines that there is no potential for nitrosamine impurities, there is no need to take further action.

If a risk of nitrosamines in a drug product is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods.[46] If a nitrosamine impurity is detected, manufacturers should investigate the root cause and implement changes in the manufacturing process to mitigate or reduce nitrosamine impurities.[47]

1. Control of Nitrosamine Impurities in Drug Products

Drug product manufacturers must test representative samples of all incoming components, including lots of at-risk API, prior to use, as required under 21 CFR 211.84.[48] To meet the CGMP

[45] All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (see 21 CFR 314.70(b)(2)) and the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)).

[46] Testing using appropriately validated methods may be conducted by the API manufacturer or by a qualified laboratory.

[47] See section V in this guidance for reporting changes to approved applications and DMFs.

[48] At-risk APIs include APIs with secondary, tertiary, and quaternary amine functional groups. They also include any API with an ROS using at-risk materials (see section II.B in this guidance).

regulations in 21 CFR 211 subpart E and be consistent with the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009), drug product manufacturers should continue testing API lots until they have verified that the API supplier can consistently manufacture API without unacceptable levels of nitrosamine.

Drug product manufacturers, when designing their control strategy, should evaluate whether nitrites could be present during manufacturing processes where at-risk APIs are used. They should also evaluate whether nitrosamines could form in a finished drug product over the drug product's shelf life. If a nitrosamine is introduced to the drug product through exogenous sources that can be avoided, manufacturers should eliminate the source of contamination.

If a nitrosamine impurity is detected above the LOQ, the manufacturer should develop a strategy to ensure that the nitrosamine level remains within the AI limit. The control strategy should include specification limits for the identified nitrosamine. Such a control strategy is also recommended when the introduction of nitrosamine is inherent due to the API structure, the API ROS, or the manufacturing process of the API or drug product. Given existing uncertainties regarding nitrosamine impurities and their presence in drugs, testing of each batch on release should be conducted. Alternate approaches should be supported by sufficient process understanding and evidence of adequate statistical control and should be submitted to FDA in a supplement prior to implementation.[49]

If drug product batches with unacceptable levels of nitrosamine impurities are already in distribution, drug product manufacturers should contact FDA so the Agency can determine the regulatory action for the specific drug products. 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.[50] Under section 501 of the Food, Drug, and Cosmetic Act (FD&C Act),[51] 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.

IV. MAINTAINING THE DRUG SUPPLY

If any manufacturing changes or recalls are likely to lead to a disruption in the drug supply, manufacturers should immediately contact CDER's Drug Shortage Staff at drugshortages@fda.hhs.gov; FDA can work with manufacturers to mitigate the risk of nitrosamine impurities in APIs and drug products while avoiding interruptions in the drug supply. Contacting the Drug Shortage Staff can assist manufacturers in meeting any obligations to report discontinuances or interruptions in their drug manufacture under section 506C of the FD&C Act and implementing regulations under 21 CFR 314.81(b)(3)(iii). It also allows FDA to consider, as

[49] All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (see 21 CFR 314.70(b)(2)(i)) and the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)).

[50] Manufacturers can contact the recall coordinator assigned to the product type and location. Contact information for recall coordinators is available at https://www.fda.gov/safety/industry-guidance-recalls/ora-recall-coordinators.

[51] See 21 U.S.C. 351.

soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on the affected products.

V. REPORTING CHANGES TO FDA

Drug manufacturers must report changes implemented to prevent or reduce nitrosamine impurities in accordance with FDA regulations (21 CFR 314.60, 314.70, 314.96, and 314.97).

If an API DMF holder makes process changes in the ROS as a result of the risk assessment and confirmatory testing, the DMF holder must submit amendments and inform each drug product manufacturer that references the DMF (including pending and approved applications), in accordance with 21 CFR 314.420(c). If the API is manufactured by the applicant and not covered by a DMF, the manufacturer must report such ROS changes in the application in accordance with 21 CFR 314.70 and 21 CFR 314.97. If a batch of API is found to contain a nitrosamine and is reprocessed or reworked in any way, these operations should be reported in the DMF or application (as applicable).

Although each DMF may contain only a single synthetic route, if a change in synthetic process is needed to avoid nitrosamine contamination and it is not possible to immediately stop using the original manufacturing process, the API manufacturer should submit both processes in the DMF and provide an estimate for the earliest feasible timeframe for the removal of the original process. The different synthetic processes should be identified by separate codes to designate batches manufactured through each process. If the original process cannot be discontinued within a reasonable timeframe, the new or revised process should be submitted in a separate DMF.

If changes to the drug product are needed to prevent nitrosamine formation, application holders must submit a supplement to notify FDA of any changes to conditions established in the approved applications beyond the variations already provided for in their applications, as required by 21 CFR 314.70 and 314.97. Holders of pending applications must update their applications through submission of an amendment according to 21 CFR 314.60 and 314.96. Section V of this guidance includes additional information on reporting changes in APIs and drug products.

A. Recommended Timeline for Risk Assessment, Confirmatory Testing, and Submission of Required Changes

FDA recommends different implementation timelines depending on the regulatory status of the drug product.[52]

[52] New drug application (NDA) and abbreviated new drug application (ANDA) holders or sponsors, drug master file (DMF) holders, and owners of marketed products that are not the subject of approved NDAs or ANDAs (such as compounded products or products marketed under an over-the-counter (OTC) drug monograph) who are not also the manufacturer of the drug products and APIs should work with their contract manufacturers to take the steps recommended in this guidance. This applies to drug products currently available on the U.S. market as well as those with pending applications.

1. Approved or Marketed Drug Products

To ensure the safety of the U.S. drug supply, manufacturers should conclude a risk assessment of approved or marketed products *within 7 months* of publication of the original guidance, with a recommended completion date of on or before March 31, 2021. Confirmatory testing should start as soon as the risk of nitrosamine is identified from the risk assessment and should begin immediately for products considered at high risk. To ensure the safety of the U.S. drug supply, confirmatory testing of drug products and submission of required changes in drug applications should be concluded *within 3 years* of publication of the original guidance, with a recommended completion date of on or before October 1, 2023. FDA acknowledges that the implementation timeline includes investigating the root cause of the contamination or formation, identifying changes that will eliminate the root cause (e.g., change in manufacturing process, change in supplier), and confirming that any proposed changes will minimize the risk of nitrosamine contamination or formation without otherwise adversely affecting product quality. The timelines also include activities conducted by API manufacturers (i.e., risk assessment and testing) to support the drug products in which they are used. FDA may request an expedited risk assessment, confirmatory testing, or other regulatory action based on information available to the Agency.

2. Pending Applications

a. Pre-Submission Stage

FDA recommends that applicants conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed prior to submission of an original application. However, the risk assessment and submission of confirmatory testing, if needed, and changes to the DMF or application may be submitted in an amendment if they are not available at the time of the original submission filing. Such an amendment should be submitted as quickly as possible after the original submission filing to minimize any potential adverse impact on the application assessment timeline.[53]

b. Applications Pending With the Agency

Applicants with pending applications should conduct the risk assessment expeditiously and inform FDA if confirmatory testing finds nitrosamine levels above the AI limit.[54] If a nitrosamine impurity is detected above the LOQ but is within the AI limit, the applicant should amend the application as appropriate. The Agency will work with the applicant to resolve issues during the review cycle or immediately after approval, and before distribution, if determined to be necessary by the Agency.[55]

[53] For NDA submissions, manufacturers should discuss the need for an amendment with the Agency at the pre-NDA stage.
[54] For NDAs, the applicant should contact the specific product's review division. For ANDAs, the applicant should contact the project manager specified for the ANDA.
[55] In certain cases, FDA may consult with CDER's Drug Shortage Staff to ensure adequate supply on the U.S. market.

FDA generally will adhere to review goals established as part of the Prescription Drug User Fee Act reauthorization for years 2018–2022 (PDUFA VI) and the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II).

APPENDIX A. ADDITIONAL RESOURCES

The recommendations on reporting changes in APIs and drug products in this guidance are in accordance with the FDA's current regulations and guidances. The following guidances[1] are generally relevant to API and drug product impurities, including reporting changes of controls for impurities and application submission information:[2]

- Guidance for industry *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
- Guidance for industry *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)
- Guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale -Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (October 1997)
- Guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)
- ICH guidance for industry *Q9 Quality Risk Management* (June 2006)
- ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009)
- ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012)
- Guidance for industry *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)
- ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016)
- ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018)
- Draft guidance for industry *Postapproval Changes to Drug Substances* (September 2018)[3]

[1] The Agency updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] This guidance is not intended to cover all of the current good manufacturing practice (CGMP) requirements that are relevant. The DMF and drug product reporting provisions are the main focus in this section of the guidance.
[3] When final, this guidance will represent FDA's current thinking on this topic.

APPENDIX B. FDA DETERMINATION OF ACCEPTABLE INTAKE LIMITS

Identification of the acceptable intake (AI) values listed in section III of this guidance follows the procedures recommended in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018).[1] A compound-specific AI can be calculated based on rodent carcinogenicity potency data such as TD_{50} values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2) identified in the public literature. Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is achieved by simply dividing the TD_{50} by 50,000. The AI (in mg/kg/day units) can then be converted to mg/day by multiplying by the human body weight (50 kg is the assumed body weight identified in the referenced guidance). Linear extrapolation from a TD_{50} value is considered appropriate to derive an AI for M7 Class 1 impurities (known mutagenic carcinogens) with no established threshold mechanism. In many cases, the carcinogenicity data are available from the Carcinogenicity Potency Database (CPDB). When the CPDB contains a pre-calculated TD_{50} value for a selected chemical, this value may be used to calculate the AI. Where carcinogenicity study data for an impurity are of lesser quality as described in ICH M7, a surrogate compound with carcinogenicity data may be used to derive an acceptable intake but should be scientifically justified.

A summary of the AI derivation for NDMA is provided as an example. NDMA was identified as a mutagenic carcinogen in several species and is listed as a probable human carcinogen by the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) program. TD_{50} values for NDMA are 0.0959 mg/kg/day (rat, based on Peto et al.[2]) and 0.189 mg/kg/day (mouse) according to the CPDB.[3] For the AI calculation, the lower (more conservative) value of the rat is used. The resulting AI associated with a 1 in 100,000 cancer risk over 70 years of exposure is calculated by dividing the TD_{50} by 50,000 and then multiplying by 50 to account for a patient with a 50-kg body weight, resulting in 0.0000959 mg/day NDMA, or approximately 96 ng/day NDMA.

Hence, a daily lifelong intake of 96 ng/day NDMA corresponds to a theoretical cancer risk of 10^{-5} and therefore represents an AI when present as an impurity.

[1] The Agency updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] Peto, R, R Gray, P Brantom and P Grasso, 1991, Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine, Cancer Research, 51: 6452–6469

[3] Carcinogenicity Potency Database entry for N-nitrosodimethylamine (CAS 62-75-9) (NDMA) accessed at https://www.nlm.nih.gov/databases/download/cpdb.html